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Efficacy and acceptability of long-acting antipsychotics in acutely ill individuals with schizophrenia-spectrum disorders: A systematic review and network meta-analysis

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ABSTRACT

To assess the effect of Long-acting injectable (LAI) antipsychotics in acutely ill patients, we systematically searched major databases for randomized controlled trials (RCTs) comparing LAIs with other LAIs, oral antipsychotics, or placebo in acutely symptomatic adults with schizophrenia-spectrum disorders. Data were analyzed with a random-effects network meta-analysis. Co-primary outcomes were efficacy (mean change in psychopathology rating scales) and acceptability (all-cause discontinuations) at study endpoint.

Of 25 RCTs, 19 studies tested second-generation LAIs (SGA-LAIs) and six first-generation LAIs (FGA-LAIs). Due to a disconnected network, FGA-LAIs were analyzed separately, with poor data quality. The SGA-LAIs network included 8,418 individuals (males=63%, mean age=39.3 years). All SGA-LAIs outperformed placebo in reducing acute symptoms at study endpoint (median follow-up=13 weeks). They were more acceptable than placebo with the only exception of olanzapine, for which no differences with placebo emerged. Additionally, we distinguished between different LAI formulations of the same antipsychotic to explore potential pharmacokinetic differences. Most formulations outperformed placebo in the very short-term (2 weeks or less), regardless of the need for initial oral supplementation.

SGA-LAIs are evidence-based treatments in acutely ill individuals with schizophrenia-spectrum disorders. Findings support the use of SGA-LAIs to manage psychopathology and improve adherence right from the acute phases of illness.

1. Introduction

Schizophrenia spectrum disorders (SSDs) are serious mental illnesses affecting approximately 0.9% of the population (James et al., 2018). Large network meta-analyses (NMAs) showed oral antipsychotics to be efficacious for acute psychotic symptoms (Huhn et al., 2019), and oral and long-acting injection (LAI) antipsychotics to be equally effective for relapse prevention (Ostuzzi, Bertolini, et al., 2022) in clinically stable individuals. As LAIs might have advantages over oral formulations in terms of medication adherence, timely use of LAIs has been recommended by evidence-based guidelines (Kane and Garcia-Ribera, 2009; Llorca et al., 2013). However, evidence concerning LAIs' efficacy and acceptability in the acute phase of illness is yet to be substantiated by robust evidence (Liu et al., 2015; Reymann et al., 2022). A NMA by Leucht and colleagues (Leucht et al., 2023) assessed the medium-to-long-term efficacy of oral and LAI antipsychotics in acutely

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ill individuals with SSD. However, only trials with at least six months of follow-up were included, and the paucity of data on LAIs prevented a comparison between the LAI and oral formulations, which were grouped in the analysis. Of relevance, a pairwise meta-analysis by Wang and colleagues (Wang et al., 2023) assessed the differential efficacy of LAIs and oral antipsychotics against placebo in acutely ill individuals with SSD, finding these formulations to be similarly efficacious. However, only trials comparing the two formulations of the same medication were included, and the pairwise approach did not allow for the comparative comparison of different antipsychotics.

Against this background, we conducted a systematic review and NMA aiming to assess the differential efficacy and acceptability of LAIs and oral antipsychotics in acutely ill individuals with SSDs.

2. Methods

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for NMAs (Page et al., 2021) (Suppl.A). The study protocol was registered in advance on Open Science Framework (available at: https://osf.io/v7ehp/), and post-hoc amendments to the protocol are described in the Suppl.B.

2.1. Search strategy

We searched the electronic databases Medline, EMBASE, PsycINFO, CENTRAL, and CINAHL from database inception to August 31, 2023, without language or study date restrictions (for search strategy, see Suppl. C). Additionally, we searched databases of regulatory agencies (i.e., FDA and EMA), and online trial registers (e.g., clinicaltrials.gov).

2.2. Study selection and data extraction

We searched for randomized-controlled trials (RCTs) including adults (≥18 years old) diagnosed with SSDs (including schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and psychotic disorders not otherwise specified) according to validated diagnostic systems (i.e., DSM or ICD), either at their first or recurring episode, who were acutely ill at the time of randomization, as defined by each study. If acute symptoms were not clearly described, we assumed their presence based on clinical data (e.g., recent hospitalization) or a mean baseline score ≥75 on the Positive and Negative Syndrome Scale (PANSS), a mean baseline score ≥44 on the Brief Psychiatric Rating Scale (BPRS) and a mean baseline score ≥4 on the Clinical Global Impressions-Severity scale (CGI-S) (Busner and Targum, 2007; Leucht et al., 2005).

Only RCTs comparing LAIs with placebo, with oral antipsychotics, or between each other were included. Interventions included all available LAIs according to the WHO ATC/DDD classification (World Health Organization, 2023). RCTs randomizing to a single LAI against a mix of different oral antipsychotics were excluded (e.g. risperidone LAI vs generic oral SGA therapy).

Two authors independently assessed titles, abstracts, and full texts of potentially relevant articles, and extracted data following recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2023) (DPol, AC). Two authors (GV, DPol) assessed the risk of bias of included studies using the Cochrane Risk of Bias tool, version 2 (RoB2) (Sterne et al., 2019). Disagreements were resolved by discussion or arbitration by a third senior author (GO, CB, CUC).

2.3. Outcomes

The two co-primary outcomes were efficacy, defined as the mean change score at validated rating scales measuring psychopathology at the end of the study, and acceptability, defined as all-cause discontinuations.

Secondary outcomes included: (a) study-defined response or imputed from symptomatology rating scales (Furukawa et al., 2005) (b) response defined as a decrease ≥30% of PANSS mean score; (c) short-term response, between 4 and 12 weeks of follow-up, giving preference to the timepoint closest to 4 weeks; (d) medium-term response, between 12 and 24 weeks of follow-up, giving preference to the timepoint closest to 12 weeks; (e) long-term response, after 24 weeks of follow-up, giving preference to the latest timepoint available; (f) inefficacy-related discontinuation; (g) intolerability-related discontinuation; (h) mean change score on validated rating scales measuring functioning at the end of the trial; (i) common antipsychotic-related adverse events, including sedation, weight gain, hyperprolactinemia, extrapyramidal symptoms, akathisia, QTc prolongation; (j) proportion of participants experiencing at least one serious adverse event at study end; (k) proportion of deceased participants by the end of the trial. As the primary analysis pooled together different LAI formulations of the same medication, which may differ in terms of frequency of administration, onset of action, and oral supplementation, we performed a *post-hoc* efficacy analysis separating such formulations, and pooling very short-term data (i.e., timepoint closest to two weeks), considering that differences related to pharmacokinetic properties are more apparent in the early stages, and tend to diminish over time as the therapeutic plasma concentrations of the medication are reached.

