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COMPARATIVE EFFICACY OF FIRST AND SECOND GENERATION LONG-ACTING INJECTABLE ANTIPSYCHOTIC IN SCHIZOPHRENIC PATIENTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Abstract

Introduction: Long-acting injectable antipsychotics (LAIA) can influence the course of treatment and have the potential to improve treatment adherence. This systematic review and network meta-analysis aimed to evaluate the efficacy of second-generation LAIAs (SG-LAIAs) and first-generation LAIAs (FG-LAIAs) in the treatment of schizophrenia. **Methods**: The present study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and is registered in Prospero (ID CRD42019128700). A comprehensive search was conducted in Medline, Embase, Web of Science, and Scopus databases. The search encompassed the period from June 17, 2020, with an update from June 2020 until September 14, 2021. **Results**: The standardized mean differences (SMDs) for four antipsychotics (80%) demonstrated significant reductions in PANSS scores compared to the placebo. The SMDs ranged from -0.72 (95% CrI -0.99 to -0.46) for haloperidol to -0.45 (-0.54 to -0.37) for paliperidone. Eight studies provided usable results for both negative and positive symptoms, involving a comparison of four antipsychotics. The SMDs for three antipsychotics (75%) significantly reduced negative symptoms compared to placebo, ranging from -0.40 (95% CrI -0.53 to -0.26) for aripiprazole to -0.32 (-0.44 to -0.19) for risperidone. The SMDs for the three drugs (100%) that significantly reduced positive symptoms compared to placebo ranged from -0.50 (95% CrI -0.63 to -0.37) for aripiprazole to -0.19 (-0.57 to 0.20) for zuclopenthixol. **Discussion**: Our findings suggest that all long-acting injectable antipsychotics, except for zuclopenthixol, exhibit comparable efficacy in symptom reduction. **Conclusions**: The majority of LAIAs demonstrate similar effectiveness in reducing overall symptoms, and the differences between individual LAIAs are not statistically significant.

Keywords: *Schizophrenia, antipsychotics, long-acting injectable antipsychotics*

Introduction

Schizophrenia, a severe chronic disorder, affects more than 21 million people worldwide[1,2] It has been recognized as a crucial mental health concern within the Grand Challenges in Global Mental Health Initiative.[3–6] The diagnosis of schizophrenia profoundly impacts life expectancy, with mortality rates increasing 2-3 times among younger individuals.[7]

Long-acting injectable antipsychotics (LAIA) have the potential to lead the course for schizophrenia treatment and to increase adherence, as well as reduce healthcare costs in the long term. Additionally, LAIAs have been associated with a lower risk of all-cause mortality, relapses, and hospitalizations compared to other antipsychotics.[8–11]

However, the question of LAIA efficacy in the treatment of schizophrenia remains uncertain. Previous systematic reviews comparing second-generation (SG) and first-generation (FG) LAIAs have primarily focused on mortality risk[12] or discontinuation rates.[13] Only one meta-analysis conducted by our research group[14] has specifically addressed efficacy and tolerability; nevertheless, results are considered preliminary due to the lack of evidence.

Considering the critical role of depot antipsychotics for long-term symptom stability, we performed a systematic review and network meta-analysis of randomized clinical trials (RCT) of patients with diagnosis of schizophrenia who are at least 18 years old with a minimum >12 weeks of treatment, in which SGA-LAIs were compared to FG-LAIs or placebo, to evaluate efficacy through clinimetry (PANSS global score, PANSS Positive subscale, and PANSS Negative subscale) and clinical criteria.

Methods

Search strategy and selection criteria

This network meta-analysis adheres to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (the PRISMA checklist is available in the supplementary material). The protocol for this study was registered in PROSPERO under the registration number CRD42019128700. An experienced librarian (EG), in collaboration with the lead researcher, developed and implemented the search strategy across multiple databases, including Medline, Embase, Web of Science, and Scopus, from database inception to June 17, 2020, with an update from June 2020 to September 14, 2021. Additionally, references from eligible studies and reviews were also screened for eligibility (search can be found in supplementary material Table 1).

