Comprehensive evaluation of 45 augmentation drugs for schizophrenia: a network meta-analysis

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Summary

Background Antipsychotics are the gold standard treatment for schizophrenia, but many patients who receive treatment experience persistent symptoms. The aim of this network meta-analysis was to determine the efficacy of augmentation drugs for the treatment of schizophrenia.

Methods In accordance with the PRISMA statement, the PubMed, Web of Science, Google Scholar, CENTRAL, clinical trial and EUDRACT databases were searched from inception to May 15th, 2023. To ensure the robustness of the results, only double-blind randomised controlled trials with a low risk of bias (measured by the Risk Of Bias v2 (ROB2) tool) were included. The studies were categorised according to the background regimen: participants were treated with risperidone, mixed antipsychotics or clozapine. A Bayesian network meta-analysis was conducted using a random effects model. PROSPERO register: CRD42023420964.

Findings A total of 44 trials (comprising 45 augmentation drugs and 3358 participants) were included in the analysis. One-third of the drugs (16 drugs) demonstrated significant efficacy vs. placebo for at least one outcome. The most notable effect sizes (ESs) were observed for the use of tropisetron (standard mean difference: −0.83 [95% interval confidence −1.12 to −0.55]), memantine (−0.50 [−0.66 to −0.32]) and minocycline (−0.56 [−0.72 to −0.39]) to treat negative symptoms among patients treated with risperidone (moderate-to-high ESs). Studies involving mixed antipsychotics yielded lower ESs (small-to-moderate). Sodium benzoate (−0.41 [−0.60 to −0.21]) and memantine (−0.23 [−0.36 to −0.11]) were found have significant effects on positive symptoms, while memantine demonstrated efficacy for negative symptoms (−0.32 [−0.45 to −0.19]) and general psychopathology (−0.32 [−0.44 to −0.20]). Studies focusing exclusively on patients treated with clozapine revealed that duloxetine produced the best results (negative symptoms: −1.12 [−1.35 to −0.91]). Sodium benzoate was the only augmentation drug that demonstrated efficacy in relieving persistent positive symptoms (−0.32 [−0.59 to −0.08]) among patients treated with clozapine. Treatment with clozapine in combination with antipsychotics yielded small-to-moderate ESs.

Interpretation The GRADE framework indicated that the quality of the evidence among the included studies was moderate, primarily due to the limited number of randomised controlled trials with a low risk of bias. Important drugs did not appear in these results due to insufficient low-risk-of-bias data for these medications. These results highlight new pathways for treating schizophrenia that should be incorporated into future guidelines after further validation.

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Research in context

Evidence before this study

Augmentation treatments (i.e., treatments added to antipsychotic therapy to enhance efficacy) were explored herein due to the recognition that antipsychotic therapy, which is the standard treatment for schizophrenia, may fall short in various clinical scenarios owing to efficacy issues or tolerance concerns. To address this issue, we comprehensively searched the PubMed, Web of Science, Google Scholar, Embase, ClinicalTrials.gov, and EUDRACT databases up to May 15th, 2023, without language restrictions. The following search terms were used: (schizophrenia OR schizo-affective) AND (adjunctive OR augmentation OR other synonyms) AND (randomised clinical trial OR other synonyms). Studies were considered eligible for inclusion if they compared augmentation medications (administered in either capsule or oral tablet form) with either a placebo or an alternative augmentation medication among patients with chronic schizophrenia. To ensure the reliability of the evidence, only studies with a low risk of bias were included. Due to the potential heterogeneity introduced by the choice of initial antipsychotic treatment, we categorised studies into three groups: augmentation of risperidone, clozapine, or mixed antipsychotics.

Added value of this study

The results of this network meta-analysis, encompassing 45 drugs and 3358 participants, revealed promising properties for 16 drugs across diverse symptom domains, primarily focusing on negative symptoms—a crucial area given the limited efficacy of antipsychotics for these symptoms compared to positive symptoms. Depending on the baseline antipsychotic regimen, this study emphasises the potential beneficial effects of augmentation treatments on symptoms within specific subdomains.

Implications of all the available evidence

Our recommendations were graded as moderate (grade 2 level) because of an insufficient number of randomised controlled trials with a low risk of bias for each drug. This network meta-analysis emphasises the need for additional trials with a low risk of bias. While commonly prescribed antipsychotic combinations yield small-to-moderate effects, other augmentation strategies have shown more promise in improving symptom subdomains.