2.4. Statistical analysis

We conducted a random-effects network meta-analysis (NMA) using the R netmeta package (Shim et al., 2019) and the Stata mvmeta package (White, 2007). For dichotomous outcomes, we pooled relative risks (RRs) with 95% confidence intervals (CIs) using a strict intention-to-treat approach (i.e. all randomized individuals as the denominator), while for continuous outcomes, we pooled mean differences (MDs) or standardized mean differences (SMDs) as appropriate. In cases where studies included different doses of the same antipsychotic, we pooled them into a single arm (Higgins et al., 2023), provided they fell within a therapeutic dose range (Gardner et al., 2010). Missing data were either obtained from trial authors or imputed using validated statistical methods (Aydin and Yassikaya, 2022; Furukawa et al., 2006; Higgins et al., 2023). Heterogeneity was assessed visually and with $\tau 2$ and I2 statistics (Higgins et al., 2023). The transitivity assumption was evaluated by comparing potential effect modifiers across treatments, followed by meta-regression analyses(Cipriani et al., 2013). Inconsistency was assessed both globally and locally (Bucher et al., 1997; Shih and Tu, 2021). Treatment rankings were generated using P-scores (Rücker and Schwarzer, 2015). Confidence in evidence was evaluated using the Confidence in Network Meta-Analysis (CINeMA) methodology (Salanti et al., 2014). (see Suppl.J: E-methods for details).

3. Results

Altogether, 1546 records were identified after database and hand searches. After removing duplicates and screening titles and abstracts, 95 records underwent full-text assessment. Of these, 25 primary studies, including 9027 individuals, provided meta-analyzable data for at least one outcome. The flowchart of included studies is available in suppl.I (E-Fig. 1), while a bibliography of included studies is available in suppl. K. Nineteen studies provided data on second-generation (SGA) LAIs, and 6 on first-generation (FGA) LAIs (Table 1). The two pharmacological classes were analyzed separately since the two networks were not connected for any of the outcomes of interest.

3.1. First-generation antipsychotics

The six studies on FGA-LAIs included 609 individuals (age=35.5 years, male=59%). The mean follow-up was 37.3 weeks. Five out of six

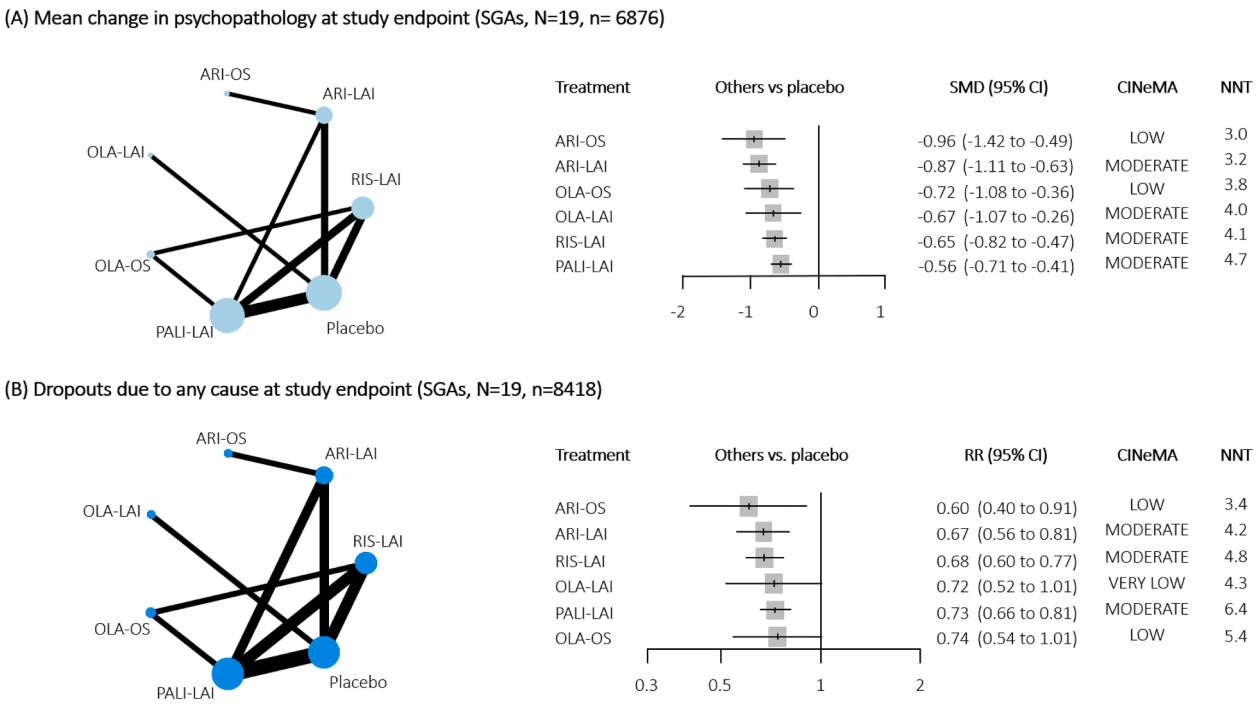

Fig. 1. Netmaps and forest plots for the analyses of (A) mean change in psychopathology at the study endpoint and (B) drop-outs due to any cause at the study endpoint.
Legend: ARI=aripiprazole; LAI=long-acting injectable antipsychotic; NNT= Number needed to treat; OLA= Olanzapine; OS= oral; Pali= Paliperidone; RIS= Risperidone; RR= Risk Ratio; SMD= Standardized mean difference; SGAs= Second-generation Antipsychotics;.

studies were double-blind and no study included placebo as a comparator. Treatments included fluphenazine LAI (FLUPH-LAI; $N = 4$, $n = 207$, mean age=29.3 years), fluspirilene LAI (FLUS-LAI; $N = 2$ studies, $n = 35$, mean age=33.2 years), clopenthixol LAI (CLOP-LAI; $N = 1$, $n = 87$, mean age not reported), flupentixol LAI (FLUPEN-LAI; $N = 1$, $n = 17$, mean age=42.6 years), perphenazine LAI (PERPH-LAI; $N = 1$, $n = 85$, mean age not reported), pipothiazine LAI (PIPO-LAI; $N = 1$, $n = 18$, mean age not reported), trifluoperazine OS (TRI-OS, $N = 1$, $N = 13$, mean age=33.2), fluphenazine OS (FLU-OS, $N = 1$, $n = = 147$, mean age=29.0).