To be included in this systematic review and network meta-analysis, studies were required to be randomized controlled trials (RCTs) investigating depot antipsychotics, both typical (first generation) and atypical (second generation), comparing them with each other, or placebo, and that also meet the following criteria: A) Inclusion of patients aged 18 years or older with a confirmed diagnosis of schizophrenia based on recognized diagnostic criteria, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Classification of Diseases 10th Edition (ICD-10); B) Evaluation of depot antipsychotics efficacy measured by various scales, including the Positive and Negative Symptoms Scale (PANSS), the Clinical Global Impression (CGI), the Brief Psychiatric Rating Scale (BPRS), as well as assessments of the quality of life, treatment adherence, suicide risk, aggressiveness, relapse, and rehospitalization; and C) Minimum treatment duration of ≥12 weeks. Studies were eligible for inclusion if they compared one LAIA treatment with another or with a placebo. Studies were excluded if they were nonrandomized clinical trials, involved patients with treatment-resistant schizophrenia or with a diagnosis other than schizophrenia, treatment durations of less than 12 weeks, or comparisons with oral antipsychotics or other psychotropic medications; studies not measuring efficacy were also not considered.

Three pairs of investigators (ESU, AFG, FCM, PLCM, RM, and PJGM) independently selected the studies, reviewed the primary reports and supplementary materials, extracted the relevant information from the included trials, and assessed the risk of bias. Before each screening phase, pilots were conducted to ensure satisfactory inter-rater reliability, with a Fleiss' kappa value exceeding 0.70.[15] Any discrepancies were resolved through consensus and arbitration by a panel of investigators within the review team (FCN and PLCM).

Outcomes of interest and data extraction

A web-based extraction form was developed and evaluated by all reviewers before data extraction. General information from the included studies (author names, publication year, country of origin, funding sources, and study design) was extracted. The primary efficacy outcome of interest was symptoms, assessed by changes in the Positive and Negative Syndrome Scale (PANSS) total score. The PANSS score was chosen as the primary measure due to its utility in defining symptom severity.[16,17]

Secondary efficacy outcomes encompassed changes in the PANSS Positive and Negative subscales.

Data analysis

Effect sizes for each treatment comparison reported in the included studies were estimated with odds ratios (OR). Subsequently, frequentist network meta-analysis models were constructed to examine the primary and secondary efficacy outcomes, with placebo serving as the reference group in all models.

Pairwise meta-analytical techniques were employed to estimate effect sizes based on the mean changes in the PANSS score reported in each study. If the degree of statistical heterogeneity was considerable (i.e., an I2 statistic >50%), both random and fixed effects models were explored. In cases of a significant Q test for heterogeneity, the random effects results were utilized.

In the network meta-analysis models, both random effects and fixed effects models were considered. The assumption of transitivity was assessed using network graphs containing at least one closed loop; inconsistency within the models was evaluated through the Q statistics and the netsplit techniques (i.e., comparing the difference between indirect and direct estimates in closed loops within the network graph). If a significant level of inconsistency was detected, the results from the random effects model were reported. Treatment comparisons without direct estimates did not allow for the assessment of inconsistency. Treatment ranking was conducted using the P-score technique, and the results were presented in a forest plot that depicted the pooled effect sizes of each treatment estimated using the network meta-analysis.

A significance level of $p < 0.10$ was considered indicative of statistical significance for all analyses of heterogeneity and inconsistency. For all other analyses, a threshold of $p < 0.05$ was considered. Data analysis was performed using the R software (version 4.1.2), in conjunction with RStudio (version 2022.02.03+492) and the following packages: "meta", "netmeta", and "dmetar".

Risk of bias

The risk of bias in the included studies was assessed following the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[18] Two independent reviewers (RM, SM), working in duplicate, evaluated the risk of bias for each individual RCT using the Cochrane risk of bias tool 2.0 (RoB2.0). This tool encompasses six domains, which include bias arising from the randomization process, deviations from the intended intervention, missing outcome data, mismeasurement of outcomes, and selection of reported results. According to the tool, the overall risk of bias for each study was classified as low, moderate (referred to as "with some concerns" in the tool), or high.[19] In the event of any discrepancies between the reviewers, resolution was achieved through consensus or, if necessary, by consulting a third reviewer.

