Technical University of Munich
TUM School of Medicine and Health

Comparative efficacy and tolerability of long-acting injectable versus oral second-generation antipsychotics in acute schizophrenia

Dongfang Wang

Complete reprint of the dissertation approved by the TUM School of Medicine and Health of the Technical University of Munich for the award of the

Doktor der Philosophie (Dr. phil.).

Chair: apl. Prof. Dr. Klaus Linde

Examiners:

1. apl. Prof. Dr. Stefan M. Leucht
2. Priv.-Doz. Dr. Wolfgang C. Strube

The dissertation was submitted to the Technical University of Munich on 30 September 2024 and accepted by the TUM School of Medicine and Health on 5 February 2025.

Table of Contents

Acknowledgements

I never imagined I would be doing a PhD abroad, especially at the Technical University of Munich in Germany. This journey has been amazing! I want to sincerely thank the following individuals and organizations who have significantly contributed to the completion of this doctoral thesis.

First, I would like to express my heartfelt gratitude to my supervisor, Prof. Josef Priller, for the great honour of being your student.

My deepest gratitude goes to Prof. Dr. Leucht Stefan, who kindly invited me to join his team. This thesis would not have been possible without his invaluable guidance, unwavering support, and timely feedback. He believed in my abilities and gave me many training opportunities, for which I am deeply grateful. His enthusiasm, creativity, and rigorous approach to research have always inspired me. Additionally, I am very grateful for his support during my PhD studies in the position of Assistant Research Fellow in Evidence-Based Psychiatry.

I would also like to thank all my colleagues and friends, including Dr. Spyridon Siafis, Dr. Johannes Schneider-Thoma, and many others. The Evidence-Based Psychiatry group is very harmonious and helpful. Their professional and personal support and discussions have been invaluable in shaping my thinking and enriching my life in Munich.

I also want to thank Miss Ina BrÜngel and Prof. Dr. Felix Ehrlenspiel for their help during my studies at the Faculty of Sport and Health Sciences, which enabled me to complete the requirements for my graduation.

Summary (English)

This thesis examines the efficacy and side effect profiles of second-generation antipsychotics (SGAs) in both long-acting injectable (LAI) and oral forms for treating acute schizophrenia through a comprehensive analysis of two meta-analytic studies. The research reaffirms the superior efficacy of SGAs over placebo and delineates the comparable effectiveness of LAIs to oral formulations. LAIs may offer a more favourable side effect profile, particularly regarding extrapyramidal symptoms. The analysis, however, highlights the need for cautious interpretation due to limitations such as the reliance on indirect evidence and the focus on randomized trials limiting generalizability. The findings support more personalized treatment in people with acute schizophrenia, emphasizing the potential benefits of LAIs and the necessity for further research, including direct comparisons and investigations in naturalistic settings, to optimize therapeutic outcomes for individuals with schizophrenia.

Summary (German)

In dieser Arbeit werden die Wirksamkeit und die Nebenwirkungsprofile von Antipsychotika der zweiten Generation (SGAs) in langwirksamer injizierbarer (LAI) und oraler Form zur Behandlung akuter Schizophrenie anhand einer umfassenden Analyse in Form von zwei metaanalytischen Studien untersucht. Die Untersuchung bestätigt die überlegene Wirksamkeit von SGAs gegenüber Placebo und beschreibt die vergleichbare Wirksamkeit von LAIs gegenüber oralen Darreichungsformen. LAIs hatten in manchen Bereichen ein günstigeres Nebenwirkungsprofil, insbesondere im Hinblick auf extrapyramidale Symptome. Die Analyse macht jedoch deutlich, dass eine vorsichtige Interpretation erforderlich ist, da sich die Ergebnisse auf indirekte Belege stützen und nur randomisierte Studien einbezogen wurden, was die Generalisierbarkeit einschränkt. Die Ergebnisse legen eine personalisierte Therapie von Menschen mit akuter Schizophrenie nahe und unterstreichen den potenziellen Nutzen von LAI sowie die Notwendigkeit weiterer Forschung, einschließlich direkter Vergleiche und Untersuchungen unter naturalistischen Bedingungen, um die therapeutischen Ergebnisse für Menschen mit Schizophrenie zu optimieren.

List of publications

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

   Wang D, Schneider-Thoma J, Siafis S, Burschinski A, Dong S, Wu H, Zhu Y, Davis JM, Priller J, Leucht S. Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. Schizophr Bull. 2024 Jan 1;50(1):132-144. doi: 10.1093/schbul/sbad089. PMID: 37350486; PMCID: PMC10754166.

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

   Wang D, Schneider-Thoma J, Siafis S, Qin M, Wu H, Zhu Y, Davis JM, Priller J, Leucht S. Efficacy, acceptability and side-effects of oral versus long-acting- injectables antipsychotics: Systematic review and network meta-analysis. Eur Neuropsychopharmacol. 2024 Jun;83:11-18. doi: 10.1016/j.euroneuro.2024.03.003. Epub 2024 Mar 15. PMID: 38490016.

List of abbreviations

Abbreviation	Full Form
LAIs	Long-acting injectable antipsychotics
OAs	Oral antipsychotics
SGA	Second-generation antipsychotics
RLAI-MS	Risperidone long-acting injection microspheres
RLAI-polymer	Risperidone 2-Syringe Mixing System Suspension Polymer
ISM	Risperidone in situ microparticles
PP1M	Paliperidone palmitate once monthly
PP3M	Paliperidone palmitate once every 3 months
PP6M	Paliperidone palmitate every 6 months
AOM	Aripiprazole monohydrate once-monthly
AL	Aripiprazole lauroxil
RCTs	Controlled randomized controlled trials
NMA	Network meta-analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines
PANSS	The Positive and Negative Syndrome Scale
BPRS	The Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
MMRM	Repeated-measures mixed models
LOCF	Last-observation-carried-over multiple imputations
CSGSBR	Cochrane Schizophrenia Group's Study-Based Register
EPS	Extrapyramidal symptoms
HDRS	Hamilton Depression Rating Scale
MADRS	Montgomery–Åsberg Depression Rating Scale
QOLS	Quality of Life Scale
GAF	Global Assessment of Functioning
BARS	Barnes Akathisia Scale
DIEPSS	The drug-induced extrapyramidal symptoms scale
SAS	Simpson–Angus Scale
ESRS	The Extrapyramidal Symptom Rating Scale
ITT	Intention-to-treat
MMRM	Repeated-measures mixed models
LOCF	Last-observation-carried-over multiple imputation

List of Tables

1. Introduction

1.1 Schizophrenia

Schizophrenia, a severe psychiatric disorder (American Psychiatric Association & Association, 2013), affects over 23.6 million people worldwide (GBD 2019 Mental Disorders Collaborators, 2022). It is associated with comorbid medical illnesses, a higher chance of being homeless and jobless (Holm et al., 2021; Javitt, 2014) and a life span which is, on average, shortened by 15 years (Hjorthøj et al., 2017). Schizophrenia ranks 20th in terms of the global disease burden (GBD 2019 Mental Disorders Collaborators, 2022).

Schizophrenia has significant cost implications for society, not only in terms of direct expenses for health care but also, and maybe more importantly, in terms of indirect costs which stem from early disability retirements (schizophrenia typically starts in early adulthood). It is estimated that the direct and indirect costs of schizophrenia in the United States total approximately $343.2 billion (Kadakia, Catillon, et al., 2022). Similarly, a survey conducted in 30 European countries found that the total healthcare costs for schizophrenia in 2010 were 29 billion € and that the average direct healthcare costs per patient per year were approximately 5,800 € (Olesen et al., 2012). Moreover, the total cost for people with schizophrenia in Germany is three times that of France, and Germany has the highest direct cost of schizophrenia in terms of the percentage of GDP (0.28 per cent) (Kovács et al., 2018).

1.2 The current treatment

Oral antipsychotics (OAs) are the primary intervention for treating schizophrenia (Huhn et al., 2019; Schneider-Thoma et al., 2022), but many patients do not take them as prescribed. Only 40-60% of people with schizophrenia adhere to their antipsychotic medication (Cramer & Rosenheck, 1998; Lacro et al., 2002; Velligan et al., 2009). This poor adherence to OAs is one of the main reasons for high relapse and readmission rates (Velligan et al., 2009).

Compared to OAs, the main advantage of long-acting injectable antipsychotics (LAIs) is that adherence is assured. The most up-to-date meta-analysis on maintenance treatment in stable patients showed that LAIs are associated with lower relapse rates than OAs (Kishimoto et al., 2021). Currently, LAIs are available for the following first-generation antipsychotics: fluphenazine decanoate, flupentixol decanoate, fluspirilene, haloperidol decanoate, pipotiazine palmitate, perphenazine enanthate and zuclopenthixol decanoate. Several second-generation are also available as LAIs: aripiprazole maintena and lauroxil, olanzapine pamoate, paliperidone palmitate, and risperidone microspheres, in-situ-microimplants and risperidone extended-release injectable suspension are available (Citrome, 2021). Compared to first-generation antipsychotics, second-generation antipsychotics have better tolerability in terms of extrapyramidal side effects (Huhn et al., 2019) and are increasingly used in clinical practice (Janzen et al., 2020). This thesis focuses on second-generation LAIs.

1.3 Pharmacokinetic advantages of LAIs

Compared to oral formulation, LAIs have advantages in terms of their pharmacokinetic profiles, which refer to drug absorption, distribution, metabolism, and elimination (Fan & de

Lannoy, 2014). After injection, the antipsychotic is slowly and gradually released into the circulation, leading to a longer blood concentration duration (Correll et al., 2021). With LAIs, antipsychotics are absorbed continuously, which leads to smaller differences between the highest (Cmax) and the lowest (Cmin) plasma levels. This effect is potentially associated with fewer side effects (Sheehan et al., 2012). Moreover, LAIs can improve bioavailability by bypassing the liver (called the first-pass effect) compared to OAs and thus be associated with smaller total doses administered (Fan & de Lannoy, 2014; Waller et al., 2021).

1.4 The second-generation long-acting injectable antipsychotics.

Four second-generation antipsychotics are currently available as long-acting injectables on the market, including risperidone LAIs, paliperidone LAIs, aripiprazole LAIs, and olanzapine LAIs (Citrome, 2021). Detailed information can be found in Table 1.

"Risperidone long-acting injection microspheres (RLAI-MS)", introduced in 2003, was the first SGA-LAI (Harrison & Goa, 2004). "Risperidone 2-syringe mixing system suspension polymer (RLAI-polymer)" and "risperidone in situ microparticles (RLAI-ISM)" were introduced in 2018 (Krogmann et al., 2019) and 2024 (Laboratorios Farmacéuticos Rovi, S.A., 2024), respectively.

RLAI-MS is a solution containing small particles of risperidone encapsulated in a material called 7525 polylactic acid-co-polyethylene glycol. The RLAI-MS drug is given biweekly, with the highest concentration in the blood in the fourth week and a half-life of 4-6 days (Gefvert et al., 2005). As the polymer only starts dissolving after 3 weeks, it is necessary to provide oral risperidone as a supplement for a duration of 3 weeks (Thyssen et al., 2010). RLAI-MS require

eight weeks to reach steady-state plasma concentrations (Correll et al., 2021). RLAI-polymer, a new type of risperidone LAI, is administered monthly by injection into the subcutaneous tissue of the abdomen (Laffont et al., 2015).

The RLAI-polymer uses the ATRIGEL® delivery system, a biodegradable polymer in which risperidone is dispersed for the stable release of risperidone. It has a half-life of 9 to 11 days with two peaks of absorption, one within 4-6 hours and the other within 10-14 days. Therefore, RLAI-polymer does not need oral supplementation compared to RLAI-MS (Correll et al., 2021).

Risperidone-ISM utilizes a patented platform to deliver drugs in a controlled, sustained manner after injection. The active drug is encapsulated in microparticles within a polymeric matrix made from “poly lactic-co-glycolic acid (PLGA)” and “dimethyl sulfoxide (DMSO)”, which act together to form an injectable suspension. Upon intramuscular injection, this matrix precipitates, releasing a portion of the drug quickly as the DMSO diffuses into the bloodstream, while the remaining drug is gradually released as the PLGA matrix undergoes hydrolysis over time (Álamo, 2022; Anta et al., 2018).

Paliperidone LAIs can be divided into three types depending on the interval: “paliperidone palmitate once-monthly (PP1M)”, “paliperidone palmitate 3-monthly (PP3M)”, and “paliperidone palmitate 6-monthly (PP6M)”.

PP1M, a nanoscale risperidone, is one-tenth the size of conventional powder particles, thereby effectively increasing the surface area of the solution (Citrome, 2010). Therefore, PP1M can rapidly attain a stable state and maintain it for an extended period (Morris & Tarpada, 2017). PP1M achieves its peak plasma concentration after 13 days and has a half-life of 25 to 49 days (Samtani et al., 2009).

PP3M utilizes the same method of suspending nanoparticles in water as PP1M, except with bigger particles and a doubled dosage, resulting in an extended paliperidone-release. PP3M has a half-life of around 84~95 days and reaches maximum blood levels at 30~33 days (Correll et al., 2021).

PP6M has very low water solubility and can dissolve slowly and release gradually from the injection site, thus maintaining therapeutic levels in the bloodstream for up to 6 months. This slow-release mechanism also keeps plasma paliperidone concentrations low for a long period, thus ensuring sustained symptom control without frequent dosing (Blair, 2022). Therefore, in clinical practice, PP6M is used for patients adequately treated with PP1M or PP3M (Najarian et al., 2023).

Aripiprazole, a dopamine-D2 and serotonin-5-HT1A receptor partial agonist and 5-HT2A receptor antagonist, is thought to balance dopamine and serotonin pathways (Shirley & Perry, 2014). It is available in two LAI formulations, “aripiprazole monohydrate once a month (AOM)” and “Aripiprazole Lauroxil (AL)”.

AOM is a liquid suspension consisting of a mixture of lyophilized substance and sterile water, with aripiprazole as the main active ingredient, followed by dehydroariprazole. AOM reaches peak plasma concentrations in approximately 6 days, with a half-life between 29.9 and 46.5 days (Correll et al., 2021).

AL is a drug consisting of the non-ester prodrug N-lauroloxymethyl aripiprazole (Hard, Mills, Sadler, Turncliff, et al., 2017). Depending on the administered dose, AL is administered once a month (q4w), every six weeks (q6w) or every eight weeks (q8w) (Frampton, 2017). AL

achieves its maximum blood concentration after 40 days (Hard, Mills, Sadler, Turncliff, et al., 2017) and has a half-life of 53.9~57.2 days (Hard, Mills, Sadler, Wehr, et al., 2017).

Olanzapine pamoate, a combination of olanzapine and pamoic acid, is administered every two or four weeks (Citrome, 2009). Once exposed to the bloodstream, olanzapine pamoate has the potential to dissolve rapidly within minutes to hours. This may lead to high drug concentrations in the body, predisposing to Post-injection Delirium Sedation Syndrome (PDSS) (McDonnell et al., 2010). PDSS associated with olanzapine LAI typically occurs at a rate of approximately 0.07% per injection (Bushe et al., 2015; Novakovic et al., 2013). On a patient-level, across multiple injections, the cumulative incidence of PDSS ranges approximately from 0.46% to 1.4% (Bushe et al., 2015; Detke et al., 2010; Luedecke et al., 2015; McDonnell et al., 2014; Novakovic et al., 2013). Therefore, it is recommended to monitor patients for 3 hours after the administration of olanzapine pamoate in a clinical setting (Citrome, 2009). The drug reaches its highest concentration in the blood after two to six days and has a half-life of thirty days (Heres et al., 2014; Mitchell et al., 2013).

Table 1 Overview of SGA-LAIs.

Antipsychotic	Formulation	Delivery: frequency of administration	Peak Plasma	Half-Life	Delivery: route of administration	Notes
Risperidone	RLAI-MS	Every two weeks	4th week	4-6 days	Intramuscular, typically injected into the deltoid or gluteal muscle.	It takes 8 weeks to reach a steady state. Oral supplementation is needed for three weeks after the first injection. Microspheres in aqueous suspension.
	RLAI-polymer	Every 4 weeks	4-6 h & 10-14 days	9-11 days	Subcutaneous, typically injected into the abdomen.	Does not require oral supplementation.
	Risperidone-ISM	Every 4 weeks	24-48 h	9-11 days	Intramuscular, typically injected into the deltoid or gluteal muscle.	Does not require oral supplementation.
Paliperidone	PP1M	Every 4 weeks	13 days	25-49 days	Intramuscular, typically injected into the deltoid or gluteal muscle.	PP1M requires a booster injection one week after the initial injection.
	PP3M	Every 3 months	30-33 days	84-95 days	Intramuscular, typically injected into the deltoid or gluteal muscle	-
	PP6M	Every 6 months	33-35 days	148-159 days	Intramuscular, typically injected into the deltoid or gluteal muscle	PP6M is indicated for patients who have been adequately treated with PP1M or PP3M.

Table 1 (continued) Overview of SGA-LAIs.

Antipsychotic	Formulation	Delivery: frequency of administration	Peak Plasma	Half-Life	Delivery: route of administration	Notes
Aripiprazole	AOM	Every 4 weeks	5-7 days	30-47 days	Intramuscular, typically injected into the deltoid or gluteal muscle	-
	AL	Every 4 weeks, every 6 weeks or every 8 weeks	40 days	54-57 days	Intramuscular, typically injected into the deltoid or gluteal muscle	-
Olanzapine	Olanzapine pamoate	Every 2 weeks or every 4 weeks	2-6 days	30 days	Intramuscular, typically injected into the deltoid or gluteal muscle	Because of the risk of PDSS, monitoring is required for at least 3 hours after injection.

1.5 The context of this dissertation

It has been established that LAIs reduce relapse and rehospitalisation rates compared to oral medication (Efthimiou et al., 2024; Kishimoto et al., 2021; Taipale et al., 2018). Treatment guidelines also recommend the use of LAIs for relapse prevention, especially when adherence is a problem (Gaebel et al., 2019; Keepers et al., 2020; National Institute for Health and Care Excellence [NICE], 2014). Nevertheless, for various reasons, the utilization of LAIs in clinical practice remains low (Carbon & Correll, 2014; Heres, 2014; Kane et al., 2013; Novick et al., 2010).