Regarding efficacy, three studies and 106 individuals contributed to the analysis. The RoB2 showed "high" risk of bias for 67% of studies, and "some concerns" for 33% (Suppl. E.1). Both the efficacy and acceptability network were poorly populated and connected, with no closed loops, preventing the assessment of heterogeneity and inconsistency. Both trifluoperazine OS, and FLUS-LAI were more efficacious than FLUPH-LAI, while no differences in acceptability emerged with any of the other treatments (Suppl. G). All comparisons had a "very low" certainty of evidence (Suppl. H.4-H.5).

As for secondary outcomes, a network meta-analysis was feasible only for extrapyramidal symptoms, which showed FLUS-LAI to be better tolerated than FLUPH-LAI. The analysis was however based on a sparsely populated and connected network, for which inconsistency and heterogeneity could not be measured (Suppl. F.4.1). For the remaining secondary outcomes, a meta-analytical approach was not feasible, and results of single studies are reported in the Suppl. G.3-G.4.

3.2. Second-generation antipsychotics

All 19 studies contributed to the two co-primary outcomes. These studies included 8418 individuals, 63% of whom were male, with a mean age of 39.3 years. The mean follow-up duration was 16.6 weeks. Sixteen out of 19 (84.2%) studies were double-blind, and 11 out of 19 (57.9%) included a placebo as a comparator. LAIs included paliperidone palmitate 1-monthly (PALI-LAI; $N = 11$, $n = 2818$, mean age 39.9 years, mean dose 88.6 mg/4 weeks), olanzapine pamoate (OLA-LAIN=1; $n = 306$, mean age 40.8 years, mean dose 238.3 mg/4 weeks), risperidone long-acting (RIS-LAI) in the formulation of microspheres ($N = 5$, $n = 1755$, mean age 36.9 years, mean dose 36.8/2 weeks), subcutaneous injection (RBP-7000; $N = 1$, $n = 235$, mean age 41.1 years, mean dose 120 mg/4 weeks), in-situ microparticles (RIS-ISM; $N = 1$, $n = 291$, mean age 41.7 years, mean dose 87.5 mg/4 weeks), aripiprazole long-acting (ARI-LAI) in the formulation of aripiprazole monohydrate (ARI-MH; $N = 3$, $n = 436$, mean age 38.1 years, mean dose 398.2 mg/4 weeks), aripiprazole lauroxil/4 weeks (ARI-Lauroxil/4 w; $N = 1$, $n = 415$, mean age 39.7 years, mean dose 661.5 mg/4 weeks), aripiprazole lauroxil/8 weeks (ARI-Lauroxil/8 w; $N = 1$, $n = 99$, mean age 43.4 years, mean dose 723.8 mg/8 weeks), oral olanzapine ($N = 2$, $n = 329$, mean age 28.9 years, mean dose 17.1 mg/die) and oral aripiprazole ($N = 1$, $n = = 218$, mean age 33.9 years, mean dose 16.9 mg/die).

Regarding efficacy (mean change at psychopathology rating scales), 19 studies and 6876 participants contributed to the analysis. The RoB2 showed that the risk of bias was "high" for 15.8% of studies, "low" for 21.1%, and "some concerns" for 63.1% (Suppl. E.1). The efficacy network was well connected, with 5 out of 7 treatments included in closed loops (Fig. 1). The transitivity assumption was not violated for any of the potential effect modifiers analyzed (Suppl. F.6). All treatments outperformed placebo, with moderate certainty of evidence (according to CINeMA) for aripiprazole LAI (ARI-LAI), olanzapine LAI (OLA-LAI), risperidone LAI (RIS-LAI), paliperidone LAI (PALI-LAI), and low certainty for aripiprazole OS (ARI-OS) and olanzapine OS (OLA-OS) (Fig. 1). NNTs for LAIs ranged from 3.2 (ARI-LAI) to 4.7 (PALI-LAI). When compared head-to-head, no differences emerged, except for ARI-LAI outperforming PALI-LAI (very low certainty) (Table 2). This analysis was characterized by moderate heterogeneity (τ^2=0.03; I^2=69.6%), while consistency was preserved both globally ($p = 0.82$) and locally (Suppl. F.1). Sensitivity analyses yielded results largely consistent with the primary analysis in terms of effect sizes of treatments and degree of heterogeneity, except for the analysis excluding studies for which the standard deviation was imputed, where heterogeneity notably

Table 1
Characteristics of included studies*.

