Comparative efficacy and tolerability of 31 oral and long-acting injectable antipsychotics for maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis

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SUMMARY

Background

Schizophrenia is a common, severe and usually chronic disorder. Maintenance treatment with antipsychotic drugs can prevent relapse but also causes side effects.

We aimed to compare efficacy and tolerability of antipsychotics during maintenance treatment among non-treatment resistant patients.

Methods

We conducted a systematic review with network meta-analysis (PROSPERO-registration-number: CRD42016049022) of randomised controlled trials (RCTs).

We included RCTs (≥12 weeks of follow-up) with adult participants in a stable state of schizophrenia and treated with antipsychotics (monotherapy; oral or long-acting-injectable) or placebo, but excluded RCTs with participants with specific comorbidities or treatment-resistance.

Two authors independently selected eligible RCTs from Cochrane-Schizophrenia-Group's specialized register and MEDLINE (last update 11/01/2021) and extracted aggregate data.

We synthesized relapse rates and 13 additional efficacy and tolerability outcomes using Bayesian network meta-analysis and graded results using the Confidence-In-Network-Meta-Analysis framework (CINeMA).

Findings

We identified 130 eligible RCTs (18152 participants) about 31 antipsychotics.

All antipsychotics were superior to placebo for relapse prevention with risk ratios ranging from 0·20 (95% Credible Interval 0·05 to 0·41) for paliperidone oral to 0·65 (0·16 to 1·14) for cariprazine oral (confidence in estimates moderate to low). However, there was no clear evidence for differences between antipsychotics.

This finding for relapse prevention was confirmed by additional efficacy outcomes and did not substantially change in sensitivity and network meta-regression analyses.

Differences between antipsychotics in tolerability outcomes were more distinct.

Interpretation

As we found no clear differences between antipsychotics for relapse prevention, we conclude that the choice of antipsychotic for maintenance treatment should be guided mainly by their tolerability.

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INTRODUCTION

Schizophrenia is among the most debilitating disorders worldwide.[1] It is often characterized by repeated relapses of psychotic symptoms.[2] As demonstrated by pairwise meta-analyses restricted to placebo-controlled trials,[3,4] continuation of antipsychotic drugs (maintenance treatment) after successful treatment of an acute episode reduces the risk of relapse. Therefore, it is recommended by guidelines[5,6] despite known side effects.[7]

Multiple antipsychotics are available with some similarity (dopamine antagonism) but also differences in pharmacodynamics (magnitude of dopamine antagonism, affinity for dopamine receptor subtypes and receptors of other neurotransmitters) [8] and pharmacokinetics, in particular oral and long-acting injectable (LAI) applications.

To date, it is unclear whether and to what extent these pharmacological differences find their expression in differences in efficacy to prevent relapse and side effects during maintenance treatment. Evidence from acute-phase randomised controlled trials (RCTs),[9] long-term RCTs,[10] and observational studies[11] suggest possible differences in efficacy and side effects. However, this evidence is either not specific for the maintenance-phase or scattered due to the limitations of pairwise meta-analyses or potentially confounded in observational studies. The only two network meta-analysis on relapse prevention conducted so far were limited by investigating LAIs only[12] and by the small number of included trials and antipsychotics.[13]

However, as relapses can have dramatic consequences, and as maintenance treatment is often used for years, sound knowledge about differences in efficacy and tolerability is highly relevant for both experts and general practitioners, who are frequently at the forefront of treatment of afflicted individuals.

In this context we conducted a comprehensive network meta-analysis of RCTs of oral and depot antipsychotics for maintenance treatment in schizophrenia.

METHODS

In reporting, we followed the PRISMA extension statement for network meta-analysis[14] (checklist in Appendix1).

The study protocol was registered on PROSPERO (CRD42016049022, Appendix2).

Search strategy and selection criteria

For this systematic review with network meta-analysis, we searched the Cochrane Schizophrenia Group's specialized register (compiled by monthly searches in multiple electronic databases, trial registries and conference proceedings), MEDLINE (for the last update on 11/01/2021) and related systematic reviews[3,4,9,10,13,15–17] (detailed search strategy in Appendix3.1).