While previous reviews and guidelines have focused on relapse prevention, whether LAIs can also be used for *acutely ill patients* has so far not been addressed in the meta-analytic literature. Reservations may pertain to the impossibility of slowly titrating LAIs and rapidly switching them when necessary. Other concerns are side effects, especially that due to the long half-life of LAIs, it is not possible to stop the drug if a potentially life-threatening neuroleptic malignant syndrome (NMS) occurs. However, a recent review of case reports showed that the outcome of NMS is not worse under LAIs compared to OAs (Guinart et al., 2020). Moreover, in terms of the shortage of psychiatrists even in highly developed countries such as Germany and a trend to treat more and more acutely ill patients in outpatient settings, their advantages in terms of adherence and convenience—typically monthly injections rather than daily discussion about drug intake, time which can be spent on other problems of patients—could make them an option also for the acute phase (Correll et al., 2021; Kane et al., 2021).

This situation was the context to systematically review the effects of LAIs compared to placebo, their oral formulations, and their comparisons with one another in acutely ill patients by meta-analysis.

1.6 Research question and aims.

The objective of the thesis was to conduct a thorough analysis of the effects of SGA-LAIs compared to placebo and SGA-OAs for acutely ill patients with schizophrenia, using both pairwise comparisons and network meta-analyses of randomized-controlled studies (RCTs).

1.6.1 Study 1: Research Question and Aims:

The main aim of Study 1 was to investigate the effects of currently available SGA-LAIs ("olanzapine LAIs", "risperidone LAIs", "paliperidone LAIs", and "aripiprazole LAIs") compared to placebo. Conventional pairwise meta-analysis was applied for this purpose. It also assessed whether SGA-LAIs are superior to their oral equivalents in terms of efficacy and tolerability, but it turned out that one RCT which compared SGA-LAI and SGA-OA directly was available. Comparisons between LAI and oral formulations could only be made via subgroup tests via placebo. This limitation made Study 2 necessary, which applied network meta-analysis.

1.6.2 Study 2: Research Question and Aims:

Study 1 used pairwise meta-analysis to examine how effective and safe different formulations of the same compound were compared to placebo, but it could not analyze well how SGA-LAIs compared to SGA-OAs, and it could not examine at all how different

drugs compared (e.g., olanzapine oral vs aripiprazole LAI). Therefore, Study 2 aimed to address the limitations of Study 1 by the application of network meta-analysis (NMA). Network meta-analysis can integrate both direct evidence (for example trials comparing “drug A” with “drug B”) and indirect evidence (for example “drug A” compared to “drug B” derived from “drug A” versus “drug C” and “drug B” versus “drug C”. Consequently, NMA can utilize all randomized data, provide results on the above-mentioned comparisons, increase precision, and produce hierarchies in terms of the various outcomes (Salanti & Higgins, 2022).

2. Method

2.1 Overview of the approach

Study 1 used pairwise meta-analysis to assess the relative efficacy of SGA-LAIs versus placebo and their oral counterparts in the acute phase of treatment. In addition, Study 1 conducted subgroup analyses comparing the efficacy of SGA-LAIs versus placebo and the efficacy of corresponding SG-OAs versus placebo to determine the efficacy of SGA-LAIs versus their oral counterparts. Study 1 followed the "*Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)*" guidelines (Liberati et al., 2009). Pairwise meta-analysis had the advantage of producing pooled estimates based on straightforward, direct evidence. Focusing only on direct evidence avoids the potential additional bias of indirect comparisons, in particular, a potential violation of the transitivity assumption (Salanti, 2012). The results are graphically presented in so-called forest plots. These allow a visualisation in which the results of each study are plotted, making the results highly transparent and interpretable at a glance.

Study 2 applied network meta-analysis; consequently, it followed the PRISMA reporting guidelines for NMA (Hutton et al., 2015). The approach implied broader inclusion criteria and an approximately two times larger sample size. It allowed us to expand the analysis to comparisons of different oral and LAI antipsychotics (e.g. oral olanzapine versus LAI risperidone). In addition, the usage of indirect evidence helps to fill in the gaps in evidence and constructs a ranking system of which drug is optimal, which drug is sub-optimal, etc., in a given area. Thus, Study 2 did not only verify and corroborate the findings of Study 1, but it also

yielded further findings about the comparative efficacy, acceptability and tolerability of the antipsychotic drugs in question. Network meta-analyses provide clinicians with an overall assessment that helps them make informed clinical decisions across a wider range of treatment options, especially in the absence of direct comparative evidence.

More information can be obtained from the corresponding publications (Wang et al., 2023, 2024).

2.2 Search strategy and study selection

The search strategy used for Study 1 was via the *"Cochrane Schizophrenia Group's Study-Based Register (CSGSBR)"*, which is compiled by regular searches of multiple electronic databases and also encompasses the clinical trial registries of "*clinicaltrials.gov"* and "*WHO-ICTRP"*, from the beginning of the database until March 2022 (Wang et al., 2023).

The study 2 search was based on a previous meta-analysis conducted by our group about acute schizophrenia (Huhn et al., 2019; Leucht et al., 2023; Wang et al., 2023). Additionally, updated searches of the CSGSBR were also conducted on 6/14/2021, 9/21/2021, 6/3/2022, and 6/25/2023 (Wang et al., 2024). The detailed search terms can be found in the study protocol and publications.

2.3 Criteria for inclusion

2.3.1 Study design

Study 1 and Study 2 included only RCTs without considering blinding methods such as open, single-blind and double-blind. To ensure rigorous quality control and reliable outcomes,

studies from mainland China were not included in our analysis. This decision was made because of quality concerns regarding randomization, which had been raised by several previous analyses. Many studies from mainland China are actually not appropriately randomized, although they are stated as such in the publications (Leucht et al., 2022; Parry, 2017; Tong et al., 2018). To prevent carry-over effects, only the first phase of crossover experiments was utilized. Study 1 only covered studies with short-term treatment lengths (3-13 weeks), while Study 2 covered all relevant RCTs, including those with treatment lengths of more than three weeks.

2.3.2 Participants

Study 1 and Study 2 used the same criterion for selecting participants who had a diagnosis of schizophrenia or similar conditions, in particular schizoaffective disorder, according to the diagnostic systems used in the original studies. The included studies were required to have a minimum of 80% of participants with these diagnoses. Both Study 1 and 2 targeted acutely ill patients, deliberately excluding trials involving stabilized individuals aimed at relapse prevention or dosage tapering. 'Acute schizophrenia' was characterized by patients presenting with exacerbated or active symptoms and at the initiation phase of the study. If the stability status was not clearly stated, patients were considered to be in an acute phase. There were no limitations based on age, gender, ethnicity, or the clinical setting of the participants. This approach ensured a coherent study population focused on the acute phase of schizophrenia, thus enhancing the relevance and applicability of the findings to a specific patient group in clinical settings.

2.3.3 Interventions and control

Study 1 and Study 2 examined oral and injectable forms of four particular SGAs — olanzapine, paliperidone, risperidone, and aripiprazole.

For Study 1, the inclusion criteria were limited to RCTs that provided direct comparisons between the LAI and oral forms of these medications or placebo-controlled trials involving any of the above these four SGAs (Wang et al., 2023). All of the comparisons below were included in Study 1:

1. Placebo-controlled trials of the four SGAs were included. This means that any particular of these four SGAs, whether long-acting injectable or oral, was included in the study as long as it was compared to a placebo in study 1.
2. Head-to-head RCTs of SGA-LAIs with corresponding oral medications, e.g., trials comparing olanzapine LAIs with olanzapine oral.

Building upon Study 1, Study 2 expanded the scope to encompass RCTs that conducted any form of head-to-head comparison among these four SGAs, in addition to placebo-controlled trials involving any of the specified SGAs (Wang et al., 2024). All of the comparisons below were included in Study 2:

1. Placebo-controlled trials of any of these four SGAs, which is the same as Study 1.
2. Head-to-head comparisons among the four SGAs, irrespective of their formulation (LAI or oral). I.e., compared to Study 1, not only, for example, olanzapine LAI versus olanzapine oral, but also, for example, risperidone LAI versus olanzapine oral or risperidone oral versus olanzapine oral.

2.4 Outcomes

The outcomes evaluated in Study 1 and Study 2 were largely consistent, with some minor variations highlighted. Results specific to Study 1 are denoted with (***S1***), those exclusive to Study 2 are marked with (***S2***), and outcomes included in both studies are indicated by (***S1&S2***).

2.4.1 Primary outcomes (S1&S2)

Overall symptom change was the co-primary outcomes in Study 1 (Wang et al., 2023) and Study 2 (Wang et al., 2024). Change in overall symptoms could have been assessed by either the total score of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) or the total score of the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1988). Other scales that had been published in peer-reviewed publications assessing overall symptoms of schizophrenia would have also been considered.

2.4.2 Secondary outcomes

2.4.2.1 Efficacy outcomes

1) Response to Treatment: Authors' definitions of treatment response were considered, prioritizing the following ones: At least a 50% decrease in total scores of PANSS/BPRS, Clinical Global Impression (CGI) at least greatly improved, followed by a 20-40% decrease in score of PANSS/BPRS, and CGI at least minimally improved ***(S1)***;

2) Positive symptoms change: Evaluated using the PANSS positive subscale (Kay et al., 1987) or the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), focusing on changes from baseline ***(S1&S2)***;

3) Negative symptoms change: Assessed with the PANSS negative subscale (Kay et al., 1987) or the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) ***(S1&S2)***;

4) Depressive symptoms: The Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979), the Calgary Depression Scale (CDS) (Addington et al., 1993) or other published scales were used ***(S1&S2)***;

5) Quality of Life: The Quality of Life Scale (QOLS) (Heinrichs et al., 1984) or other published QLS scales ***(S1&S2)***;

6) Functional Outcomes: The Global Assessment of Functioning (GAF) (Jones et al., 1995) or other published scales on functioning ***(S1&S2)***;

7) Number of dropouts (due to any reason, inefficacy, adverse events, side effect) ***(S1&S2)***

2.4.2.2 Side effect outcomes

1) The number of individuals who had at least one anticholinergic event ***(S1&S2)***;

2) The number of persons suffering from constipation ***(S1)***;

3) The number of persons suffering from blurred vision ***(S1)***;

4) The number of persons suffering from dry mouth ***(S1)***;

5) The number of persons suffering from sedation ***(S1&S2)***;

6) Extrapyramidal symptoms (EPS): The number of participants taking antiparkinsonian drugs ***(S1&S2)***;

7) Extrapyramidal symptom severity: assessed using scales such as SAS (Simpson et al., 1970), DIEPSS (Inada & Yagi, 1995), or ESRS (Chouinard & Margolese, 2005) ***(S1)***;

8) Akathisia: assessed by scales such as the akathisia subscale of the ESRS (Chouinard & Margolese, 2005), the BARS (Barnes, 1989), or DIEPSS Akathisia Subscale (Inada & Yagi, 1995) ***(S1)***; Furthermore, the number of participants with akathisia was also assessed ***(S1&S2)***;

9) Number of persons who gained more than 7% of their body weight ***(S1&S2)***; Furthermore, the mean weight gain in kilograms ***(S1&S2)***;

10) Mean change of prolactin levels (ng/ml) ***(S1&S2)***;

11) Mean change of QTc interval (milliseconds) ***(S1&S2)***;

Mortality: (1) deaths from any cause, (2) deaths from natural causes, and (3) deaths from suicide ***(S1)*** (Hutton et al., 2015).

2.5 Study selection, data extraction and risk of bias.

2.5.1 Procedure

Both Study 1 and Study 2 followed similar procedures.

These two studies were planned and led by the primary investigator, who drafted the protocol and led all stages of the research, including protocol drafting, participant selection,

data extraction, and bias risk assessment. For the purpose of quality control, study selection, data selection, and risk of bias assessment had to be duplicated by an additional person. Collaboration was established with co-authors listed in the original publications (Wang et al., 2023, 2024). All disputes were addressed through discussions or by involving other experienced reviewers in Professor Leucht's team. The process of selecting studies was divided into two stages. First, potentially relevant titles/abstracts were scrutinized and selected in the Citavi reference managing program. Second, full texts were obtained and examined to determine whether they met the inclusion criteria. More detailed information can be found in published articles (Wang et al., 2023, 2024).

2.5.2 Data extraction

The same data extraction process was used for Study 1 and Study 2. A Microsoft Access database was used to extract data. This database allowed double entry of the data so that discrepancies between reviewers could easily be identified. If the information was flawed or ambiguous, the authors of the studies were contacted using the contact information provided in the text. The general data extracted from each included study is the follows:

1) Study characteristics:
    - Name of the first author and publication year.
    - Information on randomisation, allocation and blinding methods.
    - Length of each trial.
    - Diagnostic criteria applied.
2) Treatment:

- Intervention and application: details on the antipsychotic and its administration.
- Dosing: frequency and dosage administered.

3) Participant demographics and baseline characteristics:

- Enrollment: number of participants randomized.
- Demographics: percentage of females and average age.
- Clinical background: average duration of illness and severity at study start, with mean scores and standard deviations of scales measuring overall symptoms.

For continuous results, the mean, standard deviation (SD), and number of people after random assignment were extracted. Data from intention-to-treat (ITT) analyses were preferred, e.g., repeated-measures mixed models (MMRM), multiple imputation (MI) and last-observation-carried-forward (LOCF), which are currently preferred to completer data (Nich & Carroll, 2002). Either change from baseline to endpoint or at endpoint data could be used in the analysis, with changing data taking preference.

In terms of fixed-dose trials, only LAI doses authorized by the summary of product characteristics (SmPC) (*DailyMed*, n.d.) were included. For oral formulations, the maximum fixed doses determined in accordance with the International Consensus on Antipsychotic Dosage (Gardner et al., 2010) were included. In addition, all flexible-dose trials in which the physician could adjust the dose were included.

When studies had more than one dose group, the groups were merged using appropriate methods (Higgins, 2019).

2.5.3 Risk of bias

Study 1 and Study 2 used the risk of bias tool version 1 (ROB 1) (Higgins et al., 2011), which included seven dimensions (Higgins et al., 2011); see Table 2:

Table 2 Risk of bias assessment of the RCT.

Criteria	Describe
Sequence generation	This criterion refers to the method used for randomly assigning participants to different experimental groups, ensuring the allocation process is unbiased.
Allocation concealment	This measure conceals the group assignments from both participants and researchers until the participants are officially enrolled in the study, preventing selection bias.
Blinding of participants and personnel	This process conceals group information from both participants and researchers to avoid their expectations or behaviours in reaction to the assigned drug, which could influence the study outcomes.
Blinding of outcome assessment	This category involves concealing group information from those who measure or evaluate the outcomes, ensuring that this knowledge does not bias their assessment.
Missing outcome data	This bias category refers to situations where some participants do not complete all study measurements or follow-up assessments, leading to unknown outcomes.
Selecting reporting	This bias occurs when researchers only report some of the measured outcomes, potentially ignoring or omitting other relevant data.
Other biases	This category includes any additional practices or factors that could introduce bias into the study results, not covered by the other specified criteria.

Each dimension can be categorized into three degrees: Low, Unclear and High risk of bias. Then, the overall risk of bias for all included studies was categorized into three grades: Low ("No domains at high risk of bias and less than four domains with unambiguous bias"), Medium ("One domain at high risk of bias or no domains at high risk of bias and more than three domains

with unambiguous bias"), and High ("All other cases") following the approach by (Furukawa et al., 2016).

2.6 Data analysis

Effect size indices: standardized mean differences (SMDs) were used for mean values of rating scales, while mean differences (MDs) were used for prolactin levels (ng/ml), weight increase (kg), and QTc prolongation (milliseconds). In both studies, a random effects model (DerSimonian & Laird, 1986) was used to combine the results of the different studies.

When missing SDs were encountered, the following methods were used:

1) SDs calculated from standard errors (SE), using the formula: SD = SE * $\sqrt{N}$,
2) Derived from "confidence intervals", "p-values", "t-values", "F-values" (Higgins et al., 2019),
3) Estimation from median and range (Wan et al., 2014),
4) Using the mean SD from other studies in the review (Furukawa et al., 2006),
5) Contacting study authors.

Odds ratios (OR) were used for dichotomous data.

2.6.1 Data analysis in Study 1

Study 1 used pairwise, random effects meta-analyses to compare SGA-LAIs with identical oral formulations and SGA-LAIs with placebo. In addition, studies of SGA-OAs (olanzapine, aripiprazole, paliperidone, risperidone) versus placebo were included for the purpose of subgroup testing.

2.6.1.1 Subgroup analysis in Study 1

It turned out that there was only one RCT that directly compared a SGA-LAI with its oral counterpart. In Study 1, simple subgroup analyses were conducted comparing the effect sizes of LAIs versus placebo with those of their oral formulations versus placebo. These were used to compare the differences in efficacy and side effects of LAIs versus oral medications with the same antipsychotics.

Moreover, the main analysis combined different LAI formulations that had the same antipsychotic component (e.g., aripiprazole monohydrate once a month and aripiprazole lauroxil). In a subgroup analysis of the primary outcome, the different LAI formulations of the same antipsychotic were examined separately.

2.6.1.2 Sensitivity analysis in Study 1

To ensure the robustness of the findings, two sensitivity analyses of the primary outcome were performed for doses close to the maximum efficacy threshold dose and for data at 6 to 8 weeks. Following the recommendations of Leucht et al. (Leucht et al., 2020), sensitivity analyses only included those dosages that were close to maximum efficacy. These doses were aripiprazole LAI at dosages of 440 mg every four weeks, olanzapine LAI at 210 mg every two weeks, risperidone LAI at 50 mg every two weeks, and paliperidone LAI at 100 mg every four weeks.