First author	Treatment 1	Treatment 2	Mean baseline symptoms (SD)	Length of oral tolerability assessment prior to LAI start (days)	Oral supplementation	n	M %	W%	Age (SD)	Diagnosis	Setting	FU weeks	Blind
Second-generation antipsychotics LAI													
Correll 2020	RIS LAI ISM 75–100 mg/4 w, fixed	Placebo	96.3 (PANSS)	2–3 days	No	438	34	52.6	41.7 (11.08)	SCZ	NR	12	DB
Cuomo 2018	ARI LAI monohydrate up to 400 mg/4 w, flex (mean dose: NR)	PALI LAI, up to 150 mg/ 4 w, flex (mean dose: NR)	5.76 (CGI)	7 days	ARI-LAI: 2w	101	16	NR	31.9 (12.08)	SCZ + other (<20)	IN	52	OL
Fleischhacker 2012	PALI LAI, 25–100 mg/4 w, flex (mean dose: 63.5 mg/4 w)	RIS LAI, 25–50 mg/2 w, flex (mean dose: 32.4 mg/2 w)	81.5 (PANSS)	4 days	RIS: 3 w	749	56	92	40.7 (11.95)	SCZ	OUT	53	DB
Gopal 2010	PALI LAI, 50–150 mg/4 w, flex (mean dose:79.9 mg/4 w)	Placebo	91.7 (PANSS)	4 days	No	357	31	40	40 (10.8)	SCZ	IN/ OUT	13	DB
Huang 2018	PALI-LAI 50–150 mg/4 w, flex (mean dose: 128.85 mg/ 4 w)	OLA-OS 5 mg/die, flex (mean dose: 17.8 mg/ die)	87.9 (PANSS)	2 days	No	57	35	0	22.68 (5.81)	SCZ	NR	13	OL
Kane 2003	RIS LAI, 25–75/2 w, flex (mean dose: 49.46 mg/2 w)	Placebo	81.5 (PANSS)	2 days	RIS: 3 w	400	25	41.5	37.71 (9.88)	SCZ	IN/ OUT	12	DB
Kane 2014	ARI LAI monohydrate, 400 mg/4 w, flex (mean dose: 396.4 mg/4 w)	Placebo	103.5 (PANSS)	2 days	ARI-LAI: 2 w	340	21	31,5	42.4 (10.94)	SCZ	IN/ OUT	10	DB
Keks 2007	RIS LAI 25–75 mg/die, flex (mean dose: 40.7 mg/4 w)	OLA OS, 5–20 mg/die, flex (mean dose: 14.6 mg/die)	78.6 (PANSS)	NR	RIS: 3 w	547	43	96.5	35.2 (11.87)	SCZ+SCZ-AFF	IN/ OUT	13	DB
Kramer 2010	PALI LAI, 50–100 mg/ 4 w, fixed	Placebo	86.9 (PANSS)	7 days	No	247	38	80.6	38.44 (10.89)	SCZ	IN/ OUT	9	DB
Lauriello 2008	OLA LAI, 210–300 mg/2w-405 mg/4 w, fixed	Placebo	101 (PANSS)	7 days	No	404	29	55.9	40.83 (11.15)	SCZ	IN/ OUT	8	DB
Li 2011	PALI LAI, 50–100 mg/ 4 w, flex (mean dose:115.8 mg/4 w)	RIS LAI, 25–50/2 w, flex (mean dose: 29.8 mg/2 w)	83.2 (PANSS)	4–6 days	RIS: 84 days	452	60	0	31.8 (10.88)	SCZ	NR	13	OL
Meltzer 2015	ARI LAI-Lauroxil 441–882 mg/4 w, fixed	Placebo	92.8 (PANSS)	2 days	ARI-LAI: 2w	622	32	46,7	39.7 (11.02)	SCZ	IN/ OUT	12	DB
Meltzer 2015	PALI LAI, 25–50–100 mg/ 4 w, fixed	Placebo	90.8 (PANSS)	7 days	No	518	33	NR	40.8 (11.3)	SCZ	IN/ OUT	13	DB
Nasser 2016	RIS LAI RBP-7000, fixed 90–120 mg/4w	Placebo	94.4 (PANSS)	2 days	No	354	21	24.6	NR	SCZ	IN	8	DB
Pandina 2010	PALI LAI, 25–100–150 mg/ 4 w, fixed	Placebo	86.6 (PANSS)	4–6 days	No	652	27	54	39 (NA)	SCZ	IN/ OUT	13	DB
Pandina 2011	PALI LAI, 50–100 mg/ 4 w, flex (mean dose: 104.5 mg/4 w)	RIS LAI, 25–50 mg/4 w, flex (mean dose: 31.7 mg/2 w)	83.8 (PANSS)	4–6 days	RIS: 3 w	1220	33	78.5	39 (11.98)	SCZ	IN/ OUT	13	DB
Takahashi 2013	PALI LAI, 75–100 mg/4 w, flex (mean dose: 75 mg/4 w)	Placebo	84.6 (PANSS)	14 days	No	224	41	0	45 (13)	SCZ	NR	13	DB
Weiden2020	ARI LAI-Lauroxil NC, 1064 mg/ 8 w, fixed	PALI LAI 234 mg/4 w, fixed	94.3 (PANSS)	2 days	ARI-LAI:1d	200	23	21	43.4 (10.3)	SCZ	IN/ OUT	25	DB
Xiao 2022	ARI LAI monohydrate MH, 400 mg/4 w, flex (mean dose: 398,1 mg/4 w)	ARI OS, 10–20 mg/ day, flex (mean dose: 16.9 mg/day)	90.3 (PANSS)	3 days	ARI-LAI: 2w	436	72	NR	33.9 (10.6)	SCZ	IN/ OUT	10	DB
First-Generation antipsychotics LAI													
Ahlfors 1973	FLU-LAI 50 mg/2 w, flex (mean dose: NR)	PIPO LAI [3] 25 mg/2 w, flex (mean dose: NR)	NR*	NR	NR	41	NR	NR	NR	SCZ	IN	4	DB

(*continued on next page*)

Table 1 (*continued*)

First author	Treatment 1	Treatment 2	Mean baseline symptoms (SD)	Length of oral tolerability assessment prior to LAI start (days)	Oral supplementation	n	M %	W%	Age (SD)	Diagnosis	Setting	FU weeks	Blind
Ahlfors et al., 1980	CLOP-LAI 50–800 mg/2 w, flex (mean dose: NR)	PER-LAI 20–600 mg/2 w, flex (mean dose: NR)	4.8 (CGI)	NR	No	172	34	NR	NR	SCZ-S-D	IN	26	DB
Bankier 1973	FLUS-LAI, flex (mean dose: 6.70 mg/week)	TRI OS, flex mean dose (42.5 mg/die)	48 (BPRS)	NR	NR	24	38	NR	NR	SCZ	IN	16	DB
Magnus 1979	FLU-LAI, 50–100 mg/3 w, flex (mean dose:NR)	FLUS-LAI, 6–12 mg/week, flex (mean dose: NR)	NR*	NR	NR	50	NR	NR	NR	SCZ	IN/OUT	26	OL
Schooler 1980	FLU LAI, 12.5–199 mg/3 w, flex (mean dose: 34.2 mg/3 w)	FLU OS, 2.5–60 mg/day, flex (mean dose: 24.8 mg/die)	4.5 (CGI)	7 days	No	190	42	69	29 (9)	SCZ	IN	52	DB
Wistedt and Ranta, 1983	FLU LAI, flex (mean dose: 27 mg/3 w)	FLUP LAI, flex (mean dose: 31 mg/3 w)	4.8 (CGI)	NR	6w	32	53	NR	42.62 (NR)	SCZ	NR	100	DB