GRADE assessment

The certainty of the evidence for outcomes with significant clinical significance, such as PANSS, positive symptoms, and negative symptoms was assessed and categorized using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[19] To determine the certainty of treatment effect estimates from the network meta-analysis, it was necessary to evaluate the level of evidence for both direct and indirect comparisons, as well as the best estimates derived from both direct and indirect evidence, including the network meta-analysis (combining direct and indirect evidence).[20] The quality of evidence was classified as high, moderate, low, or very low, reflecting the certainty of the evidence for the meta-analysis.

Results

The initial search included a total of 6,525 citations, from which 5,658 unique reports were identified. After screening the titles and abstracts, 215 full-text articles were retrieved, resulting in 17 studies with a total of 7,139 participants.

An additional search update was conducted from June 2020 to September 14, 2021, which identified 184 citations; only 26 articles were selected for full-text assessment, however, no articles met the inclusion criteria. The PRISMA flowchart depicting the study selection process, including reasons for exclusion, can be found in the Supplementary Material.

Among the 17 included studies, the treatment groups consisted of 7 studies using risperidone, 11 using paliperidone, 2 using aripiprazole, 1 using haloperidol, 1 using zuclopenthixol, and 10 placebo groups; with the most common comparison being between paliperidone and risperidone (5 studies).

Network Plot

Figure 1 shows the network plots, where nodes and edges represent the different LAIAs treatments, comparisons, and placebo. Overall, a well-connected network was observed. The examined comparisons focused on PANSS score and its

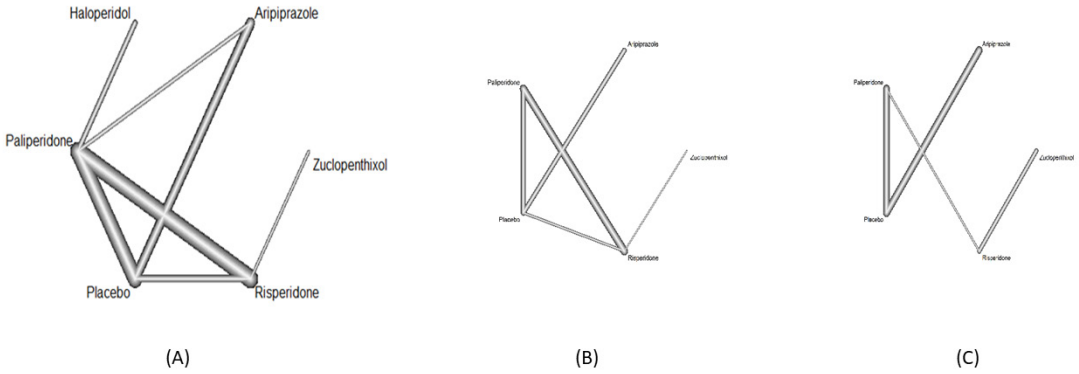

Figure 1. Network plot illustrating the meta-analysis results. A) PANSS total score, B) Negative symptoms score, C) Positive symptoms score.

Positive, and Negative symptoms subscales as reference as the primary efficacy outcome; secondary outcomes as results can be appreciated between various LAIA treatments and placebo. The most frequently examined comparisons in terms of PANSS score were between paliperidone *vs*. risperidone, as well as paliperidone vs. placebo. On the other hand, there were fewer direct comparisons between zuclopenthixol or haloperidol compared to other treatments.