Moreover, most OA-RCTs lasted 6-8 weeks, while LAI-RCTs often lasted 12 weeks. Therefore, to ensure uniformity in the assessment period, another sensitivity analysis was

conducted to obtain six weeks of data from the LAI studies while excluding studies with OAs shorter than six weeks and longer than eight weeks.

2.6.1.3 Assessment of heterogeneity in Study 1

Study 1 (pairwise meta-analysis) used the Chi-squared (χ^2) test (significance threshold at 0.10) and the I^2 statistic (>50%), indicating heterogeneity (Higgins, 2019).

2.6.2 Data analysis in Study 2

Study 2 employed network meta-analysis techniques in a frequentist framework (Rücker, 2012) to synthesize data from all RCTs, including the assimilation of indirect comparisons where no direct RCT evidence existed between interventions. Given the diversity of the data, the analysis used a random effects model (Higgins, 2019). In a frequentist approach, the P-score was used to rank each intervention in relation to others (Rücker & Schwarzer, 2015).

2.6.2.1 Heterogeneity Assessment in Study 2

Heterogeneity in NMA is defined as differences in treatment effects across research. A common between-study variance (τ^2) was used and assessed for each outcome (Higgins, 2019). Heterogeneity was categorised as low, medium or high (Rhodes et al., 2015).

2.6.2.2 Transitivity assumption and assessment of coherence

Transitivity assumption and assessment of coherence in NMA (Salanti et al., 2008, 2014).

1) The transitivity assumption means that clinical and methodological differences among studies do not significantly influence the outcomes across comparisons. It is important that direct and indirect evidence can be legitimately combined. Researchers must assess whether variations in study design or population characteristics in terms of potential effect modifiers might compromise transitivity (Salanti, 2012). Therefore, in Study 2, differences in the interventions in terms of the following effect modifiers were assessed with box plots: baseline severity, age, gender proportion and placebo response.

2) Assessment of Coherence (Efthimiou et al., 2016):

   Coherence tests whether the transitivity assumption holds by comparing direct and indirect evidence. Two types of coherence tests were applied in Study 2:

   - The local test was the "Separation of Indirect Evidence from Direct Evidence (SIDE)" method to evaluate the coherence between indirect and direct estimates (Dias et al., 2010). When 10% of closed loops showed differences between direct and indirect evidence, significant incoherence was assumed (Veroniki et al., 2013, 2021).
   - The global test was the "design-by-treatment interaction model" to assess overall network coherence (Higgins et al., 2012).

In both tests, the significance threshold was set at 0.1, given their low statistical power.

2.6.2.3 Sensitivity Analyses in Study 2

In Study 2, sensitivity analyses on the primary outcome involved excluding studies lacking standardized diagnostic criteria, non-blinded studies, those with high data attrition (over 50%), and those rated as high risk of bias. Similar to Study 1, sensitivity analyses also compared 6–8-week outcomes between LAIs and oral antipsychotics and prioritized studies using near-maximum effective doses.

2.6.2.4 Subgroup Analysis in Study 2

I compared the pooled group of all LAIs with the pooled group of all oral antipsychotics in terms of the outcome of overall symptoms.

2.6.2.5 Confidence in the evidence in Study 2

The CINeMA web application was used (Nikolakopoulou et al., 2020) to evaluate the level of confidence in the primary outcome change in overall symptoms. The assessment addressed six criteria: study bias risk, reporting biases including publication bias, study indirectness, imprecision, heterogeneity, and incoherence, categorized as “high”, “moderate”, “low”, or “very low”.

2.7 Statistical software

Data analysis was conducted using R 4.2.0. For pairwise meta-analyses, the “***meta***” package (Schwarzer, 2007) was used. Network meta-analyses were conducted employing the "***netmeta***" package (Rücker et al., 2016).

Table 3 summarizes the methodological similarities and differences between Study 1 and Study 2.

Table 3 Overview of study methods

	Study 1	Study 2
Population	Patients with acute schizophrenia	Same as Study 1
Intervention	LAI or oral formulations of aripiprazole, olanzapine, risperidone, paliperidone, and placebo.	Same as Study 1
Comparison	Included only RCTs for the following comparisons: 1. Olanzapine LAI vs olanzapine oral or placebo. 2. Aripiprazole LAI vs aripiprazole oral or placebo. 3. Paliperidone LAI vs paliperidone oral or placebo. 4. Risperidone LAI vs risperidone oral or placebo.	Included RCTs that incorporated analyses comparing any two of the following interventions: 1. Risperidone LAIs. 2. Paliperidone LAIs. 3. Aripiprazole LAIs. 4. Olanzapine LAIs. 5. Oral formulations of risperidone. 6. Oral formulations of paliperidone. 7. Oral formulations of aripiprazole. 8. Oral formulations of olanzapine. 9. Placebos, regardless of whether administered orally or through injection.
Outcomes	***Primary outcome***: "Overall symptom change" (SMD). ***Secondary outcomes***: 1) "Response rate" (N). 2) "Positive symptoms" (SMD). 3) "Negative symptoms" (SMD). 4) "Depressive symptoms" (SMD). 5) "Number of dropouts (due to any reason, inefficacy, side effects)" (N). 6) "Quality of life" (SMD). 7) "Social functioning" (SMD). 8) "The number of participants taking antiparkinsonian drugs" (N). 9) "Akathisia" (SMD / N). 10) "Weight gain" (N). 11) "Weight increase in kg (MD). 12) "Prolactin level in ng/mL" (MD). 13) "Dry mouth" (N). 14) "QTc prolongation in msec" (MD). 15) "Sedation" (N). 16) "At least one anticholinergic side effect" (N). 17) "Urinary retention" (N). 18) "Blurred vision" (N). 19) "Constipation" (N). 20) "All-cause mortality, Mortality for suicide" (N).	***Primary outcome***: "Overall symptom change" (SMD). ***Secondary outcomes***: 1) "Positive symptoms" (SMD). 2) "Negative symptoms" (SMD). 3) "Depressive symptoms" (SMD). 4) "Number of dropouts (due to any reason, inefficacy, side effects)" (N). 5) "Social functioning" (SMD). 6) "Quality of life" (SMD). 7) "Weight gain" (N). 8) "Weight increase in kg (MD)". 9) "At least one anticholinergic side effect" (N). 10) "Prolactin level in ng/mL" (MD). 11) "The number of participants taking antiparkinsonian drugs" (N). 12) "Akathisia" (N). 13) "Sedation" (N). 14) "QTc prolongation in msec" (MD).

Note: MD: Mean difference; SMD: Standard mean difference; N: the number of participants.

Table 3 (continued) 1 Overview of study methods

	Study 1	Study 2
Guideline	PRISMA	PRISMA-NMA
Protocol	https://osf. io/7gj2s/	https://osf.io/tb25u/
Search strategy	Search using the CSGSBR, clinicaltrials.gov, and WHO-ICTRP from the beginning of these databases until March 2022	Previous meta-analyses were reviewed (Leucht et al., 2023; Schneider-Thoma et al., 2022; Wang et al., 2023) and updated with searches of the CSGSBR on 6/14/2021, 9/21/2021, and 6/3/2022.
Study design	Includes short-term (3-13 weeks) RCTs of all types of blinding, including open-, single-, and double-blind.	There was no restriction on the duration of treatment for inclusion in the study as long as the patients were in the acute phase
Data analysis	Pairwise meta-analysis	Network meta-analysis
Sensitivity analyses	1. Prioritizing studies that employed doses close to the maximum effective dose. 2. Comparing LAIs and oral antipsychotics with results between 6–8 weeks.	1. Excluding studies without operationalized diagnostic criteria 2. Excluding open RCTs. 3. Excluding completer analyses. 4. Excluding studies with a high degree of missing data (exceeding 50%). 5. Excluding studies with a high risk of bias as per RoB 1 standards. 6. Prioritizing studies that employed doses close to the maximum effective dose. 7. Comparing LAIs and oral antipsychotics with results between 6–8 weeks.
Subgroup analysis	1. Comparing the effect sizes of LAIs versus placebo with those of their oral formulations versus placebo. 2. Comparing different LAI formulations that had the same antipsychotic component (e.g., aripiprazole maintena and lauroxil).	1. Comparison of pooled LAIs vs pooled oral antipsychotics in terms of overall symptoms.
Heterogeneity	χ^2 (alpha at 0.10) and I^2 (significant Heterogeneity when >50%).	Common τ^2
Transitivity assumption and incoherence assessment	Not applicable	1. Transitivity assessment by comparing the distribution of potential effect modifiers: "Placebo response", "Baseline severity", "Mean age", and "Percentage male". 2. Local and global tests were used to assess incoherence.
Confidence in the evidence	Not applicable	CINeMA
Risk of Bias	ROB 1	ROB 1

3. Main results and publication summaries

3.1 Publication 1 (peer-reviewed): Wang, D., Schneider-Thoma, J., Siafis, S., Burschinski, A., Dong, S., Wu, H., Zhu, Y., Davis, J. M., Priller, J., & Leucht, S. (2023, Jun 23). Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. Schizophrenia Bulletin. https://doi.org/10.1093/schbul/sbad089

Protocol: https://osf. io/7gj2s/

Main Author: ***Dongfang Wang***

Author contributions: DW was involved in all steps, including study design, data collection, data processing, analysis, and interpretation, and he wrote the first draft.

A systematic review and random-effects, pairwise meta-analysis was used to assess the efficacy of four SGA-LAIs (risperidone, paliperidone, aripiprazole and olanzapine) against placebos or their oral equivalents. It focused on the advantages of SGA-LAIs for acute schizophrenia based on direct evidence. Results from sixty-six studies with 16,457 participants indicated that all tested LAIs significantly reduced schizophrenia symptoms compared to placebo, and sensitivity analyses of overall symptoms yielded similar results. However, side effects were also more frequent. There were few head-to-head comparisons between LAIs and oral treatments. Therefore, a network meta-analysis which could integrate direct *and indirect* evidence was needed (→ Publication 2).

3.2 Publication 2 (peer-reviewed): Wang D, Schneider-Thoma J, Siafis S, Qin M, Wu H, Zhu Y, Davis JM, Priller J, Leucht S. Efficacy, acceptability and side-effects of oral versus long-acting- injectables antipsychotics: Systematic review and network meta-analysis. Eur

Neuropsychopharmacol. 2024 Jun;83:11-18. doi: 10.1016/j.euroneuro.2024.03.003. Epub 2024 Mar 15. PMID: 38490016.

Protocol: https://osf.io/tb25u/

Main Author: **Dongfang Wang**

Author contributions: DW contributed to all steps, including study design, data collection, processing, analysis, and interpretation and wrote the first draft.

This was a network meta-analysis which can integrate direct and indirect evidence (for example, drug A vs drug B, derived from A versus C and B versus C). It was thus approximately twice as large and included 115 randomized trials with over 25,000 participants with acute schizophrenia. The same drugs (LAI and oral formulations of risperidone, paliperidone, aripiprazole, olanzapine, and placebo) were included, but direct comparisons of oral formulations could also be used to evaluate the efficacy and tolerability of LAIs. The analysis found that there was no significant difference between LAIs and oral medications in terms of overall symptom relief. Additionally, sensitivity analyses of overall symptoms supported these results. However, there were advantages of some LAIs in terms of certain side effects. Including also indirect evidence in the statistical analysis, this study was better able to make a judgement about differences between drugs. Therefore, it supports clinician's decision-making when choosing among the available long-acting injectable and oral antipsychotic drugs.

3.3 My contribution to the publications

For two published papers included in my dissertation (Wang et al., 2023, 2024), I made the main contribution to these two articles as the first author. This included the initial

conceptualization and planning of the studies, drafting and registering the protocols, designing the search strategies, and systematic assessment of all included literature. I also searched the literature for other potentially relevant studies, extracted the data needed for this study, and assessed the risk of bias for all included studies.

At the same time, when data were missing, or information was unclear, I also contacted the original authors to obtain more information about the data, as well as to develop and perform statistical analyses, assess the robustness of the evidence, and interpret the statistical results.

My contributions also included drafting the manuscript, managing the process of manuscript submission and revision based on peer review comments, and coordinating the work of other co-authors involved in study selection, data extraction, and risk assessment.

For more information on the specific contributions of all authors, please see the author names section of each publication.

4. Findings and general discussion

This thesis offers a comprehensive examination of comparative research on SGAs in the management of acute schizophrenia based on two related methods and includes randomized-controlled trials in different studies.

4.1 Main Findings of Study 1

Study 1 included 66 studies and 16,457 participants, of which only one study compared LAI directly with an oral counterpart (aripiprazole, Kane et al., 2014). Study 1 focused on the efficacy and safety of LAIs compared to placebo in direct ("head-to-head") comparisons, but some preliminary analyses on differences between the various LAIs have already been made.

4.1.1 Efficacy in Study 1.

- All SGA-LAIs were significantly more effective than placebo in treating acute schizophrenia in terms of symptom reduction, response rates, and lower dropout rates. Olanzapine LAI, aripiprazole LAI and risperidone LAI had similar effect sizes compared to placebo in relieving overall and specific symptoms compared to placebo, while paliperidone LAI was less efficacious in some of the outcomes. This finding was important for clinicians: previous observational investigations had found that paliperidone LAI is used more frequently than the other SGA-LAIs, possibly because clinicians think that it is

more efficacious (Cai et al., 2019; Patel et al., 2018). However, our results suggest that it is somewhat less efficacious because it had the lowest effect size versus placebo.

- In subgroup analysis, compared to placebo, only aripiprazole LAI was better than its oral formulation in terms of the primary overall efficacy and several secondary efficacy outcomes. Based on a total of 8 studies, paliperidone LAI was significantly less effective than its oral formulation in social functioning. However, these findings should be treated with caution because they are based on simple subgroup analyses using a placebo as a mediator.

4.1.2 Side Effects in Study 1.

- Weight gain: This is one of the most common side effects of several SGAs (Hirsch et al., 2017). It is believed to be caused by a variety of pharmacologic mechanisms, such as the blockade of histamine receptors and 5-HT2C receptors (Siafis et al., 2018). In Study 1, all SGAs in both oral and LAI formulations caused more weight increase than placebo. Olanzapine LAI had the greatest effect on weight with 3.2 kg, which is in line with previous studies of our group, including the author of this thesis (Burschinski et al., 2023; Leucht et al., 2023). The differences in weight gain (both mean and the number of participants with >7% increase in body weight) between LAIs and oral formulations in subgroup tests were not significant. An important limitation is the usually longer duration of LAI studies (with LAI studies generally extending to 13 weeks, whereas oral studies usually lasted 4-6 weeks), which may reduce the negative impact of oral formulations on weight gain.

- EPS: EPS are seen as a main reason for nonadherence (Kadakia, Brady, et al., 2022; Lauriello & Perkins, 2019; Perkins, 2002) and can be associated with treatment-induced suicidal behaviour (Seemüller et al., 2012). SGAs usually have a lower risk of EPS than first-generation antipsychotics (FGAs) (Kumar & Sachdev, 2009; Meltzer, 2004). Study 1 provided further findings on long-acting injectable versions of SGAs concerning this question. Compared to placebo, paliperidone LAI and risperidone LAI did not show a higher risk of akathisia or use of antiparkinsonian drugs compared to placebo, which contrasts with their oral forms, which had more such side effects than placebo (Huhn et al., 2019). In contrast, aripiprazole LAI was associated with a higher risk of akathisia compared to placebo and its oral formulation. However, the results from rating scales on the Akathisia scale and EPS did not support these results, with the limitation that only one aripiprazole study (Kane et al., 2014) reported data for the Barnes Akathisia scale. LAI formulations of aripiprazole, olanzapine, and paliperidone had lower extrapyramidal symptom rating scale scores than their oral counterparts, and patients on risperidone LAI needed almost less antiparkinsonian medication than those on oral ($P = 0.05$). In summary, the evidence suggests that LAI formulations may have a lower risk of EPS compared to their oral counterparts.
- Hyperprolactinemia: It is one of the common side effects of concern of some SGAs, in particular risperidone, paliperidone and amisulpride (for which an LAI formulation is not available) that can have a serious impact on quality of life: menstrual disorders, amenorrhoea, sexual dysfunction, gynaecological inflammation, infertility, decreased bone mineral density and breast cancer (Bostwick et al., 2009). Study 1 found that

risperidone, paliperidone and oral olanzapine were associated with increased prolactin levels compared to placebo, while data on olanzapine LAI and aripiprazole were not available. Paliperidone LAI's risk for hyperprolactinemia was significantly lower than its oral formulation, while risperidone LAI also had the same trend but without a significant difference. Notably, aripiprazole oral uniquely demonstrated a reduction in prolactin levels, which is in line with previous studies (Schneider-Thoma et al., 2022; Zhu et al., 2021). The reason for this finding is probably the partial dopamine agonist mechanism of action of aripiprazole, which means that it has an intrinsic dopamine D2 receptor stimulating effect of approximately 30% (Burris et al., 2002). This pharmacological property might confer an advantage in managing hyperprolactinemia-related side effects, enhancing patient well-being. It has also been shown that adding aripiprazole to prolactin-increasing drugs such as risperidone reduces prolactin (Chen et al., 2015; Lu et al., 2022; Raghuthaman et al., 2015; Zheng et al., 2019).

- Anticholinergic side effects: Three indices (at least once anticholinergic event, dry mouth and constipation) were used to assess anticholinergic side effects. There was no significant difference between SGA-LAIs and placebo. Subgroup analyses showed that fewer patients treated with aripiprazole LAI experienced dry mouth compared with those taking oral aripiprazole, and fewer patients treated with olanzapine LAI experienced anticholinergic side effects compared with its oral formulation.
- Other side effects: No differences were found in QTc and mortality between SGA-LAIs and placebo or their oral formulations.