We included blinded or non-blinded RCTs with a minimum duration of 12 weeks recruiting adults with schizophrenia or schizoaffective disorder with stable symptoms on antipsychotic treatment.

We included all newer antipsychotics (formerly called second-generation-antipsychotics) licensed in USA/Europe, and a selection of the most important older antipsychotics (formerly called first-generation antipsychotics) informed by an expert-survey[18] (Appendix3.2) and included in our previous network meta-analysis of antipsychotic treatment for acute symptoms,[9] namely: amisulpride, aripiprazole, asenapine, benperidol, brexpiprazole, cariprazine, chlorpromazine, clopenthixol, clozapine, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, levomepromazine, loxapine, lurasidone, molindone, olanzapine, paliperidone, penfluridol, perazine, perphenazine, pimozide, quetiapine, risperidone, sertindole, sulpiride, thioridazine, tiotixene, trifluoperazine, ziprasidone, zotepine, and zuclopenthixol.

We included these antipsychotics as monotherapy in any formulation (e.g. oral, LAI), with fixed or flexible dosing regimens, and in any dose, because relatively low doses may be sufficient to prevent relapses.[19]

We excluded follow-up-studies of trials that randomised acutely symptomatic participants (so-called continuation studies), because this design can violate randomisation. We also excluded trials in which all participants belonged to specific subgroups. This was the case for studies with participants that were children/adolescents or elderly participants or had treatment resistance, predominant negative symptoms, obesity, tardive dyskinesia, substance abuse, or depression. Moreover, we excluded studies from mainland China for quality concerns.[20]

Two reviewers (JS-T, CD, ACe, MH) independently screened the references and selected eligible trials; also two reviewers (JS-T, CD, ACe, IB, MH, SL) independently extracted data in a Microsoft Access database customized for this purpose allowing automatic comparison; disagreement was resolved in discussion among reviewers or

with SL. JS-T and SL contacted the corresponding authors and sponsoring pharmaceutical companies of included trials published in the past 30 years for missing data.

Data analysis

The primary outcome was the number of participants experiencing a relapse as defined in the original studies. If several relapse definitions were available, we preferred rating-scale based definitions to clinical judgement, need of rescue-medication, and study discontinuation due to inefficacy, in this order.

Additional efficacy-outcomes were change in overall symptoms and number of participants rehospitalised for psychiatric reasons, in remission and recovered.

Tolerability-outcomes were number of participants sedated (post-hoc), using antiparkinsonian medication at least once (as an indicator of extrapyramidal symptoms), and with tardive dyskinesia, and change in corrected QT-interval (QTc), body weight, and prolactin.

Composite outcomes (combining efficacy and tolerability) were change in overall functioning and quality of life, and number of participants with premature study discontinuation for any reason.

All outcomes were analyzed at study endpoint.

Dichotomous outcomes were synthesized using odds ratios (OR).[21,22] Continuous outcomes were synthesized with standardized mean differences (SMD) when different scales were used for the same outcome; otherwise we applied mean differences (MD).

Primarily, we performed random effects network meta-analyses in a Bayesian framework. For rare dichotomous outcomes, we performed fixed effects Mantel-Haenszel network meta-analyses in a frequentist setting.[23]

All effect size measures were accompanied by their 95% credible/confidence intervals (95%CrI/CI). To facilitate interpretation of results, we transformed ORs to risk ratios (RRs) using the average outcome with placebo,[24] as estimated by single-arm meta-analyses.

We evaluated the transitivity assumption by comparing the distribution of key study characteristics across studies grouped by comparison.

We evaluated heterogeneity by estimating common-τ (the standard deviation of the distribution of the true treatment effects across comparisons)[25] and by comparing the values with empirical evidence.[26,27]

We evaluated statistical inconsistency by performing a SIDE-test[28] for each comparison ($p<0.1$ for a difference between direct and indirect evidence as threshold for inconsistent comparisons) and a Design-by-Treatment-test.[29] When substantial evidence of inconsistency was found, we present only frequentist pairwise meta-analyses (random-effects inverse-variance model or fixed-effects Mantel-Haenszel model, depending on the frequency of the outcome).