Introduction

Antipsychotic medication is widely recognised as the primary treatment for schizophrenia.[1] Among these medications, clozapine, a second-generation antipsychotic, is one of the most efficacious options available. Its effectiveness has been well documented over the years, leading to its inclusion in the latest 2021 update of the World Health Organization's list of essential medicines.[2] Despite the widespread use of antipsychotics, one-quarter of patients with schizophrenia will not respond to antipsychotics, and a large proportion of patients treated with antipsychotic monotherapy (including clozapine) experience persistent symptoms that significantly impact their quality of life.[3,4] In particular, antipsychotics have been shown to be less effective at treating negative symptoms (including blunted affects, lack of motivation, and anhedonia). Some antipsychotics, such as risperidone, have been shown to induce iatrogenic negative symptoms at higher doses due to their anti-dopaminergic action. Moreover, comorbid depression is highly prevalent among patients with schizophrenia.[5] Negative and depressive symptoms have a strong impact on the daily functioning of people with schizophrenia. Many augmentation drugs have been tested in randomised controlled trials, and several meta-analyses have shown that augmentation drugs are effective in treating schizophrenia.[6] A meta-review by Correll et al. identified meta-analyses that demonstrated the significant effects of certain drugs.[7] However, their meta-review included studies with a high risk of bias, thereby casting doubt on the potential benefit for patients. A search of the PubMed database April 2023 indicated that no comprehensive network meta-analysis has examined the efficacy of augmentation drugs and provided a clear classification of their efficacy.

Therefore, the objective of this network meta-analysis was to evaluate the efficacy of these augmentation drugs on various symptoms associated with schizophrenia via a network meta-analysis.

Methods

Search strategy and selection criteria

This study was reported in accordance with the established guidelines outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 and PRISMA network meta-analysis statement standards.[8] To ensure transparency and consistency, a detailed protocol outlining predefined eligibility criteria was registered with PROSPERO, a prospective register of systematic reviews (CRD42023420964) on May 5th, 2023.

The inclusion criteria were as follows: (i) Design: double-blind randomised controlled trials with a low risk of bias; (ii) Intervention in the experimental group: augmentation treatment with oral capsules or tablets; (iii); Intervention in the control group: placebo indistinguishable from oral active compound or another active drug; trials with treatment-only controls (e.g., clozapine only) were not included; (iv) Population: adults ([18–65] years of both sexes) with stabilised schizophrenia who were receiving antipsychotic monotherapy or combined therapy. Stabilised schizophrenia was defined by no modification of the class or dosage of the antipsychotic medication within the four weeks prior to inclusion. All classes of augmentation drugs were included.

The exclusion criteria were as follows: trials with some concerns of bias or a high risk of bias on any domain of the Risk Of Bias v2 (ROB2) tool[9]; studies with crossover designs that did not present results after the first period[10]; and any study allowing the use of drugs that could influence the outcomes of interest, even sporadically.

Two independent authors (DEE and GF) searched databases the MEDLINE®, PubMed®, Web of Science® (Clarivate®) Cochrane Central Register of Controlled Trials (Central), ClinicalTrials.gov, EU Clinical Trials Register (EUDRACT) and Google Scholar®[11] databases from inception to May 15th, 2023, with no language or date restrictions. The search strategies are presented in Supplementary Material 1. To ensure the appropriate search strategy, related meta-analyses were consulted.[7,12]

Two investigators (DEE and GF) independently performed the screening and extracted the data from the included trials, and a third investigator (LB) checked the extracted data. Discrepancies were resolved through consensus. The extracted data included interventions, the efficacy outcomes of interest at baseline and at each time point (mean/change and dispersion) and the safety outcome of interest (any serious adverse events (SAEs)). The data for all the time points found in the respective studies were collected and considered in the analyses. The primary outcome was negative symptoms. The secondary outcomes were positive symptoms, depressive symptoms, general psychopathology, and total psychotic symptomatology. General psychopathology includes depression, anxiety and heterogeneous symptoms, including attention disorders and impaired insight into illness. Total psychotic symptomatology was the sum of all other symptoms previously listed.

The risk of bias of individual trials for efficacy outcomes was assessed using the Cochrane Collaboration ROB2 tool.[9] The overall bias was judged to be low if the five domains (randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome, and selection of reported results) were at a low risk of bias and high if at least one domain was at a high risk of bias or if multiple domains had some concerns of bias. Two reviewers (DEE and GF) independently evaluated the risk of bias. Disagreements were resolved by consulting a third investigator (LB).