Treatment abbreviations: ARI= Aripiprazole; CLOP= Clopenthixol; FLU= Fluphenazine; FLUS= Fluspirilene; FLUP= Flupenthixol; OLA= Olanzapine PALI= Paliperidone; PBO= Placebo; RIS= Risperidone.
Legend: BPRS=Brief Psychiatric Rating Scale; CGI=Clinical Global Impression; CPRS=Comprehensive Psychopathological Rating Scale; DB=Double Bling; Flex=Flexible dosing schedule; FUw=Follow-up weeks; LAI=long-acting antipsychotics; mg=milligrams; M%=Percentage of included male individuals; NA=not applicable; NR=not reported; OL=Open-Label; OS=oral treatment; PANSS=Positive and Negative Syndrome Scale; SCZ=schizophrenia; SCZ-AFF=schizo-affective disorder; SCZ-S-D=Schizophrenia Spectrum Disorder; SD=Standard Deviation; *w*=weeks; W%=Percentage of included individuals of White/Caucasian ethnicity.
* Complete reference list of included studies can be accessed in supplement K of the supplementary material.

decreased (I^2=33.6%). After excluding placebo-controlled trials, heterogeneity decreased (I^2=40.5%), and no significant differences emerged between treatments (Suppl. F.5.1).

Regarding the acceptability outcome, 19 studies and 8418 participants contributed to the analysis. The risk of bias was "high" for 10.5% of the studies, "low" for 47.4%, and carried "some concerns" for 42.1% (Suppl. E.2). Most treatments outperformed placebo, with moderate certainty for ARI-LAI, RIS-LAI, and PALI-LAI, and low certainty for ARI-OS, while no differences emerged for OLA-LAI (very low certainty) and OLA-OS (low certainty) (Fig. 1). NNTs of LAIs ranged from 4.2 (ARI-LAI) to 6.4 (PALI-LAI). When compared head-to-head, no differences emerged between LAIs, except for RIS-LAI outperforming PALI-LAI (Table 2). This analysis was characterized by low heterogeneity (τ^2=0.008; I^2=36.7%), and consistency was preserved globally (p = 0.08), although three out of 7 comparisons showed local inconsistency (Suppl. F.2). Sensitivity analyses yielded results largely consistent with the primary analysis in terms of effect sizes of treatments, degree of heterogeneity and inconsistency, which however decreased after excluding trials on individuals with recent-onset disease (p = 0.58) and placebo-controlled trials (p = 0.36).

Meta-regression analyses for the co-primary outcomes did not detect any potential effect modifier among the variables of interest (Suppl. F.6).

In the post-hoc analysis which assessed efficacy at the closest point to two weeks and separated the agents in the formulations, the following treatments outperformed placebo: ARI monohydrate, ARI-OS, RIS-ISM, RIS microspheres, and PALI-LAI (moderate certainty), OLA-LAI, and ARI-Lauroxil/4 w (low certainty). No differences emerged between placebo and RIS RBP-7000, ARI-Lauroxil/8 w, and OLA-OS (very low certainty) (Fig. 2). When compared head-to-head, ARI monohydrate outperformed PALI-LAI, RIS RBP-7000, and ARI-Lauroxil/8 w (very low certainty); ARI-OS outperformed ARI-Lauroxil/8 w and OLA-OS (very low confidence); OLA-LAI was superior to OLA-OS (very low confidence). This analysis was characterized by low heterogeneity (τ^2=0.005; I^2=33.4%), while consistency was preserved both globally (p = 0.86) and locally (Suppl. F.3.1).

3.2.1. *Secondary efficacy outcomes*

Table 3 and Suppl. F.3 show secondary efficacy outcomes. All 4 SGA-LAIs outperformed placebo in reducing both positive and negative symptomatology scores at PANSS subscales. OLA-LAI, RIS-LAI, and PALI-LAI were more effective than placebo in reducing general psychopathology symptoms. ARI-LAI appeared more effective than PALI-LAI in reducing positive symptoms, while RIS-LAI was more effective than PALI-LAI in reducing general psychopathology symptoms. No other differences between treatments were observed.

All treatments outperformed placebo in terms of response, both study-defined and defined as a reduction of 30% or more in PANSS total score reductions and as inefficacy-related discontinuation. ARI-LAI, RIS-LAI, and PALI-LAI outperformed placebo regarding short-term response (1–3 months). Data on medium-term response (4–6 months) were available only for RIS-LAI and PALI-LAI, which outperformed placebo. ARI-LAI, RIS-LAI, and PALI-LAI outperformed placebo also in terms of mean change score at functioning rating scales, while no data were available for other treatments. Apart from the response according to any definition, which showed relevant inconsistency, no relevant issues emerged in terms of consistency and heterogeneity. The lack of data concerning quality of life prevented a meta-analytical approach.

3.2.2. *Tolerability outcomes*

Table 3 and Suppl. F.4 show secondary tolerability outcomes. ARI-LAI, RIS-LAI, and PALI-LAI outperformed placebo regarding intolerability-related discontinuation. RIS-LAI was associated with more extrapyramidal symptoms than placebo. All treatments, except for ARI-OS, increased body weight measured both as a continuous and as a dichotomous outcome compared to placebo. Compared to placebo,

Table 2
Netleague table of co-primary outcomes.