We investigated potential sources of heterogeneity and inconsistency of the primary outcome by network meta-regression including information on baseline severity, study duration, relapse criteria, antipsychotic dose, use of enriched design, sponsorship, sample size (post-hoc), year of publication (post-hoc) and tapering of previous antipsychotics (post-hoc). Also post-hoc, we explored the influence of study duration and baseline weight on the outcome body weight and of proportion women on prolactin.

Moreover, we investigated by meta-regression whether the risk of relapse and the overall change of symptoms on placebo changed over the last decades (because an increase in placebo response was observed in acute-phase studies.[30]).

In sensitivity analyses, we excluded studies without a double-blind design, studies judged at high risk of bias and studies with a taper period of less than 3 weeks (post-hoc), and pooled oral and LAI applications (post-hoc).

We investigated small-trial-effects (that could be associated with publication bias) by a contour-enhanced funnel-plot[31] and a Harbord-test[32] of antipsychotics versus placebo.

All analyses were conducted in R (version 3.6.2).[33] We performed Bayesian network meta-analyses and network meta-regression analyses using self-programmed routines in the package `rjags`,[34] Mantel-Haenszel network meta-analyses using the `netmetabin` function from the package `netmeta`,[35] single-arm meta-analyses using the `metaprop` function and pairwise meta-analyses using the `metabin/metacont` functions from the package `meta`[36] (more details of the data analysis in Appendix4).

We assessed risk of bias for each outcome and study using Cochrane's Risk of Bias 2 tool.[37] The overall rating for each study was then included in the judgement of confidence in the estimates using the CINeMA-approach.[38]

Role of the funding sources

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We identified 4157 references. After title/abstract-screening, we assessed 1450 full-text articles and included 501 references on 130 studies with 18152 participants (Figure1).

115 studies with 17594 participants and 31 different antipsychotics provided usable data. The median average age of participants was 40 years (interquartile range (IQR) 38-43), the median percentage of women was 40% (IQR 30-50), the median study duration was 34 weeks (IQR 24-52) and 86% (99 of 115) of the studies were double-blind (more characteristics, details and references in Appendix5). We found no clear evidence of violations of the transitivity assumption when comparing characteristics of studies across comparisons (Appendix6). However, in most outcomes the number of studies per comparison was small and the assessment of transitivity is limited.

100 studies with 30 antipsychotics (n=16812 participants) contributed to the network meta-analysis of the primary outcome relapse (Figure2). All antipsychotics had a point estimate of reduced risk of relapse as compared to placebo (Figure3); for all, except cariprazine oral, lurasidone oral, and clopenthixol oral, 95%CrIs excluded no effect (of the latter three, only cariprazine outperformed placebo in pairwise meta-analysis, see Appendix7). The highest RR compared to placebo was observed for zuclopenthixol LAI (0.07) but this estimate was based on 2 small studies with 1 event in 56 participants and thus highly uncertain (95%CrI 0.00, 0.34). The other RRs ranged between 0·20 for paliperidone oral and 0·65 for cariprazine oral. There was no clear evidence of superiority of specific antipsychotics in terms of relapse prevention (Table1).

The results on overall symptoms, rehospitalisation, remission, recovery, quality of life, and overall functioning were similar to those in the primary outcome (i.e. superiority of antipsychotic drugs over placebo; no clear evidence of differences between antipsychotics), but data were partly sparse (Appendix8).

The results on tolerability outcomes described below are presented in Figure4 and Appendix8.

In 40 studies with 22 antipsychotics (n=11905), thioridazine oral, zotepine oral, ziprasidone oral, quetiapine oral, and haloperidol oral produced more sedation than placebo (RRs between 6·00 and 1·95), and than several other antipsychotics with 95%CrIs excluding no effect.

In 44 studies with 27 antipsychotics (n=10464) fluphenazine LAI, haloperidol oral and LAI and aripiprazole LAI were associated with more use of antiparkinsonian medication than placebo (RRs between 2·68 and 1·57) and than several other antipsychotics with 95%CrIs excluding no effect.