Efficacy

Out of the 17 included studies, 15 reported usable results for PANSS score involving the comparison of five antipsychotics. The remaining two studies were excluded from subsequent analyses due to inconsistency with the rest of the LAIA treatments or placebo studies. The SMDs for the four antipsychotics (80%) that significantly reduced PANSS score compared with placebo ranged from –0.72 (95% CrI –0.99 to –0.46) for haloperidol to –0.45 (–0.54 to –0.37) for paliperidone, as shown in Figure 2. In hierarchical order, haloperidol, aripiprazole, risperidone, and paliperidone demonstrated significantly greater reduction in PANSS score compared to other drugs, contrary to the belief that newer antipsychotics are more effective than older ones. However, it is worth mentioning that there was only one study comparing haloperidol with paliperidone using the overall PANSS scale, without specifically assessing the efficacy of haloperidol in reducing negative and positive symptoms, limiting the results. Further details of the direct and indirect comparisons are presented in Figure 3.

Eight out of 11 studies assessed for negative symptoms reported usable results (four antipsychotics compared). The most common comparisons were between paliperidone and placebo (4 studies), as well as paliperidone and risperidone (3 studies). The SMDs for three antipsychotics (75%) that significantly reduced negative symptoms compared to placebo ranged between –0.40 (95% CrI –0.53 to –0.26) for aripiprazole to –0.32 (–0.44 to –0.19) for risperidone as depicted in Figure 2. In hierarchical order, aripiprazole, paliperidone, and risperidone demonstrated a significant reduction in negative symptoms compared to other drugs. Among the antipsychotics examined for negative symptoms, zuclopenthixol was the only one that did not show improvement in the negative symptoms subscale when compared to risperidone. Additional information on the direct and indirect comparisons is presented in Figure 3.

For the reduction of positive symptoms, 8 out of 11 studies provided usable results (involving the comparison of four antipsychotics). Similar to the negative symptoms section, the most common comparisons were between paliperidone and risperidone (3 studies) and paliperidone and placebo (4 studies). The SMDs for the three drugs (100%) that significantly reduced positive symptoms compared to placebo ranged from –0.50 (95% CrI –0.63 to –0.37) for aripiprazole to –0.19 (–0.57 to 0.20) for zuclopenthixol, as shown in Figure 2. In hierarchical order, aripiprazole, paliperidone, and risperidone demonstrated a significant reduction in positive symptoms compared to other drugs. Further details of the direct and indirect comparisons can be found in Figure 3.

In terms of the primary outcome, typical antipsychotic haloperidol ranked first in reducing PANSS scores, which is considered a crucial and comprehensive measure of efficacy. As for the secondary outcomes, aripiprazole exhibited the most

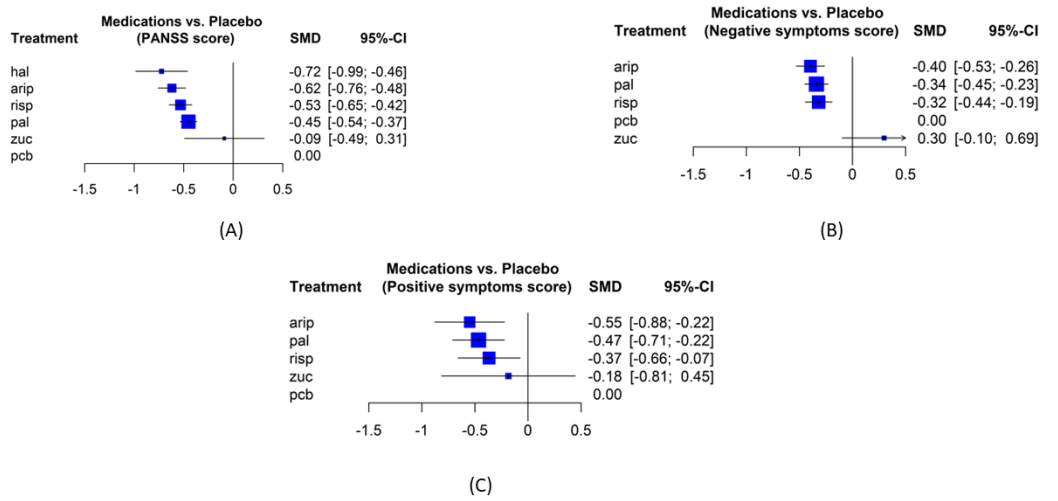

Figure 2. Treatment ranking based on the network meta-analysis of all trials. A) PANSS total score, B) Negative symptoms score, C) Positive symptoms score.