Aripiprazole LAI	1.11 (0.77 to 1.60)	0.93 (0.63 to 1.36)	0.91 (0.64 to 1.30)	0.92 (0.75 to 1.13)	**0.67 (0.56 to 0.81)**	0.99 (0.80 to 1.24)
0.09 (−0.31 to 0.48)	**Aripiprazole OS**	0.83 (0.49 to 1.41)	0.82 (0.49 to 1.36)	0.83 (0.54 to 1.26)	**0.60 (0.40 to 0.91)**	0.89 (0.58 to 1.37)
−0.21 (−0.68 to 0.27)	−0.29 (−0.91 to 0.32)	**Olanzapine LAI**	0.98 (0.62 to 1.54)	0.99 (0.70 to 1.41)	**0.72 (0.52 to 1.01)**	1.07 (0.75 to 1.53)
−0.15 (−0.57 to 0.28)	−0.23 (−0.81 to 0.35)	0.06 (−0.49 to 0.60)	**Olanzapine OS**	1.01 (0.75 to 1.37)	**0.74 (0.54 to 1.01)**	1.09 (0.82 to 1.44)
−0.31 (−0.57 to −0.05)	−0.40 (−0.87 to 0.08)	−0.11 (−0.54 to 0.32)	−0.17 (−0.52 to 0.19)	**Paliperidone LAI**	**0.73 (0.66 to 0.81)**	1.08 (0.95 to 1.22)
−0.87 (−1.11 to −0.63)	**−0.96 (−1.42 to −0.49)**	**−0.67 (−1.07 to −0.26)**	**−0.72 (−1.08 to −0.36)**	**−0.56 (−0.71 to −0.41)**	**Placebo**	**1.47 (1.30 to 1.68)**
−0.23 (−0.51 to 0.06)	−0.31 (−0.80 to 0.18)	−0.02 (−0.46 to 0.42)	−0.08 (−0.41 to 0.26)	0.09 (−0.08 to 0.26)	**0.65 (0.47 to 0.82)**	**Risperidone LAI**

Results for the first primary outcome (mean change at psychotic symptomatology rating scales at study endpoint) are reported in bottom-left part of the table, with standardized mean differences (SMDs) and 95% confidence intervals (CIs). SMDs lower than 0 favor the column-defining treatment. Results for the secondary outcome (drop-outs due to any causes) are reported in the upper-right part of the table, with risk ratios (RR) and 95% confidence intervals (CIs). RR lower than 1 favor the column-defining treatment. Results with *p*-value <0,05 are reported in bold.
Legend: CI=Confidence Interval; LAI=Long-Acting Injectables; OS=Oral; RR=Risk Ratio; SMD=Standardized Mean Difference.

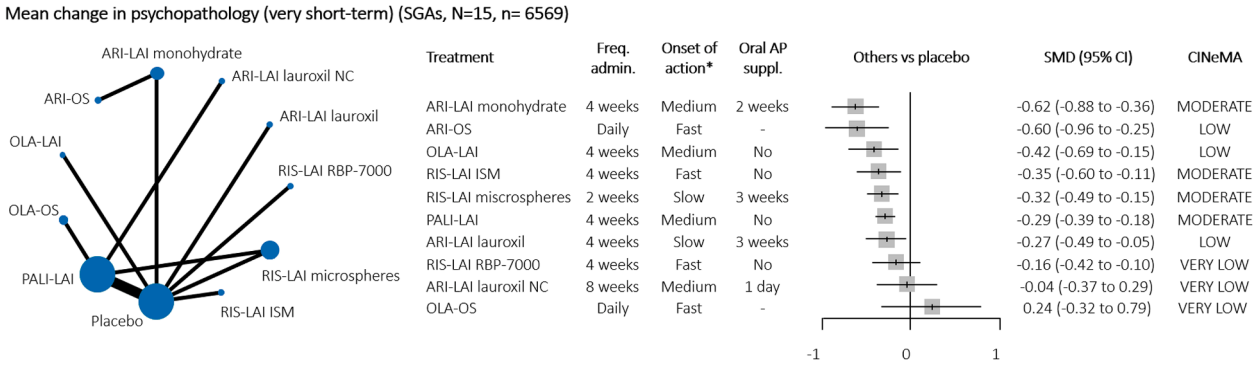

Fig. 2. Netmap and forest plot for the analysis of mean change in psychopathology at the timepoint closest to two weeks, separating different formulations of long-acting antipsychotics.
Legend: AP=antipsychotic; ARI=aripiprazole; CI=confidence interval; LAI=long-acting injectable antipsychotic; NC=nanocrystal; OLA=olanzapine; OS=oral; PALI=paliperidone; RIS=risperidone; RBP-7000=subcutaneous extended-release formulation; SGA=second-generation antipsychotic; SMD=standardized mean difference
* Classification derived from T_{max} of medications described in Correll et al. CNS Drugs 2021;35(1):39–59.

PALI-LAI increased serum prolactin, and RIS-LAI and PALI-LAI induced hyperprolactinemia. RIS-LAI, PALI-LAI, and OLA-OS outperformed placebo in terms of severe adverse events. Compared to placebo, no difference emerged in the number of deaths and QTc prolongation. Except for prolactin increase (dichotomous), which showed relevant inconsistency, no relevant issues emerged in terms of inconsistency and heterogeneity.

4. Discussion

To our knowledge, this is the largest systematic review and the first NMA comparing the efficacy and tolerability of LAIs in acutely ill individuals with SSDs.

Data on both second-generation (SGA) and first-generation (FGA) long-acting injectable antipsychotics (LAIs) yielded separate networks, precluding a single network meta-analysis (NMA). Further, the quality of data on FGA-LAIs was poor, as it included mostly old and small studies comparing medications seldom used in current clinical practice.

As for efficacy, all SGAs outperformed placebo in reducing symptoms, with effect sizes ranging from large (ARI-LAI: Cohen's d 0.87, NNT 3.2) to moderate (PALI-LAI: Cohen's d 0.56; NNT 4.7) supported by "moderate" certainty of evidence according to the CINeMA approach. No relevant differences emerged between LAIs (except ARI-LAI outperforming PALI-LAI), and between oral and LAI antipsychotics. Overall, these results were supported by sensitivity and meta-regression analyses, as well as secondary efficacy outcomes. The *post-hoc* analysis on the very short-term efficacy generally confirmed that LAI formulations not requiring oral supplementation had an efficacy profile comparable to both oral antipsychotics and LAIs with slower onset of action, requiring oral supplementation. Achieving a timely response and assuring treatment adherence is crucial to minimize the duration of symptoms and the risk of relapse and associated detrimental phenomena, e.g., structural brain damage, treatment-resistance, and functional impairment (Lin et al., 2021; Takeuchi et al., 2019). LAIs can rapidly achieve therapeutic levels, and certain formulations do not require oral supplementation, thus they could be a valid option to manage acute symptoms, especially in settings where adherence to oral treatment is suspected to be suboptimal.