In most of the 25 studies reporting, tardive dyskinesia was a rare event occurring in 1% or less of the participants. Therefore, results are uncertain (wide confidence intervals), and no estimates could be provided for several antipsychotics with no events.

In 13 studies with 10 antipsychotics (n=2982) sertindole oral had a point estimate indicating higher QTc than placebo (MD 12 ms) and than several other antipsychotics with 95%-CrIs excluding no effect.

In 18 studies with 12 antipsychotics (n=4592) zotepine oral, olanzapine oral, brexpiprazole oral, paliperidone oral and LAI, quetiapine oral and asenapine oral had point estimates indicating increased body weight compared to placebo with 95%CrI excluding no effect (MDs ranged between 4·6 and 1·2 kg, due to high inconsistency based on pairwise meta-analyses versus placebo). Aripiprazole oral and LAI, and potentially cariprazine oral and lurasidone oral, appeared rather weight neutral.

In 12 studies with 10 antipsychotics (n=2860) paliperidone oral and LAI had point estimates indicating higher prolactin as compared to placebo with 95%CrIs excluding no effect (MDs 51 and 21 ng/ml again based on pairwise meta-analyses versus placebo). Aripiprazole oral and LAI, ziprasidone oral, brexpiprazole oral and cariprazine oral appeared prolactin neutral.

In 92 studies with 28 antipsychotics (n=15362) nearly all antipsychotics were associated with less premature study discontinuation than placebo with 95%CrIs excluding no effect (RRs between 0·15 and 0·70; see Appendix8). Olanzapine oral and several older antipsychotics – clopenthixol LAI, fluphenazine oral and LAI, penfluridol oral once weekly and pimozide oral – had less study discontinuation as compared to several other antipsychotics.

Heterogeneity in the primary outcome was relatively high with common-τ 0.69 (unit=OR), which is above the 75%-quantile of the empirical distribution for mental health outcomes;[27] heterogeneity in secondary outcomes was lower with common-τ's ranging between the 0%- and the 75% quantiles (absolute values and details in Appendix15).

The network meta-regressions of the primary outcome did not indicate important effects of potential treatment effect modifiers, except for a small effect of adjusting for baseline severity. In all analyses, the results were similar to the primary analysis (Appendix9) and heterogeneity remained (Appendix10). Also results did not change in the sensitivity analyses or when we increased statistical power by pooling oral and LAI applications (Appendix11). There was no indication of a change in risk of relapse or overall symptom score in the placebo groups over the last decades (Appendix12).

Inconsistency in direct and indirect estimates was low for the outcomes relapse, overall symptoms, rehospitalisation, sedation, use of antiparkinson medication, and QTc; moderate for study discontinuation, and high for body weight, prolactin, and quality of life (Appendix13, for other outcomes not estimable). For the high inconsistency group, we refrained from presenting result of network meta-analysis and explored the role of potential treatment effect modifiers in post-hoc network meta-regression analyses, but found no explanations (Appendix14 and 15).

We found no indication of publication bias (funnel plot in Appendix16, Harbord-test p=0·54).

For the primary outcome overall risk of bias was low for 10% (10 of 100), some concerns for 63% (63 of 100) and high for 27% (27 of 100) of studies (details and judgements for secondary outcomes in Appendix17).

We present the judgement of the confidence in estimates (details in Appendix18) as a color code in the league tables and forest plots. For the primary outcome relapse, it was moderate to low.

DISCUSSION

To prevent psychotic episodes and its potentially dramatic psychosocial consequences, individuals with schizophrenia often take maintenance treatment with antipsychotic drugs for years. However, antipsychotics also have multiple side-effects which can be very unpleasant and increase non-adherence, stigmatization, physical morbidity and potentially also mortality,[7] although no-use is associated with the highest mortality.[39,40] Therefore, knowledge about comparative efficacy and tolerability during maintenance treatment is crucial to guide drug choice.