Note: Placebo serves as the reference group in both efficacy plots. SMD: standardized mean difference, OR: overall risk, Arip: ariperidone, Hal: haloperidol, Pal: paliperidone, Pcb: placebo, Risp: risperidone, Zuc: zuperidone, Flph: flupenthixol.

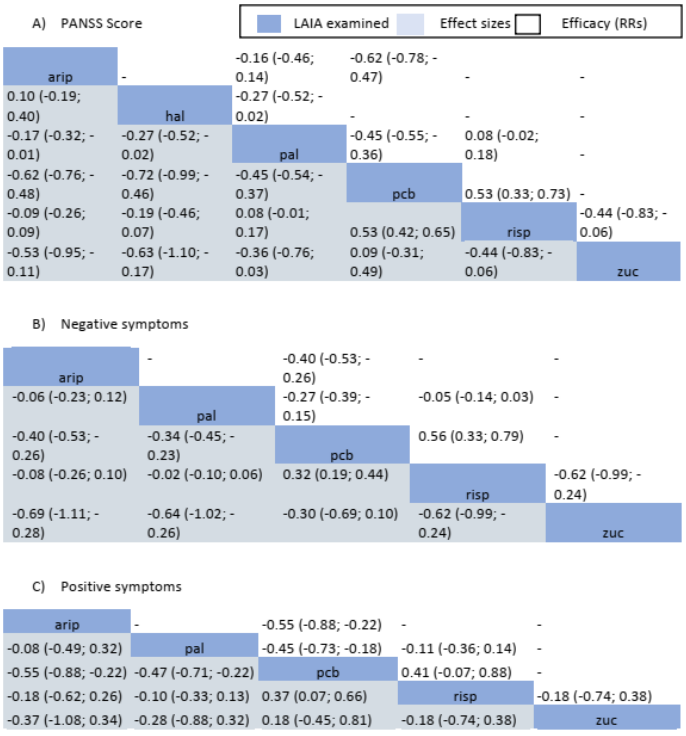

Figure 3. Direct and indirect comparisons in the network meta-analysis of all efficacy trials.

Note: The diagonal represents the various long-active injectable antipsychotics examined in the study. On the left side of the diagonal, effect sizes are presented as standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) and 95% prediction intervals, with each cell indicating values for a specific comparison between the LAIAs. On the right side of the diagonal, efficacy values are presented as relative risk (RR) with 95% CIs and 95% prediction intervals. Statistically significant data are shown in bold.

significant reductions in positive and negative symptoms and ranked second, following haloperidol, regarding PANSS score reduction. These findings indicate that one typical and one atypical antipsychotic emerged as leading treatments in terms of efficacy outcomes. These results are considered because the internal consistency of the network meta-analysis of these outcomes could be evaluated, and statistically significant differences were observed.

Discussion

In this network meta-analysis involving 17 studies and 7139 participants, we evaluated the comparative efficacy of eight different long-acting injectable antipsychotics and placebo in the treatment of schizophrenia. This study builds upon previous findings from pairwise meta-analyses that compared first versus second-generation LAIAs and examined various outcomes assessed by clinician-administered rating scales, such as positive and negative symptoms.

Our results indicate that, with the exception of zuclopenthixol, all LAIAs were more effective than placebo in reducing overall PANSS scores. The SMD ranged from –0.72 for haloperidol decanoate to –0.45 for paliperidone palmitate. However, these findings also suggest that the differences between individual LAIAs are not statistically significant. In our previous meta-analysis, we found that first and second-generation LAIAs had similar efficacy in reducing general psychopathology, although only three studies were included. The overlapping confidence intervals in this network meta-analysis further support the notion that most LAIAs have similar effectiveness in reducing overall symptoms, including haloperidol decanoate. Although node splitting assessment revealed no inconsistencies, only one study included haloperidol LAIA, which may limit the generalizability of these findings.