In terms of acceptability, ARI-LAI, PALI-LAI, and RIS-LAI were associated with fewer all-cause discontinuation than placebo (moderate certainty). Compared to placebo, ARI-LAI, PALI-LAI, and RIS-LAI were associated with fewer drop-outs due to adverse events; all SGA-LAIs were associated with an increased risk of sedation and weight gain compared to placebo; RIS-LAI and PALI-LAI were associated with prolactin increase; RIS-LAI was associated with increased risk of extrapyramidal symptoms; RIS-LAI and ARI-LAI were associated with increased risk of akathisia. As no major differences were observed between LAIs and OAPs, we did not confirm the findings of Wang et al. (2023) that some adverse events were less pronounced with LAIs than with oral formulations.

Table 3
Secondary efficacy and tolerability outcomes.

		Antipsychotic vs. placebo (common comparator)					
Outcome	**Network characteristics**	**ARI-LAI**	**OLA-LAI**	**RIS-LAI**	**PALI-LAI**	**ARI-OS**	**OLA-OS**
		Dichotomous outcomes: RR (95% CI)					
Response (study defintion)	*N* = 19; *n* = 8418 Ht=moderate Inc=relevant	**2.43 (1.80 to 3.28)**	**2.15 (1.33 to 3.45)**	**2.07 (1.67 to 2.56)**	**1.88 (1.58 to 2.25)**	**2.66 (1.77 to 3.99)**	**2.31 (1.71 to 3.13)**
Response (≥ 30% PANSS decrease)	*N* = 11; *n* = 5352 Ht=moderate/high Inc=NA	**2.56 (1.56 to 4.19)**	NA	**1.82 (1.39 to 2.38)**	**1.72 (1.38 to 2.10)**	**2.80 (1.58 to 4.95)**	**1.90 (1.20 to 3.03)**
Response short-term* (RR)	*N* = 8, *n* = 3499 Ht=moderate/high Inc=none	**2.56 (1.05 to 2.63)**	2.15 (0.89 to 5.19)	**1.99 (1.21 to 3.27)**	**2.00 (1.12 to 3.56)**	2.80 (0.85 to 9.22)	2.23 (0.80 to 6.23)
Response medium-term**	*N* = 4, *n* = 1946 Ht=moderate Inc=NA	NA	NA	**1.99 (1.21 to 3.27)**	**1.79 (1.32 to 2.44)**	NA	NA
Dropouts due to inefficacy	*N* = 19, *n* = 8418 Ht=none Inc=none	**0.31 (0.22 to 0.45)**	**0.47 (0.29 to 0.75)**	**0.44 (0.36 to 0.55)**	**0.60 (0.52 to 0.69)**	**0.14 (0.06 to 0.30)**	**0.55 (0.32 to 0.95)**
Dropouts due to adverse events	*N* = 19,*n* = 8418 Ht=none Inc=none	**0.37 (0.23 to 0.59)**	0.83 (0.29 to 2.39)	**0.66 (0.44 to 0.99)**	**0.69 (0.51 to 0.93)**	0.51 (0.14 to 1.82)	0.75 (0.28 to 1.99)
Extra-pyramidal symptoms	*N* = 19, *n* = 8418 Ht=low Inc=none	0.44 (0.04 to 5.25)	1.02 (0.70 to 1.49)	**1.50 (1.08 to 2.08)**	1.17 (0.86 to 1.58)	0.53 (0.04 to 6.52)	0.84 (0.49 to 1.43)
Akathisia (RR)	*N* = 19, *n* = 8418 Ht=none Inc=none	**2.20 (1.37 to 3.51)**	0.32 (0.01 to 16.09)	**1.87 (1.25 to 2.82)**	1.38 (0.94 to 2.02)	**3.26 (1.74 to 6.10)**	0.61 (0.28 to 1.34)
Sedation (RR)	*N* = 17, *n* = 7568 Ht=none Inc=none	**2.24 (1.01 to 4.98)**	3.52 (0.84 to 14.71)	**2.77 (1.48 to 5.17)**	**3.46 (1.88 to 6.35)**	2.44 (0.79 to 7.55)	**5.85 (2.68 to 12.76)**
Weight gain (RR)	*N* = 18, *n* = 8317 Ht=none Inc=none	**2.16 (1.31 to 3.56)**	**2.32 (1.31 to 3.56)**	**2.86 (1.89 to 4.32)**	**3.03 (2.07 to 4.42)**	1.80 (0.96 to 3.36)	**4.76 (2.95 to 7.67)**
Prolactin increase (RR)	*N* = 13, *n* = 5934 Ht=moderate Inc=relevant	0.61 (0.09 to 4.27)	NA	**4.62 (2.64 to 8.10)**	**3.47 (1.92 to 8.10)**	NA	0.84 (0.09 to 4.27)
Severe adverse events (RR)	*N* = 18. *n* = 8361 Ht=none Inc=none	0.97 (0.48 to 1.97)	0.75 (0.30 to 1.89)	**0.56 (0.43 to 0.73)**	**0.70 (0.56 to 0.89)**	0.85 (0.25 to 2.89)	**0.42 (0.22 to 0.78)**
QTc prolongation (RR)	*N* = 13, *n* = 6392 Ht=none Inc=none	0.50 (0.01 to 25.08)	4.18 (0.24 to 73.50)	0.56 (0.06 to 5.35)	0.57 (0.13 to 2.56)	1.50 (0.01 to 234.78)	0.55 (0.01 to 35.42)
Number of deaths (RR)	*N* = 7, *n* = 8418 Ht=none Inc=none	0.40 (0.06 to 2.75)	0.32 (0.01 to 16.09)	0.24 (0.06 to 1.24)	0.48 (0.14 to 1.61)	1.21 (0.03 to 50.28)	1.21 (0.03 to 50.28)
		Continuous outcomes: SMD (95% CI)					
Positive symptoms (mean change)	*N* = 14, *n* = 5456 Ht=low/moderate Inc=none	**−0.85 (−1.14 to −0.55)**	**−0.68 (−0.98 to −0.38)**	**−0.51 (−0.65 to −0.38)**	**−0.41 (−0.53 to −0.30)**	NA	**−0.41 (−0.68 to −0.13)**
Negative symptoms (mean change)	*N* = 14, *n* = 5456 Ht=low Inc=none	**−0.47 (−0.75 to −0.19)**	**−0.55 (−0.84 to −0.26)**	**−0.40 (−0.53 to −0,28)**	**−0.32 (−0.43 to −0,21)**	NA	**−0.55 (−0.82 to −0.27)**
General psychopatology symptoms (mean change)	*N* = 7, *n* = 2747 Ht=none Inc=none	NA	**−0.60 (−0.84 to −0.37)**	**−0.72 (−0.89 to −0.55)**	**−0.36 (−0.53 to −0.20)**	NA	−0.30 (−0.84 to 0.25)
Functioning scores (mean change)	*N* = 8, *n* = 3717 Ht=low/moderate Inc=none	**0.73 (0.44 to 1.01)**	NA	**0.38 (0.20 to 0.56)**	**0.28 (0.13 to 0.42)**	NA	NA
Weight (mean change)	*N* = 11, *n* = 4932 Ht=none Inc=none	**0.27 (0.14 to 0.40)**	**0.57 (0.34 to 0.80)**	**0.27 (0.14 to 0.40)**	**0.33 (0.21 to 0.45)**	0.34 (−0.02 to 0.45)	**0.54 (0.31 to 0.77**)
Prolactin (mean change)	*N* = 11, *n* = 5168 Ht=high Inc=none	−0.38 (−1.97 to 1.22)	NA	0.57 (−0.28 to 1.43)	**0.89 (0.11 to 1.67)**	−0.21 (−2.47 to 2.05)	0.85 (−0.99 to 2.69)