We found virtually all antipsychotics to be superior to placebo for prevention of relapse (only for cariprazine oral, lurasidone oral and clopenthixol LAI 95%CrIs included a small possibility of no effect), but no clear evidence for differences between antipsychotics. Differences between antipsychotics in tolerability outcomes were more distinct (in Appendix19 results of the specific outcomes are discussed in more detail).

The only other, much smaller (56 trials, 18 antipsychotics) and outdated network meta-analysis comparing oral and LAI antipsychotics for relapse prevention,[13] a recent network meta-analysis on relapse prevention limited to LAI antipsychotics,[12] and a recent pairwise meta-analysis of long-term-RCTs with very broad inclusion criteria limited to oral second-generation antipsychotics[10] basically also revealed no clear differences in efficacy for relapse prevention between most antipsychotics. Some of the very few differences between antipsychotics reported from these analyses did not match with previous knowledge[9] and were not consistent in sensitivity analyses and across reviews, e.g. aripiprazole being among the most efficacious antipsychotics[12] (in Appendix20 we present a more thorough discussion of these previous meta-analyses). In contrast, our ranking was similar to the one found in our NMA on acute treatment.[9] For example, olanzapine, paliperidone and risperidone ranked among the more efficacious drugs and quetiapine, lurasidone and partial dopamine agonists were among the less efficacious drugs. Some differences in point estimates were also substantial, e.g. OR 0.20 for olanzapine and paliperidone versus placebo compared to 0.47 for quetiapine versus placebo, but the credible intervals indicated remaining probabilities of no-difference between these drugs (Table1). Importantly, we did not find a change in response to placebo over the years - a phenomenon observed in acute-phase trials that could lead to findings of lower efficacy of more recently investigated antipsychotics.[30]

Nevertheless, given the challenges of meta-analyses of relapse prevention in general (see limitations below) and in the absence of clear differences between antipsychotics (wide and overlapping credible intervals), there is too much uncertainty for recommendations based on efficacy in our judgement. Differences in side-effects were

clearer and in line with evidence from acute-phase trials.[9] As many patients must take antipsychotics for a very long time, side-effect profiles should be crucial criteria for drug choice in the maintenance phase. Primarily dopaminergic first-generation antipsychotics such as haloperidol lead to very unpleasant extrapyramidal side-effects which are visible and thus stigmatizing. The newer second-generation antipsychotics are less prone to these Parkinson-like symptoms, but many cause weight gain which can have dramatic consequences such as cardiovascular problems and diabetes. Drugs like partial-dopamine agonists, lurasidone and ziprasidone have an overall more benign tolerability profile, but at the end all antipsychotics have some side-effects meaning that drug choice must be tailored to the clinical scenario and the preferences of each individual patient.

As in previous pairwise meta-analyses of RCTs[16,17] LAI antipsychotics were not more efficacious than their oral counterparts which could be explained by the fact that patients who consent to randomised trials are adherent per se and the procedures in trials, such as intense visits, may improve adherence further and reduce the benefits of LAIs. In contrast, observational studies in real-world settings,[11] a recent trial randomising hospitals and not patients,[41] and a recent pairwise meta-analysis combining randomised and observational studies[42] found superiority of LAIs for relapse prevention. Again, in the latter analysis, the effect was mainly driven by observational studies, whereas the effect found in RCTs with very broad inclusion criteria was very small (risk difference 2% between LAIs and oral antipsychotics).

The results of our analysis must be considered in light of the following limitations.

First, despite the high overall number of studies and participants (130 RCTs with 18152 participants), only few trials were available for each of the 31 individual drugs. Such comparably thin networks are limited in statistical power. Moreover, interventions which are connected to the network without closed loops are prone to outlying results. Thus, network plots and the number of trials and participants available for each drug and outcome reported in our figures should be considered when interpreting the result of individual comparisons (see also Appendix 18). Nevertheless, when we pooled oral and LAI formulations in a sensitivity analysis to increase statistical power and connectivity, the results did not materially change for the primary outcome (Appendix10).