4.1.3 Implications of Study 1.

The findings from Study 1 suggest that LAIs are effective in the acute treatment of schizophrenia and may provide comparable or slightly enhanced efficacy compared to oral formulations. Additionally, certain LAIs appear to be associated with favourable side effect profiles, which could potentially contribute to improved patient adherence and quality of life. Conventional pairwise meta-analysis has the advantage that it summarizes the "pure" direct evidence, while network meta-analysis uses direct and indirect evidence and must rely on further assumptions. However, as there was only one RCT comparing an LAI with an oral formulation and no RCTs which compared LAIs with one another, the possibility to assess differences in efficacy and side effects between drugs was restricted to pairwise-meta-analysis subgroup tests. This methodology is limited, and it cannot use all the randomized evidence. Therefore, Study 2, which applied network meta-analysis, was conducted.

4.2 Main Findings of Study 2

The main aim of Study 1 was to explore the relative efficacy and tolerability of SGA-LAIs compared to placebo. In contrast, the aim of Study 2 was to obtain comparisons between different SGA-LAI antipsychotics and compared to their oral counterparts through a network meta-analysis.

Study 2 represents a progression from the initial groundwork laid by Study 1, expanding the inclusion criteria to encompass 115 studies with 25,550 participants (compared to 66 studies and 16,457 participants in Study 1). NMA allows the use of both direct (e.g., all trials which compared drug A and drug B) and indirect evidence (e.g., drug A versus drug B derived from

drug A versus drug C and drug B versus drug C), providing a broader comparison of the various SGAs-LAIs and the respective SGAs-oral. This methodology helped to strengthen the evidence base, in particular by also including RCTs, which compared the oral forms of the antipsychotics in question and provided information which can be used by psychiatrists in clinical decision-making. By adopting a network meta-analysis approach, Study 2 not only corroborated but also expanded upon the insights from Study 1.

4.2.1 Efficacy in Study 2

- Both LAIs and their oral counterparts significantly reduced 'overall symptoms of schizophrenia' compared to placebo. This reaffirmed the results of Study 1. In addition, based on the findings of Study 1, Study 2 further found that olanzapine oral and risperidone LAI were significantly more efficacious than aripiprazole oral, whereas none of the other antipsychotics showed any clear differences in the inter-drug comparisons. Olanzapine stood out in efficacy compared to placebo, with the LAI form achieving the highest effect size (SMD -0.66), followed by olanzapine oral in third place (SMD -0.55). Superior efficacy of olanzapine had also been found in previous studies, which showed it to be efficacious in long-term treatment (Leucht et al., 2023) and in treatment-resistant patients (Dong et al., 2023), research projects to which the author of this thesis contributed. Study 2 distinguished between LAI and oral forms to address the efficacy of olanzapine LAI specifically. This approach provided a critical insight because previous studies combined LAI with oral drugs (Leucht et al., 2023) and thus masked the effects of each one separately. Study 2, therefore, not only supported the existing evidence but also built on

it, specifically highlighting the value of olanzapine LAIs in the treatment of acute schizophrenia.

- Similar hierarchies as for the primary outcome, 'overall symptoms of schizophrenia', were observed for positive and negative symptoms. Moreover, all drugs were superior to placebo for depressive symptoms, consistent with the results of Study 1.
- Discontinuation of antipsychotic medication significantly increases the risk of relapse in patients with schizophrenia (Forsman et al., 2019), which can lead to hospital admissions, deterioration of personal and social functioning, substance abuse and deterioration of overall health (Nielsen et al., 2015; Phan, 2016). Consequently, healthcare utilization and costs are increased, and when treatment is resumed, patients' outcomes may be worse than at the end of the previous episode (Taipale et al., 2020). Study 2 showed that all SGAs were more effective than placebo in avoiding drop-outs, with oral olanzapine being particularly effective, which was similar to the findings of previous studies (Huhn et al., 2019; Leucht et al., 2023). Although few differences were statistically significant, a consistent trend that emerged from these studies was that patients were less likely to drop out of treatment due to the inefficacy of treatment. In contrast, olanzapine and aripiprazole oral formulations had a higher risk of dropping out of treatment due to side effects. These results highlight the complex balance between antipsychotic efficacy and tolerability, emphasizing the need for individualized treatment decisions.

4.2.2 Side Effects in Study 2

- Weight gain: Weight gain is a common side effect of all antipsychotics analyzed, but the greatest increase in this side effect was seen for oral olanzapine compared to placebo, corroborating the results of Study 1. Moreover, Study 2 found a lower incidence of weight gain with olanzapine LAI compared to oral olanzapine, which may be due to reduced fluctuations in plasma levels of LAI formulations (Sheehan et al., 2012). However, this observation had a shortcoming in that only one study on olanzapine LAI was available. There were no clear differences between oral and LAI formulations of other antipsychotics. Therefore, no definitive conclusions could be drawn regarding the comparative effects of LAI and oral antipsychotics on body weight. More data are needed to understand the long-term impact of LAI antipsychotics on weight gain.
- Hyperprolactinemia: Aripiprazole stood out as the only antipsychotic which reduced prolactin levels, consistent with the results of Study 1, and although aripiprazole LAI showed a larger mean effect size compared to its oral form, this was not statistically conclusive due to broad confidence intervals. Paliperidone and risperidone had the highest prolactin increase. This effect was smaller in the LAIs than in the oral formulations (statistically significantly so for paliperidone), eventually because plasma levels of LAIs are more stable and do not fluctuate much. In contrast, each oral intake leads to plasma level peaks, which may be associated with more side effects.
- EPS: Oral formulations of risperidone and paliperidone were significantly more likely to cause a higher risk of using antiparkinsonian drugs compared with placebo, whereas their LAI formulations only showed a trend in this regard. LAI may thus have a potential

advantage in reducing the incidence of such side effects, but currently, the data are inconclusive.

- Other side effects: Olanzapine LAI significantly mitigated the risk of anticholinergic side effects when compared to both its oral version and risperidone oral. Sedative effects were common to all antipsychotics, more so with olanzapine, probably due to its potent histaminergic activity, although such effects did not reach conventional levels of statistical significance with paliperidone oral, aripiprazole LAI, and olanzapine LAI. The study also observed only a small QTc interval prolongation of an average of 3.2 msec, 3.5 msec and 3.5 msec with olanzapine oral and risperidone oral and LAI, suggesting a small cardiac risk associated with these treatments. These results are consistent with Study 1.

4.2.3 Implications of Study 2

Study 1 used paired meta-analyses to directly compare LAI with placebo or the same oral medications, providing straightforward summary effects of direct evidence. Study 2 used network meta-analysis to compare multiple treatments simultaneously, using all the relevant RCT evidence by integrating direct and indirect comparisons. This approach provides treatment hierarchies for the various outcomes, which can be used in clinical decision-making and supports more individualized treatment of patients with schizophrenia.

5. Limitations

These findings should be interpreted with the following limitations. First, although a total of 115 studies with 25,550 participants were included, for olanzapine LAI, which was on top of the efficacy hierarchy, only one RCT was available. Another issue is that only one study compared LAIs and their oral medications directly. Thus, many of the findings rely on indirect evidence, which is not the most trustworthy method. Third, both studies only considered RCTs and did not include observational studies. Combining RCTs and observational studies would have violated the transitivity assumption. However, evidence from more naturalistic designs yielded clearer effectiveness advantages of LAIs than RCTs (Kishimoto et al., 2021). Fourth, studies from mainland China were excluded because of frequently raised quality concerns (Leucht et al., 2022; Parry, 2017). However, studies from Taiwan and Hong Kong or studies conducted in mainland China by international pharmacy companies met our inclusion criteria. Fifth, another challenge in evaluating LAI studies is the long duration of their regimens, often up to 13 weeks. This duration complicates the comparison with oral compounds, which are usually tested in 4-8 weeks of studies. However, this limitation was addressed by a sensitivity analysis of the primary outcome using 6 to 8-week results only, and there was no major difference from the primary result.

6. Conclusions

In summary, Studies 1 and 2 enhance our understanding of antipsychotic treatments for acute schizophrenia, showing that both LAIs and oral SGAs effectively reduce symptoms compared to placebo. LAIs, in particular, offer similar efficacy with potentially fewer side effects, such as hyperprolactinemia and some extrapyramidal symptoms, compared to oral forms. However, these findings should be interpreted with caution due to limitations such as indirect comparisons and the exclusion of real-world studies. These insights underscore the need for targeted treatment approaches and further research, especially direct comparisons and real-world studies, to optimize schizophrenia management.

7. References:

Addington, D., Addington, J., & Maticka-tyndale, E. (1993). Assessing Depression in Schizophrenia: The Calgary Depression Scale. *The British Journal of Psychiatry*, *163*(S22), 39–44. https://doi.org/10.1192/S0007125000292581

Álamo, C. (2022). Risperidone ISM as a New Option in the Clinical Management of Schizophrenia: A Narrative Review. *Advances in Therapy*, *39*(11), 4875–4891. https://doi.org/10.1007/s12325-022-02299-8

American Psychiatric Association, D., & Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5). American psychiatric association Washington, DC.

Andreasen, N. C. (1984). Scale for the assessment of positive symptoms. *Psychiatrie & Psychobiologie*.

Andreasen, N. C. (1989). The Scale for the Assessment of Negative Symptoms (SANS): Conceptual and Theoretical Foundations. *The British Journal of Psychiatry*, *155*(S7), 49–52. https://doi.org/10.1192/S0007125000291496

Anta, L., Llaudó, J., Ayani, I., Martínez, J., Litman, R. E., & Gutierro, I. (2018). A phase II study to evaluate the pharmacokinetics, safety, and tolerability of Risperidone ISM multiple intramuscular injections once every 4 weeks in patients with schizophrenia. *International Clinical Psychopharmacology*, *33*(2), 79–87. https://doi.org/10.1097/YIC.0000000000000203

Barnes, T. R. (1989). Barnes akathisia rating scale. *The British Journal of Psychiatry*.

Blair, H. A. (2022). Paliperidone palmitate intramuscular 6-monthly formulation in schizophrenia: A profile of its use. *Drugs & Therapy Perspectives*, *38*(8), 335–342. https://doi.org/10.1007/s40267-022-00931-9

Bostwick, J. R., Guthrie, S. K., & Ellingrod, V. L. (2009). Antipsychotic-Induced Hyperprolactinemia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *29*(1), 64–73. https://doi.org/10.1592/phco.29.1.64

Burris, K. D., Molski, T. F., Xu, C., Ryan, E., Tottori, K., Kikuchi, T., Yocca, F. D., & Molinoff, P. B. (2002). Aripiprazole, a Novel Antipsychotic, Is a High-Affinity Partial Agonist at Human Dopamine D2 Receptors. *Journal of Pharmacology and Experimental Therapeutics*, *302*(1), 381–389. https://doi.org/10.1124/jpet.102.033175

Burschinski, A., Schneider-Thoma, J., Chiocchia, V., Schestag, K., Wang, D., Siafis, S., Bighelli, I., Wu, H., Hansen, W.-P., Priller, J., Davis, J. M., Salanti, G., & Leucht, S. (2023). Metabolic side effects in persons with schizophrenia during mid- to long-term treatment with antipsychotics: A network meta-analysis of randomized controlled trials. *World Psychiatry*, *22*(1), 116–128. https://doi.org/10.1002/wps.21036

Bushe, C. J., Falk, D., Anand, E., Casillas, M., Perrin, E., Chhabra-Khanna, R., & Detke, H. C. (2015). Olanzapine long-acting injection: A review of first experiences of post-injection delirium/sedation syndrome in routine clinical practice. *BMC Psychiatry*, *15*(1), 65. https://doi.org/10.1186/s12888-015-0450-9

Cai, Q., Patel, C., Kim, E., Connolly, N., Tunceli, O., & El Khoury, A. C. (2019). Factors Associated with the Initiation of Long-Acting Injectable Paliperidone Palmitate Versus

Aripiprazole Among Medicaid Patients with Schizophrenia: An Observational Study. *Advances in Therapy*, *36*(4), 858–869. https://doi.org/10.1007/s12325-019-00913-w

Carbon, M., & Correll, C. U. (2014). Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues Clin Neurosci*, *16*(4), 505–524. https://doi.org/10.31887/DCNS.2014.16.4/mcarbon

Chen, J.-X., Su, Y.-A., Bian, Q.-T., Wei, L.-H., Zhang, R.-Z., Liu, Y.-H., Correll, C., Soares, J. C., Yang, F.-D., Wang, S.-L., & Zhang, X.-Y. (2015). Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose–response study. *Psychoneuroendocrinology*, *58*, 130–140. https://doi.org/10.1016/j.psyneuen.2015.04.011

Chouinard, G., & Margolese, H. C. (2005). Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophrenia Research*, *76*(2), 247–265. https://doi.org/10.1016/j.schres.2005.02.013

Citrome, L. (2009). Olanzapine pamoate: A stick in time? *International Journal of Clinical Practice*, *63*(1), 140–150. https://doi.org/10.1111/j.1742-1241.2008.01900.x

Citrome, L. (2010). Paliperidone palmitate – review of the efficacy, safety and cost of a new second-generation depot antipsychotic medication. *International Journal of Clinical Practice*, *64*(2), 216–239. https://doi.org/10.1111/j.1742-1241.2009.02240.x

Citrome, L. (2021). Long-acting injectable antipsychotics: What, when, and how. *CNS Spectrums*, *26*(2), 118–129. https://doi.org/10.1017/S1092852921000249

Correll, C. U., Kim, E., Sliwa, J. K., Hamm, W., Gopal, S., Mathews, M., Venkatasubramanian, R., & Saklad, S. R. (2021). Pharmacokinetic Characteristics of Long-Acting Injectable

Antipsychotics for Schizophrenia: An Overview. *CNS Drugs*, *35*(1), 39–59. https://doi.org/10.1007/s40263-020-00779-5

Cramer, J. A., & Rosenheck, R. (1998). Compliance with medication regimens for mental and physical disorders. *Psychiatric Services*, *49*(2), 196–201.

DailyMed. (n.d.). Retrieved April 2, 2024, from https://dailymed.nlm.nih.gov/dailymed/

DerSimonian, R., & Laird, N. (1986). Meta-analysis in clinical trials. *Controlled Clinical Trials*, *7*(3), 177–188.

Detke, H. C., McDonnell, D. P., Brunner, E., Zhao, F., Sorsaburu, S., Stefaniak, V. J., & Corya, S. A. (2010). Post-injection delirium/sedation syndrome in patients with schizophrenia treated with olanzapine long-acting injection, I: analysis of cases. *BMC Psychiatry*, *10*, 1–10.

Dias, S., Welton, N. J., Caldwell, D. M., & Ades, A. E. (2010). Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine*, *29*(7–8), 932–944. https://doi.org/10.1002/sim.3767

Dong, S., Schneider-Thoma, J., Bighelli, I., Siafis, S., Wang, D., Burschinski, A., Schestag, K., Samara, M., & Leucht, S. (2023). A network meta-analysis of efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, 1–12.

Efthimiou, O., Debray, T. P. A., van Valkenhoef, G., Trelle, S., Panayidou, K., Moons, K. G. M., Reitsma, J. B., Shang, A., Salanti, G., & Group, on behalf of G. M. R. (2016). GetReal in network meta-analysis: A review of the methodology. *Research Synthesis Methods*, *7*(3), 236–263. https://doi.org/10.1002/jrsm.1195

Efthimiou, O., Taipale, H., Radua, J., Schneider-Thoma, J., Pinzón-Espinosa, J., Ortuño, M., Vinkers, C. H., Mittendorfer-Rutz, E., Cardoner, N., Tanskanen, A., Fusar-Poli, P., Cipriani, A., Vieta, E., Leucht, S., Tiihonen, J., & Luykx, J. J. (2024). Efficacy and effectiveness of antipsychotics in schizophrenia: Network meta-analyses combining evidence from randomised controlled trials and real-world data. *The Lancet Psychiatry*, *11*(2), 102–111. https://doi.org/10.1016/S2215-0366(23)00366-8

Fan, J., & de Lannoy, I. A. (2014). Pharmacokinetics. *Biochem Pharmacol*, *87*(1), 93–120. https://doi.org/10.1016/j.bcp.2013.09.007

Forsman, J., Taipale, H., Masterman, T., Tiihonen, J., & Tanskanen, A. (2019). Adherence to psychotropic medication in completed suicide in Sweden 2006–2013: A forensic-toxicological matched case-control study. *European Journal of Clinical Pharmacology*, *75*, 1421–1430.

Frampton, J. E. (2017). Aripiprazole Lauroxil: A Review in Schizophrenia. *Drugs*, *77*(18), 2049–2056. https://doi.org/10.1007/s40265-017-0848-4

Furukawa, T. A., Barbui, C., Cipriani, A., Brambilla, P., & Watanabe, N. (2006). Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology*, *59*(1), 7–10. https://doi.org/10.1016/j.jclinepi.2005.06.006

Furukawa, T. A., Salanti, G., Atkinson, L. Z., Leucht, S., Ruhe, H. G., Turner, E. H., Chaimani, A., Ogawa, Y., Takeshima, N., & Hayasaka, Y. (2016). Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: Protocol for a network meta-analysis. *BMJ Open*, *6*(7), e010919.

Gaebel, W., Hasan, A., & Falkai, P. (2019). *S3-Leitlinie Schizophrenie*. Springer-Verlag.

Gardner, D. M., Murphy, A. L., O'Donnell, H., Centorrino, F., & Baldessarini, R. J. (2010). International Consensus Study of Antipsychotic Dosing. *American Journal of Psychiatry*, *167*(6), 686–693. https://doi.org/10.1176/appi.ajp.2009.09060802

GBD 2019 Mental Disorders Collaborators. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry*, *9*(2), 137–150.

Gefvert, O., Eriksson, B., Persson, P., Helldin, L., Björner, A., Mannaert, E., Remmerie, B., Eerdekens, M., & Nyberg, S. (2005). Pharmacokinetics and D2 receptor occupancy of long-acting injectable risperidone (Risperdal Consta™) in patients with schizophrenia. *International Journal of Neuropsychopharmacology*, *8*(1), 27–36. https://doi.org/10.1017/S1461145704004924

Guinart, D., Misawa, F., Rubio, J. M., Pereira, J., Sharma, H., Schoretsanitis, G., Kane, J. M., & Correll, C. U. (2020). Outcomes of Neuroleptic Malignant Syndrome With Depot Versus Oral Antipsychotics: A Systematic Review and Pooled, Patient-Level Analysis of 662 Case Reports. *The Journal of Clinical Psychiatry*, *82*(1), 13591. https://doi.org/10.4088/JCP.20r13272

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*(1), 56.