For positive and negative symptoms, the available data primarily originated from studies involving newer LAIAs such as paliperidone palmitate, aripiprazole, lauroxil, and risperidone microspheres, with all LAIAs exhibiting a similar effect in reducing these symptom dimensions. Even though this statement may hold true for the positive dimension, the evaluation of negative symptoms in the clinical trials included was based on the PANSS negative symptoms subscale, which does not differentiate between primary and secondary negative symptoms.[21] Therefore, it remains unclear whether the improvements observed in these core symptoms with LAIAs are directly related to their actions on the primary biochemical deficits in schizophrenia or if they are mediated through other mechanisms.

Regarding zuclopenthixol LAIA, it is worth noting that the presence of comorbid substance use disorder in the studied population may alter the homogeneity of the sample, potentially explaining the observed differences with other LAIAs.

Results obtained from the previous analyses suggest that older, less expensive LAIAs such as haloperidol decanoate exhibit comparable efficacy to second-generation LAIAs (aripiprazole, lauroxil, paliperidone palmitate, risperidone microspheres). However, only aripiprazole lauroxil (OR 0.2), risperidone microspheres (0.26), and paliperidone palmitate (0.39) demonstrated a significantly lower odds ratio (OR) for psychotic exacerbation. While clinician-administered rating scale improvements were commonly used as primary outcome measures in the included RCTs, relapse, and exacerbations are more frequently employed in clinical practice. Discrepancies in the criteria used across studies often prioritize the focus on rating scales, which may explain some differences observed between the PANSS mean changes and other outcomes.

Although the main focus of this manuscript is the efficacy of LAI´s antipsychotics, our protocol also encompasses data on safety and tolerability. Due to the heterogeneous nature of these studies (inconsistency among studies and evaluation methods), a separate analysis and discussion of the information pertaining to efficacy were necessary.

We conducted a search for various safety variables, including treatment-emergent adverse events (TEAEs), serious treatment-emergent adverse events (sTEAEs), extrapyramidal symptoms (EPS), use of antiparkinsonian drugs, clinically significant weight gain, suicide ideation, and attempts, pain at the injection site, discontinuation due to any cause, discontinuation due to adverse effects, and discontinuation due to lack of efficacy. However, given the limited literature available on most of these variables, we were only able to provide a critical review of the literature for the following variables.

Nonetheless, we can discuss some of the results included in our protocol, considering the significant relevance of the safety aspect of antipsychotics, particularly given the prevalence of metabolic alterations and neurologic adverse events associated with this class of drugs.

Regarding TEAEs and sTEAEs, aripiprazole and risperidone demonstrated favorable outcomes when compared to placebo, respectively. However, aripiprazole exhibited a non-protective effect against sTEAEs.

Only one study reported two deaths, with the majority of studies reporting a low incidence of mortality. Among LAIs, risperidone demonstrated the lowest mortality rate compared to placebo.

The all-cause discontinuation rate of LAIs indicated a protective effect for all treatments, except for haloperidol decanoate. Aripiprazole exhibited the highest rate of treatment continuation compared to placebo. Regarding discontinuation due to adverse events, aripiprazole had the lowest rate of treatment abandonment attributed to adverse events. Please refer to Figure 4 for detailed results.

In a meta-analysis conducted by our group,[14] we aimed to assess safety aspects related to the use of LAIs. Despite the numerous variables we attempted to evaluate, measures were often reported using different methods, making it difficult to draw conclusions regarding these variables. However, indirect and direct comparisons allowed for some insights to be gained. Regarding extrapyramidal symptoms and tardive dyskinesia, SG-LAIs were more likely to be associated with these adverse events compared to placebo, although this did not impact treatment discontinuation. The metabolic profile of LAIs was evaluated in only one study that conducted a metabolic assessment including measures of glucose, HbA1c%, and lipid profile over a 24-month period.[22]

This study compared haloperidol decanoate and paliperidone palmitate, with no differences observed within this comparison. These findings are of great interest, as SGA-LAIs are associated with metabolic parameters increase. However, SGA-LAIs were associated with weight gain and increased body mass index during long-term use.