Second, although we used concise inclusion criteria, trials of long-term treatment with antipsychotics vary more in study design, outcome parameters and participant characteristics than acute-phase trials. Additional analyses in which we investigated potential effect modifiers including baseline severity, study duration, relapse criteria, antipsychotic dose, enriched design, sponsorship, year of publication, sample size, tapering, blinding, risk of bias, and relapse-risk on placebo, overall corroborated the primary results. Nevertheless, unresolved heterogeneity and

inconsistency, imprecision of the estimates, attrition (which is typically high in long-term-RCTs), "soft" and subjective rating-scale based outcomes and potentially compromised blinding by side effects reflect intrinsic limitations of schizophrenia trials and the meta-analytical approach. They reduce the reliability of data interpretation and led to mainly low to moderate confidence in the estimates according to CINeMA. The use of a core outcome set (COS) as it has been developed by the ICHOM working group on psychotic disorders[43] could help to standardize future relapse prevention studies.

Third, information on most older drugs is generally limited in terms of number of trials and sample size. Specifically, information on QTc, prolactin and weight gain is sparse for older drugs, and quality of life and social functioning, which might be highly relevant for individuals with schizophrenia, because they are composites of efficacy and side-effects, have only been assessed in recent trials. For side effects that occur early after initiation of treatment but potentially diminish over time, such as sedation and extrapyramidal symptoms (indicated by use of antiparkinsonian medication)[44,45], the adverse event results may rather reflect early stages of maintenance treatment. In contrast, tardive dyskinesia which occurs with an annual rate of only 2.6% across second-generation antipsychotics[46] would require longer trials. The NMA on acutely ill patients[9] which yielded similar treatment rankings but included more trials can be used together with the current one to inform side effect profiles.

Fourth, the NMA is mainly based on trial populations with a substantial history of illness given their age distribution (Appendix5.1 and 6.10) and trials in specific subgroups, such as treatment-resistant participants, were excluded (Figure1). Thus, no study on clozapine, which is considered to be the most efficacious antipsychotic,[47] met the inclusion criteria.

Fifth, the funnel-plot and Harbord-test did not suggest publication/small-trial bias. However, given that we searched a period of more than 50 years, it is likely that there are unpublished trials (in addition to the three trials which reported no results indicated in Appendix5.3).

While the range of point estimates comparing drugs with placebo for relapse prevention was large, we suggest that treatment choice should primarily consider side effects, because there were few clear differences in efficacy between antipsychotics. This choice should take into account the needs and preferences of the individual patient. For example, weight gaining drugs should be avoided in patients with diabetes, while patients who live in a partnership may not want to take a prolactin increasing drug and in patients with cardiac problems QTc prolonging drugs are not first choice. If a patient had no important side effect in the acute phase, it might be wise to stay on the same drug. This is particularly important because maintenance treatment must often be taken for many years

so that side-effects can accumulate. Finally, heterogeneity and inconsistency in some outcomes suggest that there are moderators of treatment effects which need to be identified by individual-patient-data meta-analyses and then implemented in treatment decisions.

RESEARCH IN CONTEXT

Evidence before this study

Maintenance treatment with antipsychotic drugs can prevent recurrence of psychotic symptoms (relapse) in patients with schizophrenia and is thus recommended by clinical guidelines. However, it is unclear whether and to what extend these drugs differ in terms of efficacy for relapse prevention and side effects during maintenance treatment.

We searched MEDLINE (last search 16.4.2021) with the search term "schizophrenia AND antipsychotic AND (maintenance OR relapse)" and filter "Article type: Meta-analysis", and with the search term "network meta-analysis AND schizophrenia AND antipsychotic" and inspected 204 references.

We found one small and outdated (56 trials, 18 antipsychotics, published 2016) network meta-analysis of randomized controlled trials (RCTs) including oral and long-acting injectable (LAI) antipsychotics, and one recent network meta-analysis investigating LAIs only. These works and also the most recent pairwise meta-analysis of RCTs, yielded no clear evidence for differences between individual antipsychotics. The reported very few differences in terms of relapse prevention were not consistent between these analyses and also not confirmed by sensitivity analyses.