Data analysis

To ensure homogeneity and transitivity in the network meta-analysis, studies with the same antipsychotic therapy at baseline were grouped into three classes: risperidone, mixed antipsychotic, and clozapine. Clozapine is the most effective antipsychotic, and patients who do not respond to clozapine are considered "ultra-resistant". Apart from clozapine, risperidone was the only antipsychotic for which we identified enough studies including only patients receiving this treatment. Bayesian network meta-analysis was performed using the Model-Based Network Meta-Analysis time (MBNMAtime) package of R software.[13,14] We assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) statement.[15]

Our hypothesis was that antipsychotic therapy administered in both groups at baseline might influence the study results. As explained in the rationale, studies that exclusively include patients treated with clozapine can be considered to include patients with a higher degree of resistance to treatment, given that clozapine is the most effective antipsychotic. Therefore, it was hypothesised that those studies might produce different results compared to the others. Apart from clozapine, risperidone was the only antipsychotic for which we identified a sufficient number of studies including only patients receiving this treatment. The other studies included a combination of antipsychotics (including clozapine, risperidone, and other antipsychotics) and were grouped together in the third category.

As we expected symptoms to be measured by different scales, we used the standardised mean difference (SMD) as a summary statistic.[16] The cut-off values for the standard mean difference were as follows: 0 to –0.20 indicated a trivial effect; –0.20 to –0.50 indicated a small-to-moderate effect; –0.50 to –0.80 indicated a moderate-to-large effect; and above –0.80 indicated a large effect.[17] To estimate treatment effects, Bayesian models were generated using Markov chain Monte Carlo (MCMC) algorithms. Noninformative priors were utilised to allow the collected trial data to determine effect estimates.[18] The log-linear function was employed to capture the general time-course function.[19] To model the correlation between time points within each study, a multivariate normal likelihood with an autoregressive AR1 structure was employed.[20] To assess the divergence of the model, the Kullback-Leibler divergence was used.[21] The model fit was evaluated using the deviance information criterion.[22] In addition to the arguments specific to the MBNMAtime in the JAGS model,[23] the following parameters were set: three

Markov chains were run, each consisting of a total of 20,000 iterations. To ensure convergence, the first 10,000 iterations were discarded to eliminate any transient behaviour. Furthermore, a thinning rate of 1 in every 10 iterations per chain was applied to optimise the storage and analysis efficiency. The drugs were ranked based on the area under the curve (AUC) value.[24] However, formal consistency testing was not possible due to the absence of closed loops of treatment comparisons in the expected network architecture, although this may still be presumed. Each result is presented as the effect size (ES) (95% confidence interval (95% CI) and rank (according to AUC).

The GRADE evaluation was performed based on various NMA parameters.[15] The risk of bias parameter assesses the extent to which there may be a systematic deviation from the truth in the included studies, which can lower the certainty of the results. Inconsistency specifically refers to disagreements between direct and indirect evidence in the network meta-analysis. To ensure valid comparisons, intransitivity assesses whether all the competing interventions in a systematic review can be randomised together. This means that it is possible to design a single multiarm randomised trial in which all the therapies are compared simultaneously, using the same population and other relevant factors (e.g., age). Indirectness considers the differences between the populations and treatments and between the results of the studies compared with the populations and treatments and between the results targeted by the network meta-analysis. It also takes into account the use of indirect comparisons. Studies with significant results are more likely to be published, which can introduce bias. Publication bias was considered to account for this potential bias in the evaluation. Imprecision is primarily assessed by examining the 95% confidence intervals and determining whether these intervals exclude clinically relevant effect sizes. Additionally, the optimal size of the information is also investigated.[25]

Since this study does not involve participants, no ethical approval or consent to participate was needed.

Role of the funding source

All the authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication. There was no funding source for this study.