Another study comparing paliperidone palmitate at different dosages (50mg, 100mg, and 150mg) versus placebo over a three-month period in acutely ill patients with schizophrenia evaluated safety outcomes. The overall incidence of TEAEs did not differ significantly between the groups. The frequency of extrapyramidal symptoms and glucose increase as TEAEs was low. However, clinically significant weight gain was more frequently observed in the paliperidone palmitate group (12% for 50 mg, 10% for 100 mg, 4% for 150 mg) compared to the placebo group (2%).[23]

A study comparing paliperidone palmitate (at dosages of 50mg, 100mg, and 150mg) and risperidone LAI (at dosages of 25mg, 37.5mg, and 50mg) over a 13-week period, assessing safety through TEAEs, clinical laboratory findings, EPS, electrocardiogram findings, and physical examination findings, found no significant differences between the two groups, with no new findings compared to previous studies.[24]

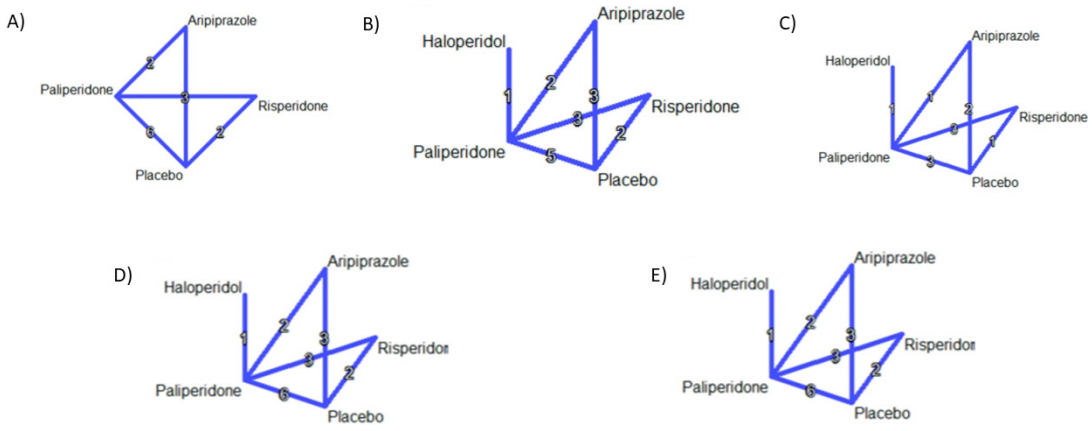

Figure 4. Safety outcomes. A) Treatment Emergent Adverse Events (TEAEs), B) Serious Treatment Emergent Adverse Events (STEAEs), C) Deaths, D) All-cause discontinuation, E) Discontinuation due to adverse events.

Strengths and limitations

To the best of our knowledge, this network meta-analysis represents the first attempt to compare the efficacy of first and second-generation long-acting injectable antipsychotics (LAIAs) and placebo in the treatment of schizophrenia. Previous meta-analyses in this area have primarily focused on mortality risk or discontinuation rates, without considering evidence regarding efficacy.

Overall, our analysis revealed no evidence of network inconsistency, while the risk of bias ranged from low to moderate across the included studies. The quality of evidence varied from very low to high. Detailed results pertaining to the risk of bias and the GRADE assessment can be found in the supplementary material.

When interpreting our findings, several limitations should be taken into account. We were unable to examine all variables that previous studies have identified as potentially influencing the efficacy of LAIAs, such as discontinuation rates, mortality, or adverse events. Our focus was specifically on assessing efficacy based on PANSS scores within the included trials, aiming for precision. However, we have identified other variables that may be worthwhile to explore in future research. Lastly, it should be noted that unpublished studies were not included in our analysis.

Conclusions

Clinical practice guidelines recommend individualized antipsychotic selection based on side effect profiles. The distinct pharmacokinetics of oral and depot antipsychotics pose challenges in managing adverse events, necessitating careful consideration before drug selection. In terms of PANSS scores, all LAIAs demonstrated similar performance compared to the placebo.

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