Added value of this study

We conducted a systematic review and network meta-analysis including 130 RCTs (18152 individuals) with stabilized symptoms of schizophrenia and compared 31 oral and LAI antipsychotics for 14 different efficacy and tolerability outcomes. For the primary outcome "relapse", we additionally investigated multiple potential treatment effect modifiers.

Also in this comprehensive network meta-analysis, we found no clear evidence for superiority of specific antipsychotics in terms of relapse prevention or other efficacy outcomes.

In contrast, differences in side effects between antipsychotics were more distinct.

Implication of all the available evidence

In the absence of evidence indicating clear differences in relapse prevention between antipsychotics, we suggest that for the choice of antipsychotic for maintenance treatment, clinicians should consider primarily the side effects.

Contributors

SL was the principle investigator who supervised the project and obtained the funding. SL, JS-T, JMD, TAF, ACi, KC and GS designed the systematic review and developed the plan for data analysis. JS-T, CD, ACe, MH and SL screened the literature search, acquired reports of relevant trials and selected included studies. JS-T, CD, ACe, IB, MH, and SL extracted and verified the data. JS-T and SL contacted trial investigators and pharmaceutical companies for additional data. KC and GS performed the network meta-analyses and network meta-regression-analyses. JS-T, SS, JMD, ACi, TF, KC, GS and SL analyzed and interpreted the data. JS-T and SL drafted the report. All authors critically reviewed the report for important intellectual content and approved the final submitted version. JS-T and SL were responsible for the decision to submit the manuscript.

Declaration of interest

In the past 3 years, SL has received honoraria as a consultant/advisor from Alkermes, Angelini, Gedeon Richter, Lundbeck, Recordati, ROVI, Sandoz, and TEVA, and speaker's honoraria from Angelini, Eisai, Gedeon Richter, Janssen, Johnson & Johnson, Lundbeck, Merck Sharp and Dome, Otzuka, Recordati, SanofiAventis, Sunovion, and Medichem. TAF reports grants and personal fees from Mitsubishi-Tanabe, personal fees from MSD, personal fees from SONY, grants and personal fees from Shionogi, outside the submitted work; In addition, TAF has a patent 2018-177688 concerning smartphone CBT apps pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. Andrea Cipriani has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma, outside the submitted work. MH has received honoraria as advisor from Recordati. The other authors have no conflict of interest to declare.

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Data sharing

Some data included in the analysis have been shared confidentially by the original authors and pharmaceutical companies. We will support reasonable requests to obtain such data.

LEGENDS TO FIGURES AND TABLES

Figure1: Study selection

*References of handsearched reviews[3,4,9,10,13,15–17]. *The group "specific subgroup" comprises references to studies in which all participants (according to the inclusion criteria of the original studies) were children and adolescents (3 references) or elderly (3), or had treatment resistance (106), predominant negative symptoms (38), obesity (12), tardive dyskinesia (11), substance abuse (9), or depression (6),*

Figure2: Network plot of the primary outcome relapse.

Lines link treatments with direct comparisons in trials; thickness of lines corresponds to the number of trials evaluating the comparison; size of the nodes corresponds to the number of participants assigned to the treatment.

Abbreviations: LAI= long-acting injectable

Figure3: Forest plot of antipsychotic drugs versus placebo for the primary outcome relapse

Effect sizes are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is placebo. Risk ratios below 1 are in favor of antipsychotic treatment. Colors of lines reflect the result of the assessment of the confidence in estimates: green=high confidence in estimates, blue=moderate, orange=low, red=very low.

Abbreviations: n=number of patients, RR=risk ratio, 95%CrI=95% credibility interval, LAI=long-acting injectable, ARI=Aripiprazole, ASE=Asenapine, BRE=Brexpiprazole, CAR=Cariprazine, CPZ=Chlorpromazine, CPX=Clopenthixol, FPX=Flupentixol, HAL=Haloperidol, ILO=Iloperidone, LUR=Lurasidone, OLA=Olanzapine, PAL=Paliperidone, PEN=Penfluridol, PIM=Pimozide, PLB=Placebo, QUE=Quetiapine, RIS=Risperidone, SER=Sertindole, THIOR=Thioridazine, TIOT=Tiotixene, TRI=Trifluoperazine, ZIP=Ziprasidone, ZOT=Zotepine, ZUC=Zuclopenthixol.