Legend: AE= Adverse Events; CI=Confidence Interval; CnG=test of global consistency; CnL=SIDE test for local Consistency (number of significant differences over number of comparisons); EPS= Extrapyramidal Symptoms; Ht= heterogeneity; inc=inconsistency; LAI=Long-Acting Injectable; *N*=Number of included studies; *n*=Number of participants; NA=Not available; RR=Risk Ratio; SMD=Standardized Mean Difference.
*Response short=response between 1 and 3 months, measured at timepoint closest to 1 month.
**Response medium= response between 4 and 6 months, measured at timepoint closest to 4 months.

These findings should be interpreted considering some limitations. Firstly, we pooled together different LAI formulations of the same antipsychotic in most analyses, despite pharmacokinetic differences regarding the onset of action and need for oral supplementation, which may have introduced heterogeneity. Although we performed a *post-hoc* analysis on the very short-term efficacy of different LAI formulations, which was overall consistent with primary results, this analysis large (ARI-LAI: Cohen's d 0.87, NNT 3.2), was characterized by an impoverished and scattered network, losing precision and overall certainty of evidence. Second, for some studies, we assumed the presence of acute symptoms although this was not clearly reported by authors. We based this choice on clinically recognized cut-offs of commonly used rating scales (LEUCHT et al., 2005) . Further, a sensitivity analysis removing such studies, yielded results broadly consistent with the primary analysis. Third, we included two RCTs (Fleischhacker et al., 2012; Li et al., 2011) that allowed oral supplementation beyond the standard first three weeks for people taking RIS-LAI, potentially inflating the efficacy estimates of this arm. However, sensitivity analyses excluding such RCTs did not change the interpretation of the results. Fourth, the overall risk of bias was high for many studies. Again, after removing these RCTs through sensitivity analyses, primary results did not remarkably change.

In addition, the data on FGAs were poor in both quantity and quality, making it difficult to draw firm conclusions. The lack of available evidence is an important limitation because FGA-LAIs, such as haloperidol LAI and fluphenazine LAI are still widely used worldwide and may be the only LAI available in several settings, including low- and middle-income countries (Ostuzzi, Gastaldon, et al., 2022).

Regrettably, there has been no trial that directly compared FGA-LAIs against SGA-LAIs or placebo, making it impossible to draw comparisons between these two drug classes. Hence, our choice to concentrate on SGA-LAIs is driven solely by the available evidence and should not be misconstrued as an indication of the superior efficacy of SGA-LAIs over FGA-LAIs.

Moreover, the results for oral antipsychotics should be interpreted with caution because we did not include RCTs comparing oral antipsychotics with each other. In particular,

OLA-OS performed strikingly poorly in assessing very short-term efficacy, based on a single small (Huang et al., 2018) in which participants randomized to OLA-OS showed a slower improvement in symptoms compared with PALI-LAI, although no differences between the two treatments emerged at the end of the study. Finally, as we included few RCTs with an oral comparator, the certainty of evidence was generally poorer for oral antipsychotics compared to LAIs. Still, no clear differences emerged between SGA-

LAIs and their oral counterparts, which is in line with evidence on remitted individuals (Ostuzzi, Bertolini, et al., 2022; Schneider-Thoma et al., 2022) Despite of these limitations, results from this study significantly updates and extends previous literature on this topic (Leucht et al., 2023; Wang et al., 2023), demonstrating that most of the SGA-LAIs currently marketed in Europe and in the U.S. can be used effectively for the management of acute psychotic symptoms, helping to optimize treatment adherence from the earliest stages of disease.

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CRediT authorship contribution statement

Giovanni Vita: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Demetrio Pollini:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Andrea Canozzi:** Writing – original draft, Methodology, Data curation. **Davide Papola:** Writing – review & editing, Supervision, Conceptualization. **Chiara Gastaldon:** Writing – review & editing, Visualization, Conceptualization. **Christoph U. Correll:** Writing – review & editing, Supervision, Conceptualization. **Corrado Barbui:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Conceptualization. **Giovanni Ostuzzi:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116124.

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