Hard, M. L., Mills, R. J., Sadler, B. M., Turncliff, R. Z., & Citrome, L. (2017). Aripiprazole Lauroxil. *Journal of Clinical Psychopharmacology*, *37*(3), 289–295. https://doi.org/10.1097/JCP.0000000000000691

Hard, M. L., Mills, R. J., Sadler, B. M., Wehr, A. Y., Weiden, P. J., & von Moltke, L. (2017). Pharmacokinetic Profile of a 2-Month Dose Regimen of Aripiprazole Lauroxil: A Phase I Study and a Population Pharmacokinetic Model. *CNS Drugs*, *31*(7), 617–624. https://doi.org/10.1007/s40263-017-0447-7

Harrison, T. S., & Goa, K. L. (2004). Long-acting risperidone: A review of its use in schizophrenia. *CNS Drugs*, *18*, 113–132.

Heinrichs, D. W., Hanlon, T. E., & Carpenter, W. T., Jr. (1984). The Quality of Life Scale: An Instrument for Rating the Schizophrenic Deficit Syndrome. *Schizophrenia Bulletin*, *10*(3), 388–398. https://doi.org/10.1093/schbul/10.3.388

Heres, S. (2014). Long-acting injectable antipsychotics: An underutilized treatment option. *J Clin Psychiatry*, *75*(11), 1263–1265. https://doi.org/10.4088/JCP.14com09541

Heres, S., Kraemer, S., Bergstrom, R. F., & Detke, H. C. (2014). Pharmacokinetics of olanzapine long-acting injection: The clinical perspective. *Int Clin Psychopharmacol*, *29*(6), 299–312. https://doi.org/10.1097/yic.0000000000000040

Higgins, J. (2019). *Cochrane Handbook for Systematic Reviews of Interventions* (Second Editionsec). Wiley Online Library.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savović, J., Schulz, K. F., Weeks, L., & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj*, *343*.

Higgins, J. P., Eldridge, S., & Li, T. (2019). Including variants on randomized trials. *Cochrane Handbook for Systematic Reviews of Interventions*, 569–593.

Higgins, J. P., Jackson, D., Barrett, J. K., Lu, G., Ades, A. E., & White, I. R. (2012). Consistency and inconsistency in network meta-analysis: Concepts and models for multi-arm studies. *Res Synth Methods*, *3*(2), 98–110. https://doi.org/10.1002/jrsm.1044

Hirsch, L., Yang, J., Bresee, L., Jette, N., Patten, S., & Pringsheim, T. (2017). Second-Generation Antipsychotics and Metabolic Side Effects: A Systematic Review of Population-Based Studies. *Drug Safety*, *40*(9), 771–781. https://doi.org/10.1007/s40264-017-0543-0

Hjorthøj, C., Stürup, A. E., McGrath, J. J., & Nordentoft, M. (2017). Years of potential life lost and life expectancy in schizophrenia: A systematic review and meta-analysis. *The Lancet Psychiatry*, *4*(4), 295–301.

Holm, M., Taipale, H., Tanskanen, A., Tiihonen, J., & Mitterdorfer-Rutz, E. (2021). Employment among people with schizophrenia or bipolar disorder: A population-based study using nationwide registers. *Acta Psychiatrica Scandinavica*, *143*(1), 61–71.

Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., Bäckers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., & Leucht, S. (2019). Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *Lancet*, *394*(10202), 939–951. https://doi.org/10.1016/s0140-6736(19)31135-3

Hutton, B., Salanti, G., Caldwell, D. M., Chaimani, A., Schmid, C. H., Cameron, C., Ioannidis, J. P., Straus, S., Thorlund, K., & Jansen, J. P. (2015). The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Annals of Internal Medicine*, *162*(11), 777–784.

Inada, T., & Yagi, G. (1995). Current topics in tardive dyskinesia in Japan. *Psychiatry and Clinical Neurosciences*, *49*(5–6), 239–244. https://doi.org/10.1111/j.1440-1819.1995.tb01895.x

Janzen, D., Bolton, J., Kuo, I. F., Leong, C., & Alessi-Severini, S. (2020). Trends in the Use of Long-Acting Injectable Antipsychotics in the Province of Manitoba, Canada. *J Clin Psychopharmacol*, *40*(1), 6–13. https://doi.org/10.1097/jcp.0000000000001148

Javitt, D. C. (2014). Balancing therapeutic safety and efficacy to improve clinical and economic outcomes in schizophrenia: A clinical overview. *Am J Manag Care*, *20*(8 Suppl), S160-5.

Jones, S. H., Thornicroft, G., Coffey, M., & Dunn, G. (1995). A Brief Mental Health Outcome Scale: Reliability and Validity of the Global Assessment of Functioning (GAF). *The British Journal of Psychiatry*, *166*(5), 654–659. https://doi.org/10.1192/bjp.166.5.654

Kadakia, A., Brady, B. L., Dembek, C., Williams, G. R., & Kent, J. M. (2022). Burden of EPS in commercial patients with schizophrenia initiating atypical antipsychotics. *American Journal of Managed Care*, *28*(9).

Kadakia, A., Catillon, M., Fan, Q., Williams, G. R., Marden, J. R., Anderson, A., Kirson, N., & Dembek, C. (2022). The economic burden of schizophrenia in the United States. *The Journal of Clinical Psychiatry*, *83*(6), 43278.

Kane, J. M., Kishimoto, T., & Correll, C. U. (2013). Non-adherence to medication in patients with psychotic disorders: Epidemiology, contributing factors and management strategies. *World Psychiatry*, *12*(3), 216–226. https://doi.org/10.1002/wps.20060

Kane, J. M., McEvoy, J. P., Correll, C. U., & Llorca, P.-M. (2021). Controversies surrounding the use of long-acting injectable antipsychotic medications for the treatment of patients with schizophrenia. *CNS Drugs*, 1–17.

Kane, J. M., Peters-Strickland, T., Baker, R. A., Hertel, P., Eramo, A., Jin, N., Perry, P. P., Gara, M., McQuade, R. D., Carson, W. H., & Sanchez, R. (2014). Aripiprazole once-monthly in the acute treatment of schizophrenia: Findings from a 12-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*, *75*(11), 1254–1260. https://doi.org/10.4088/JCP.14m09168

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276.

Keepers, G. A., Fochtmann, L. J., Anzia, J. M., Benjamin, S., Lyness, J. M., Mojtabai, R., Servis, M., Walaszek, A., Buckley, P., Lenzenweger, M. F., Young, A. S., Degenhardt, A., & Hong, S.-H. (2020). The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *American Journal of Psychiatry*, *177*(9), 868–872. https://doi.org/10.1176/appi.ajp.2020.177901

Kishimoto, T., Hagi, K., Kurokawa, S., Kane, J. M., & Correll, C. U. (2021). Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: A systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry*, *8*(5), 387–404. https://doi.org/10.1016/s2215-0366(21)00039-0

Kovács, G., Almási, T., Millier, A., Toumi, M., Horváth, M., Kóczián, K., Götze, À., Kaló, Z., & Zemplényi, A. T. (2018). Direct healthcare cost of schizophrenia – European overview. *European Psychiatry*, *48*(1), 79–92. https://doi.org/10.1016/j.eurpsy.2017.10.008

Krogmann, A., Peters, L., Hardenberg, L. von, Bödeker, K., Nöhles, V. B., & Correll, C. U. (2019). Keeping up with the therapeutic advances in schizophrenia: A review of novel and emerging pharmacological entities. *CNS Spectrums*, *24*(S1), 38–69. https://doi.org/10.1017/S109285291900124X

Kumar, R., & Sachdev, P. S. (2009). Akathisia and second-generation antipsychotic drugs. *Current Opinion in Psychiatry*, *22*(3), 293–299.

Laboratorios Farmacéuticos Rovi, S.A. (2024). *FDA Approves Risvan*. https://www.drugs.com/newdrugs/fda-approves-risvan-risperidone-schizophrenia-6239.html#:~:text=Madrid%20%E2%80%93%202%20April%2C%202024%20%E2%80%93,treatment%20of%20schizophrenia%20in%20adults.

Lacro, J. P., Dunn, L. B., Dolder, C. R., & Jeste, D. V. (2002). Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: A comprehensive review of recent literature. *The Journal of Clinical Psychiatry*, *63*(10), 15489.

Laffont, C. M., Gomeni, R., Zheng, B., Heidbreder, C., Fudala, P. J., & Nasser, A. F. (2015). Population pharmacokinetic modeling and simulation to guide dose selection for RBP-7000, a new sustained-release formulation of risperidone. *J Clin Pharmacol*, *55*(1), 93–103. https://doi.org/10.1002/jcph.366

Lauriello, J., & Perkins, D. O. (2019). Managing transitions in care and adherence to improve outcomes in schizophrenia. *Journal of Clinical Psychiatry*, *80*(2), 27731.

Leucht, S., Crippa, A., Siafis, S., Patel, M. X., Orsini, N., & Davis, J. M. (2020). Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. *Am J Psychiatry*, *177*(4), 342–353. https://doi.org/10.1176/appi.ajp.2019.19010034

Leucht, S., Li, C., Davis, J. M., Bighelli, I., Zhu, Y., & Furukawa, T. A. (2022). About the issue of including or excluding studies from China in systematic reviews. *Schizophrenia Research*, *240*, 162–163.

Leucht, S., Schneider-Thoma, J., Burschinski, A., Peter, N., Wang, D., Dong, S., Huhn, M., Nikolakopoulou, A., Salanti, G., & Davis, J. M. (2023). Long-term efficacy of antipsychotic drugs in initially acutely ill adults with schizophrenia: Systematic review and network meta-analysis. *World Psychiatry*, *22*(2), 315–324. https://doi.org/10.1002/wps.21089

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., Clarke, M., Devereaux, P. J., Kleijnen, J., & Moher, D. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *Annals of Internal Medicine*, *151*(4), W-65. https://doi.org/10.7326/0003-4819-151-4-200908180-00136

Lu, Z., Sun, Y., Zhang, Y., Chen, Y., Guo, L., Liao, Y., Kang, Z., Feng, X., & Yue, W. (2022). Pharmacological treatment strategies for antipsychotic-induced hyperprolactinemia: A systematic review and network meta-analysis. *Translational Psychiatry*, *12*(1), 1–14. https://doi.org/10.1038/s41398-022-02027-4

Luedecke, D., Schöttle, D., Karow, A., Lambert, M., & Naber, D. (2015). Post-injection delirium/sedation syndrome in patients treated with olanzapine pamoate: Mechanism, incidence, and management. *CNS Drugs*, *29*(1), 41–46. https://doi.org/10.1007/s40263-014-0216-9

McDonnell, D. P., Detke, H. C., Bergstrom, R. F., Kothare, P., Johnson, J., Stickelmeyer, M., Sanchez-Felix, M. V., Sorsaburu, S., & Mitchell, M. I. (2010). Post-injection delirium/sedation

syndrome in patients with schizophrenia treated with olanzapine long-acting injection, II: investigations of mechanism. *BMC Psychiatry*, *10*, 45. https://doi.org/10.1186/1471-244x-10-45

McDonnell, D. P., Landry, J., & Detke, H. C. (2014). Long-term safety and efficacy of olanzapine long-acting injection in patients with schizophrenia or schizoaffective disorder: A 6-year, multinational, single-arm, open-label study. *International Clinical Psychopharmacology*, *29*(6), 322. https://doi.org/10.1097/YIC.0000000000000038

Meltzer, H. Y. (2004). What's atypical about atypical antipsychotic drugs? *Current Opinion in Pharmacology*, *4*(1), 53–57.

Mitchell, M., Kothare, P., Bergstrom, R., Zhao, F., Jen, K. Y., Walker, D., Johnson, J., & McDonnell, D. (2013). Single- and multiple-dose pharmacokinetic, safety, and tolerability profiles of olanzapine long-acting injection: An open-label, multicenter, nonrandomized study in patients with schizophrenia. *Clin Ther*, *35*(12), 1890–1908. https://doi.org/10.1016/j.clinthera.2013.09.023

Montgomery, S. A., & Åsberg, M. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382–389.

Morris, M. T., & Tarpada, S. P. (2017). Long-Acting Injectable Paliperidone Palmitate: A Review of Efficacy and Safety. *Psychopharmacol Bull*, *47*(2), 42–52. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5472171/pdf/PB-47-2-42.pdf

Najarian, D., Turkoz, I., Knight, R. K., Galderisi, S., Lamaison, H. F., Zalitacz, P., Aravind, S., & Richarz, U. (2023). Long-Term Efficacy and Safety of Paliperidone 6-Month Formulation: An Open-Label 2-Year Extension of a 1-Year Double-Blind Study in Adult Participants With

Schizophrenia. *International Journal of Neuropsychopharmacology*, *26*(8), 537–544. https://doi.org/10.1093/ijnp/pyad028

National Institute for Health and Care Excellence [NICE]. (2014). Psychosis and schizophrenia in adults: Prevention and management. *NICE Guidelines*. https://www.nice.org.uk/guidance/cg178

Nich, C., & Carroll, K. M. (2002). 'Intention-to-treat' meets 'missing data': Implications of alternate strategies for analyzing clinical trials data. *Drug and Alcohol Dependence*, *68*(2), 121–130. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651592/

Nielsen, J., Jensen, S. O., Friis, R. B., Valentin, J. B., & Correll, C. U. (2015). Comparative effectiveness of risperidone long-acting injectable vs first-generation antipsychotic long-acting injectables in schizophrenia: Results from a nationwide, retrospective inception cohort study. *Schizophrenia Bulletin*, *41*(3), 627–636.

Nikolakopoulou, A., Higgins, J. P., Papakonstantinou, T., Chaimani, A., Del Giovane, C., Egger, M., & Salanti, G. (2020). CINeMA: an approach for assessing confidence in the results of a network meta-analysis. *PLoS Medicine*, *17*(4), e1003082.

Novakovic, V., Adel, T., Peselow, E., & Lindenmayer, J.-P. (2013). Long-acting injectable antipsychotics and the development of postinjection delirium/sedation syndrome (PDSS). *Clinical Neuropharmacology*, *36*(2), 59–62.

Novick, D., Haro, J. M., Suarez, D., Perez, V., Dittmann, R. W., & Haddad, P. M. (2010). Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. *Psychiatry Res*, *176*(2–3), 109–113. https://doi.org/10.1016/j.psychres.2009.05.004

Olesen, J., Gustavsson, A., Svensson, M., Wittchen, H.-U., Jönsson, B., Group, on behalf of the C. study, & Council, the E. B. (2012). The economic cost of brain disorders in Europe. *European Journal of Neurology*, *19*(1), 155–162. https://doi.org/10.1111/j.1468-1331.2011.03590.x

Overall, J. E., & Gorham, D. R. (1988). The Brief Psychiatric Rating Scale (BPRS): Recent developments in ascertainment and scaling. *Psychopharmacology Bulletin*.

Parry, J. (2017). China vows to clamp down on academic fraud amid medical journal scandal. *BMJ: British Medical Journal (Online)*, *357*.

Patel, R., Chesney, E., Taylor, M., Taylor, D., & McGuire, P. (2018). Is paliperidone palmitate more effective than other long-acting injectable antipsychotics? *Psychol Med*, *48*(10), 1616–1623. https://doi.org/10.1017/s0033291717003051

Perkins, D. (2002). Predictors of noncompliance in patients with schizophrenia. *Journal of Clinical Psychiatry*, *63*(12), 1121–1128.

Phan, S. V. (2016). Medication adherence in patients with schizophrenia. *The International Journal of Psychiatry in Medicine*, *51*(2), 211–219.

Raghuthaman, G., Venkateswaran, R., & Krishnadas, R. (2015). Adjunctive aripiprazole in risperidone-induced hyperprolactinaemia: Double-blind, randomised, placebo-controlled trial. *BJPsych Open*, *1*(2), 172–177. https://doi.org/10.1192/bjpo.bp.115.001248

Rhodes, K. M., Turner, R. M., & Higgins, J. P. T. (2015). Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data. *Journal of Clinical Epidemiology*, *68*(1), 52–60. https://doi.org/10.1016/j.jclinepi.2014.08.012

Rücker, G. (2012). Network meta-analysis, electrical networks and graph theory. *Res Synth Methods*, *3*(4), 312–324. https://doi.org/10.1002/jrsm.1058

Rücker, G., & Schwarzer, G. (2015). Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol*, *15*, 58. https://doi.org/10.1186/s12874-015-0060-8

Rücker, G., Schwarzer, G., Krahn, U., König, J., & Schwarzer, M. (2016). *Package 'netmeta': Network Meta-Analysis using Frequentist Methods. 2019*.

Salanti, G. (2012). Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: Many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods*, *3*(2), 80–97. https://doi.org/10.1002/jrsm.1037

Salanti, G., Del Giovane, C., Chaimani, A., Caldwell, D. M., & Higgins, J. P. (2014). Evaluating the quality of evidence from a network meta-analysis. *PLoS One*, *9*(7), e99682. https://doi.org/10.1371/journal.pone.0099682

Salanti, G., Higgins, J. P., Ades, A., & Ioannidis, J. P. (2008). Evaluation of networks of randomized trials. *Statistical Methods in Medical Research*, *17*(3), 279–301. https://doi.org/10.1177/0962280207080643

Salanti, G., & Higgins, J. P. T. (2022). Network Meta-Analysis. In *Systematic Reviews in Health Research* (pp. 238–257). John Wiley & Sons, Ltd. https://doi.org/10.1002/9781119099369.ch13

Samtani, M. N., Vermeulen, A., & Stuyckens, K. (2009). Population Pharmacokinetics of Intramuscular Paliperidone Palmitate in Patients with Schizophrenia. *Clinical Pharmacokinetics*, *48*(9), 585–600. https://doi.org/10.2165/11316870-000000000-00000

Schneider-Thoma, J., Chalkou, K., Dörries, C., Bighelli, I., Ceraso, A., Huhn, M., Siafis, S., Davis, J. M., Cipriani, A., Furukawa, T. A., Salanti, G., & Leucht, S. (2022). Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: A systematic review and network meta-analysis. *Lancet*, *399*(10327), 824–836. https://doi.org/10.1016/s0140-6736(21)01997-8

Schwarzer, G. (2007). meta: An R package for meta-analysis. *R News*, *7*(3), 40–45.