Table1: League table of the primary outcome relapse

Order of treatments is in alphabetic order. Results of the network meta-analysis are presented in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the risk ratio and the corresponding 95% credible interval (95%CrI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). Bold print indicates 95%CrI excluding no effect.

In the left lower half, i.e. the results of the network meta-analysis, the background colors of cells reflect the result of the assessment of the confidence in estimates: green=high confidence in estimates, blue=moderate, orange=low, red=very low.

The statistical analysis was conducted with odds ratios (OR). To increase interpretability of results, we transformed the OR (and their 95%CrI) to risk ratios (RR) using the formula given in the appendix. For this transformation, we assumed a risk of relapse with placebo of 60% as the control-event-rate for all comparisons of antipsychotics versus placebo. 60% was the average risk of relapse in all placebo arms as estimated by a single-arm meta-analysis. For each comparison of antipsychotic versus antipsychotic, we used the event rate from the comparison versus placebo as the control-event-rate.

Abbreviations: NA=Not available, LAI=long-acting injectable, ARI=Aripiprazole, ASE=Asenapine, BRE=Brexpiprazole, CAR=Cariprazine, CPZ=Chlorpromazine, CPX=Clopenthixol, FPX=Flupentixol, HAL=Haloperidol, ILO=Iloperidone, LUR=Lurasidone, OLA=Olanzapine, PAL=Paliperidone, PEN=Penfluridol, PIM=Pimozide, PLB=Placebo, QUE=Quetiapine, RIS=Risperidone, SER=Sertindole, THIOR=Thioridazine, TIOT=Tiotixene, TRI=Trifluoperazine, ZIP=Ziprasidone, ZOT=Zotepine, ZUC=Zuclopenthixol.

Figures4a-f should be part of a panel of tolerability-outcomes (like in Huhn et al.[9]). For readability during the review process we provide here separate figures:

Figure4a: Forest plot of antipsychotic drugs versus placebo for number of participants with sedation

Figure4b: Forest plot of antipsychotic drugs versus placebo for number of participants using antiparkinsonian medication at least once

Figure4c: Forest plot of antipsychotic drugs versus placebo for number of participants with tardive dyskinesia

Figure4d: Forest plot of antipsychotic drugs versus placebo for QTc in ms

Figure4e: Forest plot of antipsychotic drugs versus placebo for weight in kg

Figure4f: Forest plot of antipsychotic drugs versus placebo for prolactin in ng/ml

Effect sizes for figures a-d are from network meta-analyses. Effect sizes for figures e and f are from pairwise meta-analyses because of inconsistency observed in the network meta-analysis; therefore, differences in the magnitude of the effect need be interpreted with caution. Order of treatments is according to the mean effect size. Reference is placebo. Risk ratios below 1 and mean differences below 0 are in favor of antipsychotic treatment. Colors of lines reflect the result of the assessment of the confidence in estimates: green=high confidence in estimates, blue=moderate, orange=low, red=very low.

Abbreviations: n=number of patients, kg=kilogram, ng/ml=nanogram per milliliter, ms=millisecond, RR=risk ratio, MD=mean difference, 95%CrI=95% credible interval, 95%CI=95% confidence interval, LAI= long-acting injectable, ARI=Aripiprazole, ASE=Asenapine, BRE=Brexpiprazole, CAR=Cariprazine, CPZ=Chlorpromazine, CPX=Clopenthixol, FPX=Flupentixol, HAL=Haloperidol, ILO=Iloperidone, LUR=Lurasidone, OLA=Olanzapine, PAL=Paliperidone, PEN=Penfluridol, PIM=Pimozide, PLB=Placebo, QUE=Quetiapine, RIS=Risperidone, SER=Sertindole, THIOR=Thioridazine, TIOT=Tiotixene, TRI=Trifluoperazine, ZIP=Ziprasidone, ZOT=Zotepine, ZUC=Zuclopenthixol.

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