Seemüller, F., Lewitzka, U., Bauer, M., Meyer, S., Musil, R., Schennach, R., Riedel, M., Doucette, S., & Möller, H.-J. (2012). The relationship of Akathisia with treatment emergent suicidality among patients with first-episode schizophrenia treated with haloperidol or risperidone. *Pharmacopsychiatry*, *45*(07), 292–296.

Sheehan, J. J., Reilly, K. R., Fu, D.-J., & Alphs, L. (2012). Comparison of the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. *Innovations in Clinical Neuroscience*, *9*(7–8), 17.

Shirley, M., & Perry, C. M. (2014). Aripiprazole (ABILIFY MAINTENA®): A review of its use as maintenance treatment for adult patients with schizophrenia. *Drugs*, *74*(10), 1097–1110. https://doi.org/10.1007/s40265-014-0231-7

Siafis, S., Tzachanis, D., Samara, M., & Papazisis, G. (2018). Antipsychotic drugs: From receptor-binding profiles to metabolic side effects. *Current Neuropharmacology*, *16*(8), 1210–1223.

Simpson, G. M., B., M., B., Gh., Angus, J. W. S., P., F. R. C., & M., D. P. (1970). A Rating Scale for Extrapyramidal Side Effects. *Acta Psychiatrica Scandinavica*, *45*(S212), 11–19. https://doi.org/10.1111/j.1600-0447.1970.tb02066.x

Taipale, H., Mehtälä, J., Tanskanen, A., & Tiihonen, J. (2018). Comparative Effectiveness of Antipsychotic Drugs for Rehospitalization in Schizophrenia—A Nationwide Study With 20-Year Follow-up. *Schizophrenia Bulletin*, *44*(6), 1381–1387. https://doi.org/10.1093/schbul/sbx176

Taipale, H., Tanskanen, A., Mehtälä, J., Vattulainen, P., Correll, C. U., & Tiihonen, J. (2020). 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry*, *19*(1), 61–68.

Thyssen, A., Rusch, S., Herben, V., Quiroz, J., & Mannaert, E. (2010). Risperidone Long-Acting Injection: Pharmacokinetics Following Administration in Deltoid Versus Gluteal Muscle in Schizophrenic Patients. *The Journal of Clinical Pharmacology*, *50*(9), 1011–1021. https://doi.org/10.1177/0091270009355156

Tong, Z., Li, F., Ogawa, Y., Watanabe, N., & Furukawa, T. A. (2018). Quality of randomized controlled trials of new generation antidepressants and antipsychotics identified in the China National Knowledge Infrastructure (CNKI): A literature and telephone interview study. *BMC Medical Research Methodology*, *18*(1), 1–11.

Velligan, D. I., Weiden, P. J., Sajatovic, M., Scott, J., Carpenter, D., Ross, R., & Docherty, J. P. (2009). *The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness*.

Veroniki, A. A., Tsokani, S., White, I. R., Schwarzer, G., Rücker, G., Mavridis, D., Higgins, J. P., & Salanti, G. (2021). Prevalence of evidence of inconsistency and its association with

network structural characteristics in 201 published networks of interventions. *BMC Medical Research Methodology*, *21*, 1–10.

Veroniki, A. A., Vasiliadis, H. S., Higgins, J. P. T., & Salanti, G. (2013). Evaluation of inconsistency in networks of interventions. *International Journal of Epidemiology*, *42*(1), 332–345. https://doi.org/10.1093/ije/dys222

Waller, D. G., Sampson, A., & Hitchings, A. (2021). *Medical pharmacology and therapeutics E-Book*. Elsevier Health Sciences.

Wan, X., Wang, W., Liu, J., & Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology*, *14*(1), 135. https://doi.org/10.1186/1471-2288-14-135

Wang, D., Schneider-Thoma, J., Siafis, S., Burschinski, A., Dong, S., Wu, H., Zhu, Y., Davis, J. M., Priller, J., & Leucht, S. (2023). Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. *Schizophr Bull*. https://doi.org/10.1093/schbul/sbad089

Wang, D., Schneider-Thoma, J., Siafis, S., Qin, M., Wu, H., Zhu, Y., Davis, J. M., Priller, J., & Leucht, S. (2024). Efficacy, acceptability and side-effects of oral versus long-acting-injectables antipsychotics: Systematic review and network meta-analysis. *European Neuropsychopharmacology*, *83*, 11–18. https://doi.org/10.1016/j.euroneuro.2024.03.003

Zheng, W., Cai, D.-B., Yang, X.-H., Zheng, W., Ungvari, G. S., Ng, C. H., Shi, Z.-M., Hu, M.-L., Ning, Y.-P., & Xiang, Y.-T. (2019). Adjunctive aripiprazole for antipsychotic-related

hyperprolactinaemia in patients with first-episode schizophrenia: A meta-analysis. *General Psychiatry*, *32*(5), e100091. https://doi.org/10.1136/gpsych-2019-100091

Zhu, Y., Zhang, C., Siafis, S., Zhuo, K., Zhu, D., Wu, H., Liu, D., Jiang, K., Wang, J., Leucht, S., & Li, C. (2021). Prolactin levels influenced by antipsychotic drugs in schizophrenia: A systematic review and network meta-analysis. *Schizophr Res*, *237*, 20–25. https://doi.org/10.1016/j.schres.2021.08.013

8. Appendix

8.1 Publication 1

This dissertation was adapted from my prior work, "Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. Schizophrenia Bulletin. https://doi.org/10.1093/schbul/sbad089 ". The reuse of this content complies with the copyright policy of the publisher (License Number: 5757120766804, Copyright © [Mar 27, 2024] by [OXFORD UNIVERSITY PRESS]), and written permission has been obtained.

OXFORD UNIVERSITY PRESS LICENSE TERMS AND CONDITIONS

Apr 11, 2024

This Agreement between Mr. Dongfang Wang ("You") and Oxford University Press ("Oxford University Press") consists of your license details and the terms and conditions provided by Oxford University Press and Copyright Clearance Center.

License Number	5757120766804
License date	Mar 27, 2024
Licensed Content Publisher	Oxford University Press
Licensed Content Publication	Schizophrenia Bulletin
Licensed Content Title	Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials
Licensed Content Author	Wang, Dongfang; Schneider-Thoma, Johannes
Licensed Content Date	Jun 23, 2023
Type of Use	Thesis/Dissertation
Institution name	
Title of your work	Comparative efficacy and tolerability of long-acting injectable vs. oral second-generation antipsychotics in acute schizophrenia
Publisher of your work	Technical University of Munich
Expected publication date	Apr 2024
Permissions cost	0.00 EUR
Value added tax	0.00 EUR
Total	**0.00 EUR**
Title of new work	Comparative efficacy and tolerability of long-acting injectable vs. oral second-generation antipsychotics in acute schizophrenia
Institution name	Technical University of Munich
Expected presentation date	Apr 2024
Requestor Location	Mr. Dongfang Wang Ismaninger Str. 22 81675 München München, 81675 Germany Attn: Mr. Dongfang Wang
Publisher Tax ID	GB125506730
Total	**0.00 EUR**

Terms and Conditions

STANDARD TERMS AND CONDITIONS FOR REPRODUCTION OF MATERIAL FROM AN OXFORD UNIVERSITY PRESS JOURNAL

1. Use of the material is restricted to the type of use specified in your order details.
2. This permission covers the use of the material in the **English** language in the following territory: *world*. If you have requested additional permission to translate this material, the terms and conditions of this reuse will be set out in clause 12.
3. This permission is limited to the particular use authorized in (1) above and does not allow you to sanction its use elsewhere in any other format other than specified above, nor does it apply to quotations, images, artistic works etc that have been reproduced from other sources which may be part of the material to be used.
4. No alteration, omission or addition is made to the material without our written consent. Permission **must** be re-cleared with Oxford University Press if/when you decide to reprint.
5. The following credit line appears wherever the material is used: author, title, journal, year, volume, issue number, pagination, by permission of Oxford University Press or the sponsoring society if the journal is a society journal. Where a journal is being published on behalf of a learned society, the details of that society **must** be included in the credit line.

6. For the reproduction of a full article from an Oxford University Press journal for whatever purpose, the corresponding author of the material concerned should be informed of the proposed use. Contact details for the corresponding authors of all Oxford University Press journal contact can be found alongside either the abstract or full text of the article concerned, accessible from www.oxfordjournals.org Should there be a problem clearing these rights, please contact journals.permissions@oup.com
7. If the credit line or acknowledgement in our publication indicates that any of the figures, images or photos was reproduced, drawn or modified from an earlier source it will be necessary for you to clear this permission with the original publisher as well. If this permission has not been obtained, please note that this material cannot be included in your publication/photocopies.
8. While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by Oxford University Press or by Copyright Clearance Center (CCC)) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and Oxford University Press reserves the right to take any and all action to protect its copyright in the materials.
9. This license is personal to you and may not be sublicensed, assigned or transferred by you to any other person without Oxford University Press's written permission.
10. Oxford University Press reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.
11. You hereby indemnify and agree to hold harmless Oxford University Press and CCC, and their respective officers, directors, employs and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.
12. Unless otherwise specified, inclusion under a Creative Commons license or any other Open Access license allowing onward reuse is prohibited.
13. Where permission to translate has been agreed, the credit line and any copyright/disclaimer notices provided by OUP shall be included on the same page as the Material, translated into the language of the new work, except for trademark names: Translated and reproduced by permission of Oxford University Press on behalf of the <Society Name>. Translation Disclaimer: OUP and the <Society Name> are not responsible or in any way liable for the accuracy of the translation. The Licensee is solely responsible for the translation in this publication/reprint.
14. Other Terms and Conditions:
v1.5

Questions? E-mail us at customercare@copyright.com.

Schizophrenia Bulletin
https://doi.org/10.1093/schbul/sbad089

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

Dongfang Wang[1,2], Johannes Schneider-Thoma[2], Spyridon Siafis[2], Angelika Burschinski[2], Shimeng Dong[2], Hui Wu[2], Yikang Zhu[3], John M Davis [4], Josef Priller [1,2], and Stefan Leucht[*,]

[1]Department of Sport and Health Sciences, Technical University of Munich, Munich, Germany; [2]Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany; [3]Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [4]Psychiatric Institute, University of Illinois at Chicago, Chicago, IL, USA and Maryland Psychiatric Research Center, Baltimore, MD, USA

* To whom correspondence should be addressed; Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Klinikum rechts der Isar, Ismaningerstrasse 22, 81675 Munich, Germany; tel: +49-89-4140-4249, fax: +49-89-4140-4888, e-mail: Stefan.Leucht@tum.de

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

Key words: efficacy/depots/safety/oral antipsychotics

Introduction

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

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

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

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

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

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

Methods

Search Strategy and Selection Criteria

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

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

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

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

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

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

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

Data Analysis

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

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

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

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

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

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

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

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

Results

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

Risk of Bias

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

Primary and Secondary Outcomes

Efficacy-Related Outcomes.

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

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

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

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

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

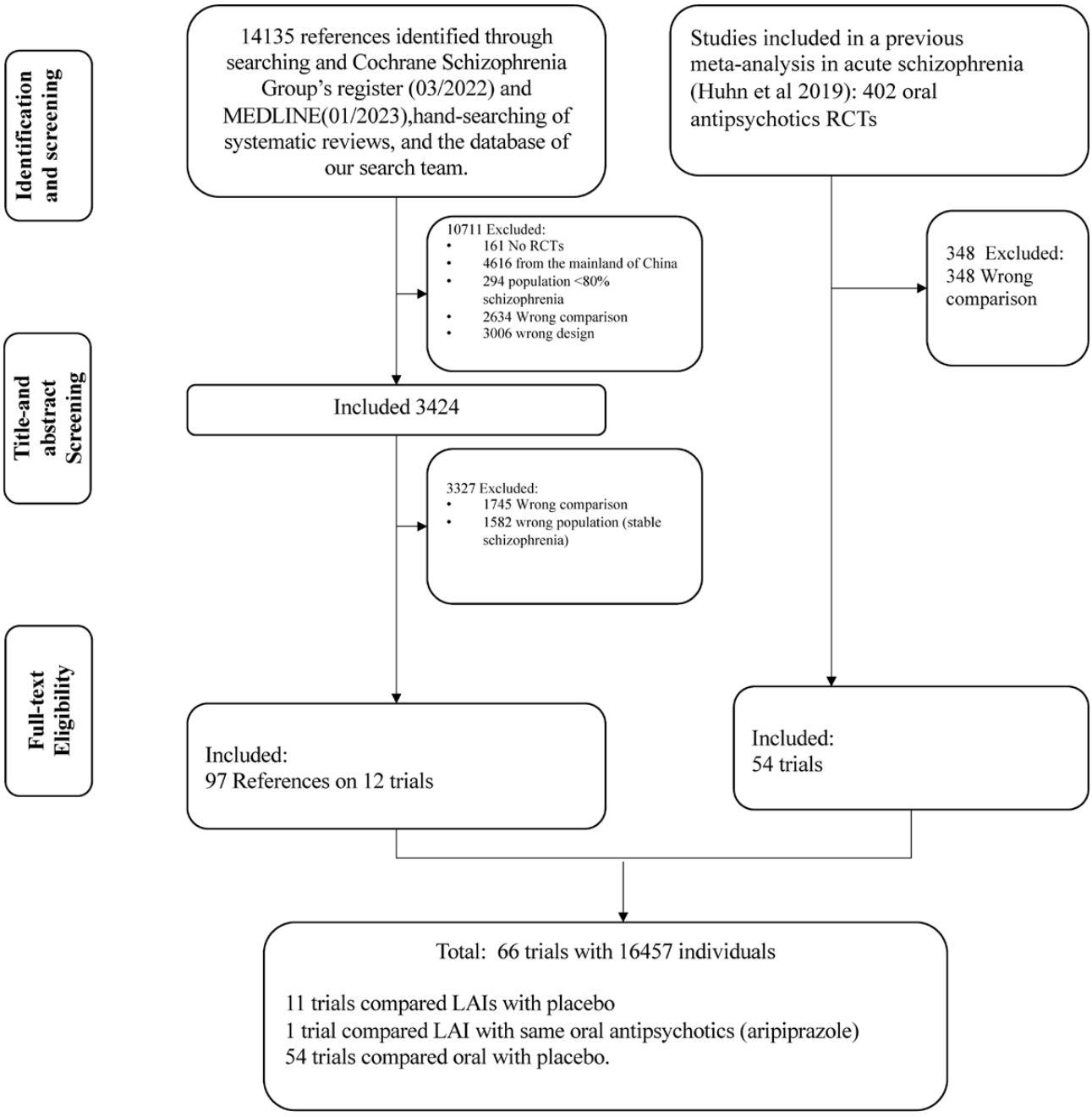

Fig. 1.

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

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

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

Side-Effect-Related Outcomes.

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

Table 1. LAIs Compared to Placebo on all Outcomes

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

Table 1. Continued

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

Table 1. Continued

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

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

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

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

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

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

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

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

Discussion

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

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

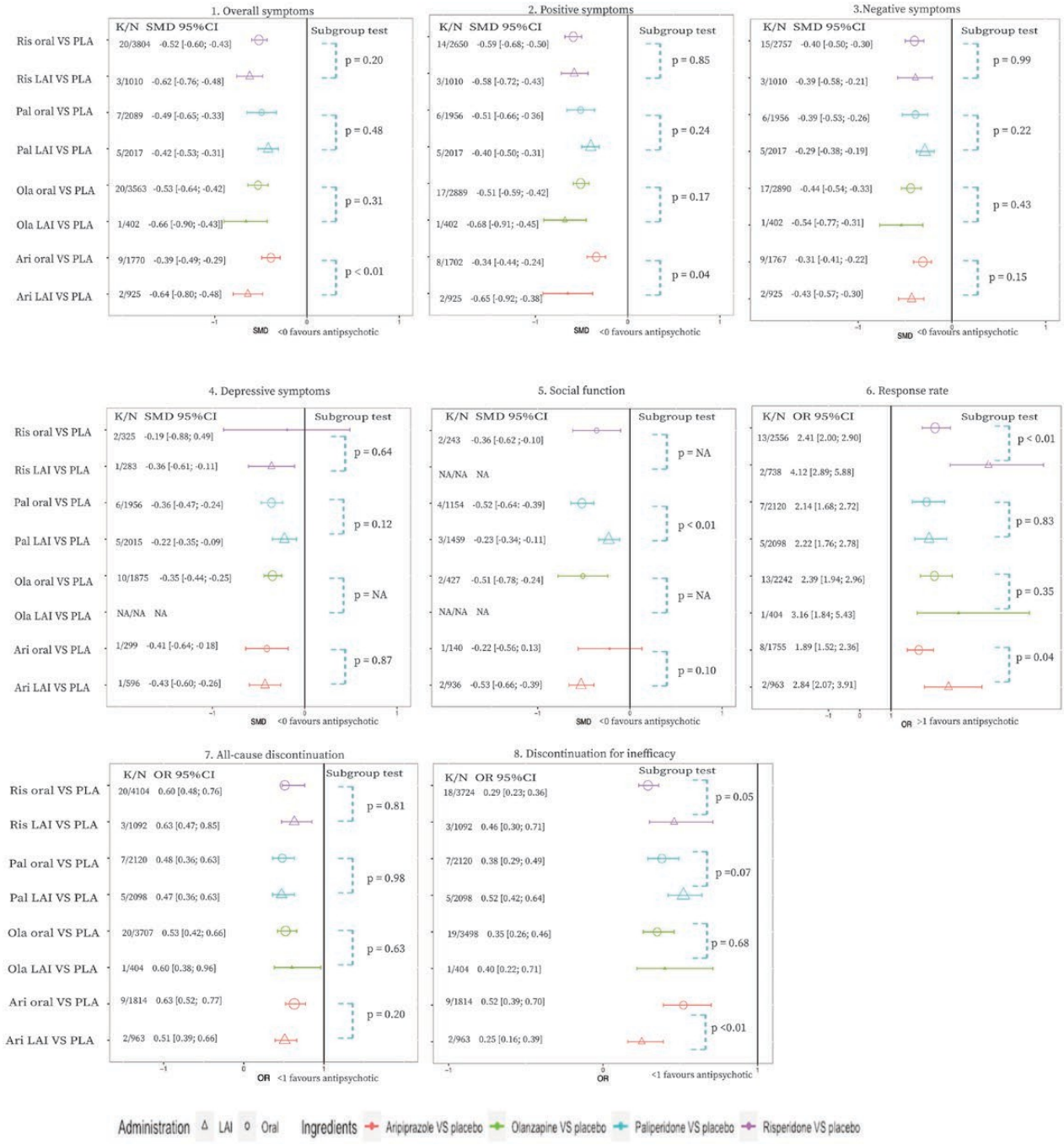

Fig. 2. Subgroup analysis for LAIs and the same oral formulations in terms of efficacy-related outcomes.

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

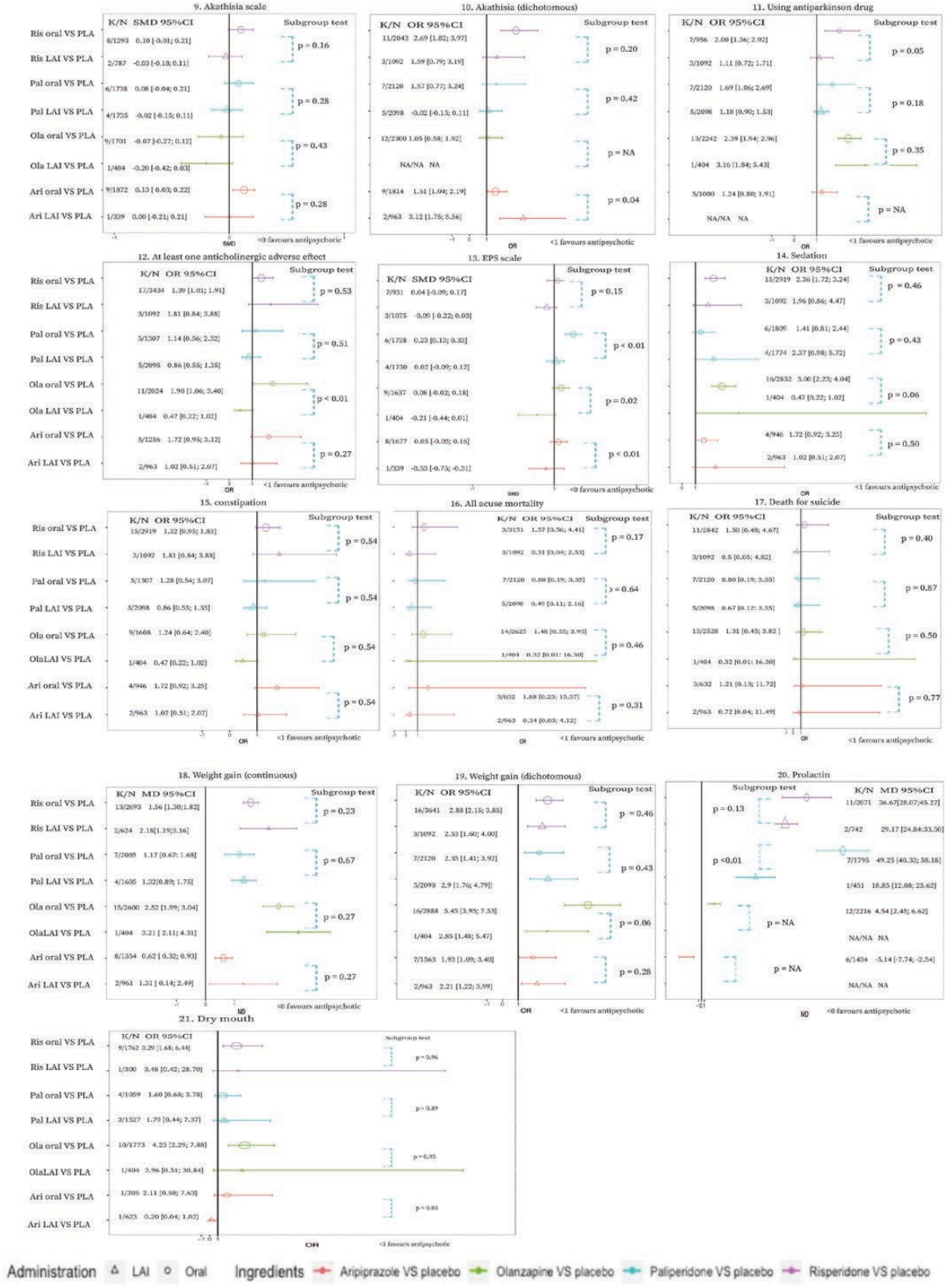

Fig. 3. Subgroup analysis for LAIs and the same oral formulations in terms of safetyrelated outcomes.

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

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

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

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

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

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

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

Supplementary Material

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

Acknowledgments

We would like to express our sincere gratitude to Mr.Liam H from the Technical University of Munich for proofreading the manuscript. DW would also like to acknowledge the China Scholarship Council (CSC) for providing his exchange scholarship for his doctorate study at the Technical University of Munich.

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

Funding

This work was supported by The National Natural Science Foundation of China (grant number: 82161138021) and the German Research Foundation (Deutsche Forschungsgemeinschaft grant number: 468853597).

Author Contribution

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

References

1. Huhn M, Nikolakopoulou A, Schneider-Tho J, *et al*. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2019;394(10202):939–951.
2. Garcia S, Martinez-Cengotitabengoa M, Lopez-Zurbano S, *et al*. Adherence to antipsychotic medication in bipolar disorder and schizophrenic patients: a systematic review. *J Clin Psychopharmacol.* 2016;36(4):355–371.
3. Lacro JP, Dunn LB, Dolder CR, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. *J Clin Psychiatry.* 2002;63(10):15489.
4. Higashi K, Medic G, Littlewood KJ, Diez T, Granström O, De Hert M. Medication adherence in schizophrenia: factors influencing adherence and consequences of nonadherence, a systematic literature review. *Ther Adv Psychopharmacol.* 2013;3(4):200–218.
5. Schneider-Thoma J, Chalkou K, Dörries C, *et al*. Comparative efficacy and tolerability of 32 oral and long-acting inject- able antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet.* 2022;399(10327):824–836.
6. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre–post studies. *Lancet Psychiatry.* 2021;8(5):387–404.
7. Ostuzzi G, Bertolini F, Tedeschi F, *et al*. Oral and long-acting antipsychotics for relapse prevention in schizophrenia-spectrum disorders: a network meta-analysis of 92 randomized trials including 22,645 participants. *World Psychiatry.* 2022;21(2):295–307.
8. Iyer S, Banks N, Roy M-A, *et al*. A qualitative study of experiences with and perceptions regarding long-acting injectable antipsychotics: part I—patient perspectives. *Can J Psychiatry.* 2013;58(5_suppl):14–22.
9. Kenakin T. *A Pharmacology Primer: Theory, Applications, and Methods*. Elsevier; 2009: 189–202.
10. Correll CU, Kim E, Sliwa JK, *et al*. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. *CNS Drugs.* 2021;35(1):39–59.
11. Spanarello S, Ferla TL. The pharmacokinetics of long-acting antipsychotic medications. *Curr Clin Pharmacol.* 2014;9(3):310–317.
12. Sheehan JJ, Reilly KR, Fu D-J, Alphs L. Comparison of the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. *Innov Clin Neurosci.* 2012;9(7-8):17–23.
13. Huang C-Y, Fang S-C, Shao Y-HJ. Comparison of long-acting injectable antipsychotics with oral antipsychotics and suicide and all-cause mortality in patients with newly diagnosed schizophrenia. *JAMA Netw Open.* 2021;4(5):e218810–e218810.
14. Leucht C, Heres S, Kane JM, Kissling W, Davis JM, Leucht S. Oral versus depot antipsychotic drugs for schizophrenia—a critical systematic review and meta-analysis of randomised long-term trials. *Schizophr Res.* 2011;127(1-3):83–92.
15. Lin C-H, Chan H-Y, Wang F-C, Hsu C-C. Time to rehospitalization in involuntarily hospitalized individuals suffering from schizophrenia discharged on long-acting injectable antipsychotics or oral antipsychotics. *Ther Adv Psychopharmacol.* 2022;12:20451253221079165.
16. Poloni N, Ielmini M, Caselli I, *et al*. Oral antipsychotic versus long-acting injections antipsychotic in schizophrenia spectrum disorder: a mirror analysis in a real-world clinical setting. *Psychopharmacol Bull.* 2019;49(2):17.

17. Wei Y, Yan VK, Kang W, *et al*. Association of long-acting injectable antipsychotics and oral antipsychotics with disease relapse, health care use, and adverse events among people with schizophrenia. *JAMA Netw Open.* 2022;5(7):e2224163 – e2224163.
18. Misawa F, Kishimoto T, Hagi K, Kane JM, Correll CU. Safety and tolerability of long-acting injectable versus oral antipsychotics: a meta-analysis of randomized controlled studies comparing the same antipsychotics. *Schizophr Res.* 2016;176(2-3):220–230.
19. Ostuzzi G, Bighelli I, So R, Furukawa TA, Barbui C. Does formulation matter? A systematic review and meta-analysis of oral versus long-acting antipsychotic studies. *Schizophr Res.* 2017;183:10–21.
20. Lin D, Thompson-Leduc P, Ghelerter I, *et al*. Real-world evidence of the clinical and economic impact of long-acting injectable versus oral antipsychotics among patients with schizophrenia in the United States: a systematic review and meta-analysis. *CNS Drugs.* 2021;35(5):469–481.
21. Kane JM, Schooler NR, Marcy P, *et al*. Effect of long-acting injectable antipsychotics vs usual care on time to first hospitalization in early-phase schizophrenia: a randomized clinical trial. *JAMA Psychiatry.* 2020;77(12):1217–1224.
22. Lian L, Kim DD, Procyshyn RM, Cázares D, Honer WG, Barr AM. Long-acting injectable antipsychotics for early psychosis: a comprehensive systematic review. *PLoS One.* 2022;17(4):e0267808.
23. Correll CU, Citrome L, Haddad PM, *et al*. The use of long-acting injectable antipsychotics in schizophrenia: evaluating the evidence. *J Clin Psychiatry.* 2016;77(suppl 3):1–24.
24. Marcus SC, Olfson M. Outpatient antipsychotic treat- ment and inpatient costs of schizophrenia. *Schizophr Bull.* 2008;34(1):173–180.
25. Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* 2015;162(11):777–784.
26. Rodolico A, Siafis S, Bighelli I, *et al*. Antipsychotic dose reduction compared to dose continuation for people with schizophrenia. *Cochrane Database Syst Rev.* 2022;11(11):CD014384–CD014384.
27. Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet.* 1997;350(9074):326–329.
28. Tong Z, Li F, Ogawa Y, Watanabe N, Furukawa TA. Quality of randomized controlled trials of new generation antidepressants and antipsychotics identified in the China National Knowledge Infrastructure (CNKI): a literature and telephone interview study. *BMC Med Res Methodol.* 2018;18(1):1–11.
29. Parry J. China vows to clamp down on academic fraud amid medical journal scandal. *BMJ.* 2017;357:j2970–j2970.
30. Leucht S, Li C, Davis JM, Bighelli I, Zhu Y, Furukawa TA. About the issue of including or excluding studies from China in systematic reviews. *Schizophr Res.* 2022;240:162–163.
31. Smail-Faugeron V, Tan A, Caille A, *et al*. Meta-analyses frequently include old trials that are associated with a larger intervention effect: a meta-epidemiological study. *J Clin Epidemiol.* 2022:145:144–153.
32. Leucht S, Leucht C, Huhn M, *et al*. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. *Am J Psychiatry.* 2017;174(10):927–942.
33. Janzen D, Bolton J, fan Kuo I, Leong C, Alessi-Severini S. Trends in the use of long-acting injectable antipsychotics in the province of Manitoba, Canada. *J Clin Psychopharmacol.* 2020;40(1):6–13.
34. Announcements D. National Library of Medicine. www.dailymed.nlm.nih.gov.
35. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry.* 2010;167(6):686–693.
36. Higgins JP, Thomas J, Chandler J, *et al*. 6.5.2.10 Combining groups. *Cochrane Handbook for Systematic Reviews of Interventions*. John Wiley & Sons; 2019.
37. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. *Am J Psychiatry.* 2020;177(4):342–353.
38. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987;13(2):261–276.
39. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. *Psychopharmacol Bull.* 1988:24:97–99.
40. Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry.* 1988;45(8):742–747.
41. Davidson J, Turnbull CD, Strickland R, Miller R, Graves K. The Montgomery-Åsberg Depression Scale: reliability and validity. *Acta Psychiatr Scand.* 1986;73(5):544–548.
42. Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull.* 1984;10(3):388–398.
43. Hall RC. Global assessment of functioning: a modified scale. *Psychosomatics.* 1995;36(3):267–275.
44. Chouinard G. The extrapyramidal symptoms rating scale. *Can J Neurol Sci.* 1980;7:233–244.
45. Inada T. Evaluation and Diagnosis of Drug-induced Extrapyramidal Symptoms. *Commentary on the DIEPSS and Guide to Its Usage*. Tokyo: Seiwa Shoten. 1996: 11–60.
46. Simpson G, Angus J. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand.* 1970;45(S212):11–19.
47. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry.* 1989;154(5):672–676.
48. Schwarzer G. meta: an R package for meta-analysis. *R News.* 2007;7(3):40–45.
49. Nasser AF, Henderson DC, Fava M, *et al*. Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, random- ized, double-blind, placebo-controlled, multicenter phase 3 study. *J Clin Psychopharmacol.* 2016;36(2):130–140.
50. Xiao L, Zhao Q, A-n Li, *et al*. Efficacy and safety of aripiprazole once-monthly versus oral aripiprazole in Chinese patients with acute schizophrenia: a multicenter, randomized, double-blind, non-inferiority study. *Psychopharmacology.* 2022;239(1):243–251.
51. Patel R, Chesney E, Taylor M, Taylor D, McGuire P. Is paliperidone palmitate more effective than other long-acting injectable antipsychotics? *Psychol Med.* 2018;48(10):1616–1623.
52. Cai Q, Patel C, Kim E, Connolly N, Tunceli O, El Khoury AC. Factors associated with the initiation of long-acting

injectable paliperidone palmitate versus aripiprazole among Medicaid patients with schizophrenia: an observational study. *Adv Ther.* 2019;36(4):858–869.

53. Fleischhacker WW, Gopal S, Lane R, *et al*. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. *Int J Neuropsychopharmacol.* 2012;15(1):107–118.
54. Pandina G, Lane R, Gopal S, *et al*. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35(1):218–226.
55. Li H, Rui Q, Ning X, Xu H, Gu N. A comparative study of paliperidone palmitate and risperidone long-acting injectable therapy in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35(4):1002–1008.
56. Winter-van Rossum I, Weiser M, Galderisi S, *et al*; EULAST Study Group. Efficacy of oral versus long-acting antipsychotic treatment in patients with early-phase schizophrenia in Europe and Israel: a large-scale, open-label, randomised trial (EULAST). *Lancet Psychiatry.* 2023;10(3):197–208.
57. Nasrallah HA, Weiden PJ, Walling DP, *et al*. Aripiprazole lauroxil 2-month formulation with 1-day initiation in patients hospitalized for an acute exacerbation of schizophrenia: exploratory efficacy and patient-reported outcomes in the randomized controlled ALPINE study. *BMC Psychiatry.* 2021;21(1):1–13.
58. Ostuzzi G, Bertolini F, Del Giovane C, *et al*. Maintenance treatment with long-acting injectable antipsychotics for people with nonaffective psychoses: a network meta-analysis. *Am J Psychiatry.* 2021;178(5):424–436.
59. Siafis S, Tzachanis D, Samara M, Papazisis G. Antipsychotic drugs: from receptor-binding profiles to metabolic side ef- fects. *Curr Neuropharmacol.* 2018;16(8):1210–1223.
60. He M, Deng C, Huang X-F. The role of hypothalamic H1 receptor antagonism in antipsychotic-induced weight gain. *CNS Drugs.* 2013;27(6):423–434.
61. Antel J, Hebebrand J. Weight-reducing side effects of the antiepileptic agents topiramate and zonisamide. *Appetite Control.* 2012;209:433–466.
62. Sugimoto Y, Yoshikawa T, Yamada J. Effects of periph- eral administration of 5-hydroxytryptamine (5-HT) on 2-deoxy-D-glucose-induced hyperphagia in rats. *Biol Pharm Bull.* 2002;25(10):1364–1366.
63. Tulipano G, Rizzetti C, Bianchi I, Fanzani A, Spano P, Cocchi D. Clozapine-induced alteration of glucose homeostasis in the rat: the contribution of hypothalamic-pituitary-adrenal axis activation. *Neuroendocrinology.* 2007;85(2):61–70.
64. Kane JM, Peters-Strickland T, Baker RA, *et al*. Aripiprazole once-monthly in the acute treatment of schizophrenia: findings from a 12-week, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry.* 2014;75(11):1254–1260.
65. Edinoff AN, Nix CA, Fort JM, *et al*. Sexual dysfunction in schizophrenia: a narrative review of the mechanisms and clinical considerations. *Psychiatry Int.* 2022;3(1):29–42.
66. Taylor D. Psychopharmacology and adverse effects of antipsychotic long-acting injections: a review. *Br J Psychiatry.* 2009;195(S52):s13–s19.
67. Samtani M, Haskins J, Alphs L, Sliwa J, Stuyckens K, Herben V, Vermeulen A. Maintenance dosing of once-monthly (4-weekly) paliperidone palmitate in schizophrenia: pharmacokinetic rationale based on population simulations. Paper presented at: Annual Meeting of the College of Psychiatric and Neurologic Pharmacists; 2009: 19–20.
68. Berwaerts J, Cleton A, Rossenu S, *et al*. A comparison of serum prolactin concentrations after administration of paliperidone extended-release and risperidone tablets in patients with schizophrenia. *J Psychopharmacol.* 2010;24(7):1011–1018.
69. McEvoy JP. Risks versus benefits of different types of long-acting injectable antipsychotics. *J Clin Psychiatry.* 2006;67(suppl 5):15–18.
70. Taipale H, Schneider-Thoma J, Pinzón-Espinosa J, *et al*. Representation and outcomes of individuals with schizophrenia seen in everyday practice who are ineligible for randomized clinical trials. *JAMA Psychiatry.* 2022;79(3):210–218.
71. Woodhead M. *80% of China's Clinical Trial Data are Fraudulent, Investigation Finds*. British Medical Journal Publishing Group (Online); 2016:355.
72. Guinart D, Misawa F, Rubio JM, *et al*. Outcomes of neuroleptic malignant syndrome with depot versus oral antipsychotics: a systematic review and pooled, patient-level analysis of 662 case reports. *J Clin Psychiatry.* 2020;82(1):13591.

8.2 Publication 2

European Neuropsychopharmacology 83 (2024) 11–18

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

REVIEW

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

Dongfang Wang [a,b], Johannes Schneider-Thoma [b], Spyridon Siafis [b,c], Mengchang Qin [b], Hui Wu [b], Yikang Zhu [d], John M Davis [e], Josef Priller [a,b,c,f,g], Stefan Leucht [b,c,*]

[a] Department Health and Sport Sciences, TUM School of Medicine and Health, Technical University of Munich, Munich, Germany
[b] Department of Psychiatry and Psychotherapy, Klinikum rechts der Isar, TUM School of Medicine and Health, Technical University of Munich, Munich, Germany
[c] German Center for Mental Health (DZPG), partner site München/Augsburg, Munich, Germany
[d] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[e] Psychiatric Institute, University of Illinois at Chicago, Chicago, IL, USA and Maryland Psychiatric Research Center, Baltimore, MD, USA
[f] Neuropsychiatry and Laboratory of Molecular Psychiatry, Charit´e – Universita¨tsmedizin Berlin and DZNE, Berlin, Germany
[g] University of Edinburgh and UK DRI, Edinburgh, UK

ARTICLE INFO

Keywords:
Long-acting injectable antipsychotics
Oral antipsychotics
Network meta-analysis
Acute schizophrenia

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 ef- ficacy 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 in- tervals: 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 effi- cacy 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 effica- cious 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

* To whom correspondence should be addressed at; Department of Psychiatry and Psychotherapy, the TUM School of Medicine and Health, Technical, University of Munich, Klinikum rechts der Isar, Ismaningerstrasse 22, 81675 Munich, Germany
E-mail address: Stefan.Leucht@tum.de (S. Leucht).

https://doi.org/10.1016/j.euroneuro.2024.03.003
Received 5 January 2024; Received in revised form 3 March 2024; Accepted 6 March 2024
Available online 15 March 2024

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 signif- icant 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 (τ^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).

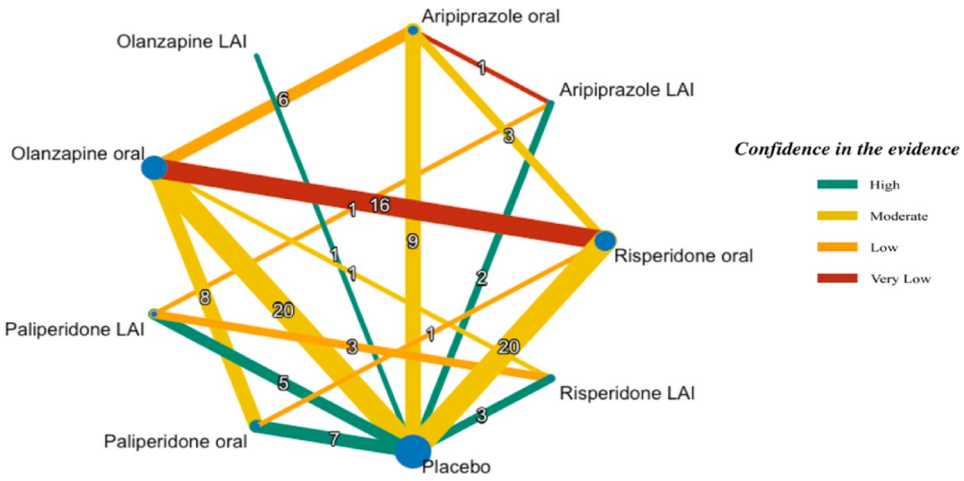

Fig. 1. Network plot for change in overall symptoms (primary outcome). The numbers on the lines represent the number of randomized controlled trials. Colors indicate the confidence in the evidence(CINeMA website): green=high, yellow=moderate, orange=low, red=very low.

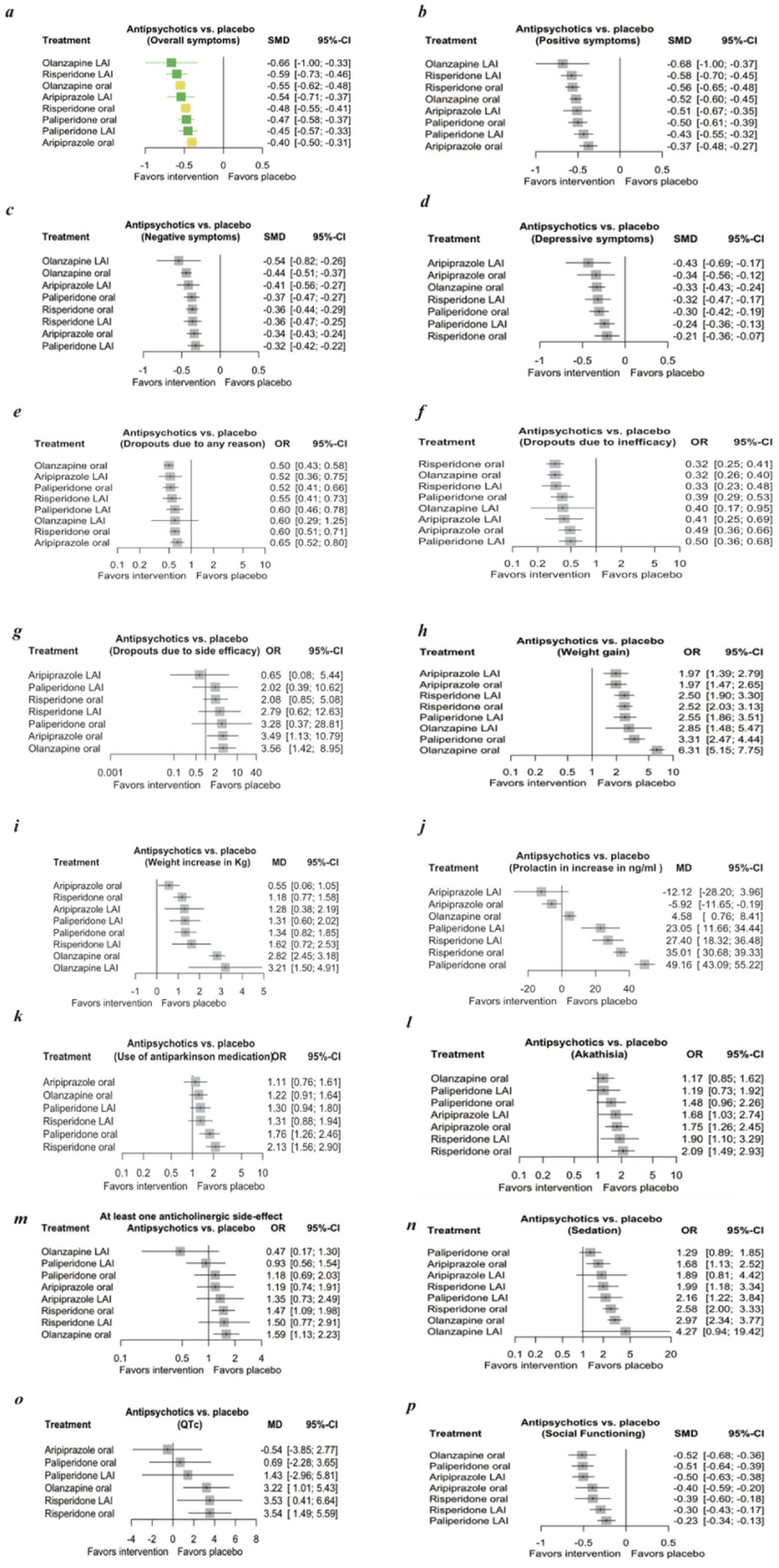

Fig. 2. Forest plots for comparing other drugs with placebo in terms of various outcomes. Note: For Fig. 2a changing overall symptoms, Colors indicate the confidence in the evidence(CINeMA website): green=high, yellow=moderate, orange=low, red=very low.

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 ($\tau 2 = 0.44$), 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 ($\tau 2 = 0.08$) 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 ques- tion about LAIs has so far been whether they reduce relapse rates compared to oral drugs in maintenance trials. The most up-to-date sys- tematic 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 .

Role of funding source

This work was supported by The National Natural Science Foundation of China (grant number: 82161138021) and the German Research Foundation (Deutsche Forschungsgemeinschaft grant number: 468853597); the National Natural Science Foundation of China and the German Research Foundation had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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.

Acknowledgments

Dongfang Wang was supported by a scholarship of the China Scholarship Council (CSC) for providing his exchange scholarship for his doctorate study at the Technical University of Munich. We thank Farhad Shokraneh for his help in doing the literature search.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2024.03.003.

References

Abi-Dargham, A., Laruelle, M., 2005. Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. Eur. Psychiatry 20, 15–27.
Bymaster, F.P., Nelson, D.L., DeLapp, N.W., Falcone, J.F., Eckols, K., Truex, L.L., Foreman, M.M., Lucaites, V.L., Calligaro, D.O., 1999. Antagonism by olanzapine of dopamine D1, serotonin2, muscarinic, histamine H1 and α1-adrenergic receptors in vitro. Schizophr. Res. 37, 107–122.
Ceraso, A., Lin, J.J., Schneider-Thoma, J., Siafis, S., Tardy, M., Komossa, K., Heres, S., Kissling, W., Davis, J.M., Leucht, S., 2020. Maintenance treatment with antipsychotic drugs for schizophrenia. The Cochrane database of systematic reviews 2020.
Collaborators, G.M.D., 2022. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry 9, 137–150.
Correll, C.U., Kim, E., Sliwa, J.K., Hamm, W., Gopal, S., Mathews, M., Venkatasubramanian, R., Saklad, S.R., 2021. Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. CNS Drugs 35, 39–59.
Dong, S., Schneider-Thoma, J., Bighelli, I., Siafis, S., Wang, D., Burschinski, A., Schestag, K., Samara, M., Leucht, S., 2023. A network meta-analysis of efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci.
Furukawa, T.A., Salanti, G., Atkinson, L.Z., Leucht, S., Ruhe, H.G., Turner, E.H., Chaimani, A., Ogawa, Y., Takeshima, N., Hayasaka, Y., 2016. Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. BMJ open 6, e010919.
He, M., Deng, C., Huang, X.-F., 2013. The role of hypothalamic H1 receptor antagonism in antipsychotic-induced weight gain. CNS Drugs 27, 423–434.
Higgins, J.P., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., Savović, J., Schulz, K.F., Weeks, L., Sterne, J.A., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 343.
Hoshino, O., 2005. Cognitive enhancement mediated through postsynaptic actions of norepinephrine on ongoing cortical activity. Neural Comput 17, 1739–1775.
Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., B¨ackers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., Leucht, S., 2019. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet 394, 939–951.
Huhn, M., Nikolakopoulou, A., Schneider-Thoma, J., Krause, M., Samara, M., Peter, N., Arndt, T., B¨ackers, L., Rothe, P., Cipriani, A., Davis, J., Salanti, G., Leucht, S., 2020. Comparative Efficacy and Tolerability of 32 Oral Antipsychotics for the Acute Treatment of Adults With Multi-Episode Schizophrenia: A Systematic Review and Network Meta-Analysis. Focus (Am Psychiatr Publ) 18, 443–455.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Kishimoto, T., Hagi, K., Kurokawa, S., Kane, J.M., Correll, C.U., 2021. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre–post studies. The Lancet Psychiatry 8, 387–404.
Koch, M.T., Carlson, H.E., Kazimi, M.M., Correll, C.U., 2023. Antipsychotic-Related Prolactin Levels and Sexual Dysfunction in Mentally Ill Youth: A 3-Month Cohort Study. J. Am. Acad. Child Adolesc. Psychiatry.
Kuroki, T., Nagao, N., Nakahara, T., 2008. Neuropharmacology of second-generation antipsychotic drugs: a validity of the serotonin–dopamine hypothesis. Prog. Brain Res 172, 199–212.
Lauriello, J., Lambert, T., Andersen, S., Lin, D., Taylor, C.C., McDonnell, D., 2008. An 8-week, double-blind, randomized, placebo-controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. J. Clin. Psychiatr. 69, 790–799.
Leucht, S., Crippa, A., Siafis, S., Patel, M.X., Orsini, N., Davis, J.M., 2020. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. Am. J. Psychiatry 177, 342–353.
Leucht, S., Li, C., Davis, J.M., Bighelli, I., Zhu, Y., Furukawa, T.A., 2022. About the issue of including or excluding studies from China in systematic reviews. Schizophr. Res. 240, 162–163.
Leucht, S., Schneider-Thoma, J., Burschinski, A., Peter, N., Wang, D., Dong, S., Huhn, M., Nikolakopoulou, A., Salanti, G., Davis, J.M., 2023. Long-term efficacy of antipsychotic drugs in initially acutely ill adults with schizophrenia: systematic review and network meta-analysis. World Psychiatry 22, 315–324.
Lu, Z., Sun, Y., Zhang, Y., Chen, Y., Guo, L., Liao, Y., Kang, Z., Feng, X., Yue, W., 2022. Pharmacological treatment strategies for antipsychotic-induced hyperprolactinemia: a systematic review and network meta-analysis. Transl Psychiatry 12, 267.
Mather, M., Clewett, D., Sakaki, M., Harley, C.W., 2016. Norepinephrine ignites local hotspots of neuronal excitation: How arousal amplifies selectivity in perception and memory. Behav. Brain Sci. 39, e200.

Nikolakopoulou, A., Higgins, J.P., Papakonstantinou, T., Chaimani, A., Del Giovane, C., Egger, M., Salanti, G., 2020. CINeMA: an approach for assessing confidence in the results of a network meta-analysis. PLoS Med 17, e1003082.
Overall, J.E., Gorham, D.R., 1988. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. Psychopharmacology bulletin.
Parry, J., 2017. China vows to clamp down on academic fraud amid medical journal scandal. BMJ: British Medical Journal (Online) 357.
Ragia, G., Dahl, M.-L., G Manolopoulos, V., 2016. Influence of CYP3A5 polymorphism on the pharmacokinetics of psychiatric drugs. Curr. Drug Metab. 17, 227–236.
Ressler, K.J., Nemeroff, C.B., 1999. Role of norepinephrine in the pathophysiology and treatment of mood disorders. Biol. Psychiatry 46, 1219–1233.
Rücker, G., Schwarzer, G., Krahn, U., Ko¨nig, J., Schwarzer, M., 2016. Package 'netmeta': Network Meta-Analysis using Frequentist Methods, 2019.
Salanti, G., Higgins, J.P., 2022. Network Meta-Analysis, Systematic Reviews in Health Research: Meta-Analysis in Context, pp. 238–257.
Sheehan, J.J., Reilly, K.R., Fu, D.-J., Alphs, L., 2012. Comparison of the peak-to-trough fluctuation in plasma concentration of long-acting injectable antipsychotics and their oral equivalents. Innovations in Clinical Neuroscience 9, 17.
Stahl, S.M., Djokic, G., 2023. Comparing the pharmacology and pharmacokinetics of antipsychotics: Choosing an antipsychotic and dosing a long-acting injectable. Eur. Neuropsychopharmacol. 73, 108–118.
Tong, Z., Li, F., Ogawa, Y., Watanabe, N., Furukawa, T.A., 2018. Quality of randomized controlled trials of new generation antidepressants and antipsychotics identified in the China National Knowledge Infrastructure (CNKI): a literature and telephone interview study. BMC Med. Res. Methodol. 18, 1–11.
Veroniki, A.A., Tsokani, S., White, I.R., Schwarzer, G., Rücker, G., Mavridis, D., Higgins, J.P.T., Salanti, G., 2021. Prevalence of evidence of inconsistency and its association with network structural characteristics in 201 published networks of interventions. BMC Med. Res. Methodol. 21, 224.
Wang, D., Schneider-Thoma, J., Siafis, S., Burschinski, A., Dong, S., Wu, H., Zhu, Y., Davis, J.M., Priller, J., Leucht, S., 2023. Long-Acting Injectable Second-Generation Antipsychotics vs Placebo and Their Oral Formulations in Acute Schizophrenia: A Systematic Review and Meta-Analysis of Randomized-Controlled-Trials. Schizophr. Bull.
Yohn, C.N., Gergues, M.M., Samuels, B.A., 2017. The role of 5-HT receptors in depression. Mol. Brain 10, 1–12.
Zhu, Y., Zhang, C., Siafis, S., Zhuo, K., Zhu, D., Wu, H., Liu, D., Jiang, K., Wang, J., Leucht, S., Li, C., 2021. Prolactin levels influenced by antipsychotic drugs in schizophrenia: A systematic review and network meta-analysis. Schizophr. Res. 237, 20–25.