Results

A total of 403 studies were identified. Ultimately, 44 studies comprising 3358 participants and 45 augmentation treatments met the inclusion criteria.[26–69] The characteristics of the included studies are presented in Table 1. The mean age of the participants was 39.5 (standard deviation = 5.8) years, and 33.5% (1124/3358) of participants were women. The most common duration of treatment was eight weeks (k = 14, 31.8%), followed by six weeks (k = 10, 22.7%). The baseline treatment was mixed antipsychotics in 25 (56.8%) studies, risperidone in 10 (22.7%) studies and clozapine in 9 (20.5%) studies. The reasons for the exclusion of the 359 nonincluded studies are presented in Supplementary Material 2. Among these 359 nonincluded studies, 27.6% (n = 99) were not included due to inadequate information on randomization procedures and/or allocation concealment; 20.3% (n = 73) of the studies were excluded because no mean or dispersion values were available; 11.4% (N = 41) of the studies were excluded because the population studied did not exclusively consist of schizophrenia or reported selected patients (such as patients with tardive dyskinesia); 11.4% (n = 41) of the studies were excluded because they involved coinitiation rather than augmentation; 5.6% (N = 20) of the studies were excluded due to focusing exclusively on one sex group receiving sex-specific treatment (e.g., sex hormones); and 4.2% (N = 15) of the studies were excluded because the analysis of the effect of assignment to the intervention was inadequate, thus leading to a lack of clarity regarding whether the measured effect could be attributed to other drugs administered on an as-needed basis for insomnia or agitation, such as lorazepam. As a result, the RoB2 assessment for domain 2 (i.e., deviations from planned interventions) was evaluated as having a high risk of bias. Furthermore, 3.9% n = 14 of the studies were excluded because the measurements of all randomised patients (whether by observed cases, intention-to-treat analysis, or imputation methods such as last observation carried forward) were not considered, introducing bias into the estimation of the intervention effect. Consequently, the RoB2 assessment for domain 3 (i.e., missing outcome data) was assessed as indicating a high risk of bias. In addition, 12 studies did not involve chronic or stable patients, ten were not double-blinded, ten were not of the desired galenic form, eight did not involve adjunctive strategies, six did not present data after the first period (crossover studies), four were not randomised controlled trials, three did not involve medication (electroconvulsive therapy, cognitive behavioural therapy), two did not present a control group and one did not have antipsychotics at the start of the study. The flowchart is provided in Fig. 1.

Outcomes

Our findings are synthetised in Table 2. No augmentation treatment was found to improve all five symptom dimensions of schizophrenia (negative, positive, depressive, general psychopathology, and total symptoms). However, 16 drugs or combined drugs have shown efficacy in at least one dimension. The statistically significant results are presented in Fig. 2. The full results for all symptom dimensions are available in Supplementary Materials 8, 15 and 21. All the results

Study (First author, publication year)	Country	Trial duration (weeks)	Schizophrenia diagnostic	In/out patient	Baseline regime	Stable dose (weeks)	Treatment	Sample size	Age (sd)	Percentage of female
Berk et al., 2008	Australia	24	DSM-IV	both	mixed	4	N acetyl cysteine	69	37.2 (10.1)	30
							placebo	71	36.1 (11.7)	30
Bobo et al., 2011	USA	6	DSM-IV-TR	both	mixed	8	armodafinil	29	44.0 (14.6)	48.3
							placebo	29	38.8 (11.7)	31
Buchanan et al., 2015	USA	12	DSM-IV	both	mixed	4	rasagiline	28	46.3 (12.2)	14.3
							placebo	29	45.9 (11.1)	24.1
Bugarski-Kirola et al., 2016	World	12	DSM-IV	outpatient	mixed	12	bitopertin 10 mg	198	40.2 (12.4)	43
							bitopertin 20 mg	199	39.1 (12.2)	43
							placebo	199	39.7 (12.7)	33
Bugarski-Kirola et al., 2022	World	6	DSM5	outpatient	mixed	8	pimavanserin	193	36.9 (9.5)	36.8
							placebo	196	37.5 (9.4)	38.8
Chang et al., 2008	Republic of Korea	8	DSM-IV	both	clozapine	12	aripiprazole	29	33.2 (8.2)	24
							placebo	32	31.7 (7.4)	19
Chen et al., 2012	Hong Kong	4	DSM-IV	both	mixed	12	HT1001	32	43.1 (8.5)	16
							placebo	32	43.7 (7.8)	25
Chengappa et al., 2012	USA	12	DSM-IV-TR	both	mixed	4	L-carnosine	33	46.6 (8.5)	36
							placebo	37	46.5 (9.0)	38
Freudenreich et al., 2007	USA	6	DSM-IV	outpatient	clozapine	8	risperidone	11	42.3 (md)	12.5
							placebo	13		
Ghaderi et al., 2019	Iran	12	DSM-IV-TR	inpatient	mixed	24	vitamin D & probiotics	30	43.2 (6.0)	6.7
							placebo	30	44.8 (8.3)	6.7
Ghajar et al., 2018	Iran	8	DSM5	outpatient	risperidone	8	citicoline	33	45.4 (11.6)	6
							placebo	33	48.9 (10.7)	15
Goff et al., 2008	USA	8	DSM-IV	outpatient	mixed	4	D-cycloserine	19	50.1 (9.2)	47.4
							placebo	19	48.0 (6.7)	31.6
Iancu et al., 2010	Israel	10	DSM-IV	both	mixed	4	escitalopram	20	35.5 (8.7)	25
							placebo	20	38.8 (6.9)	30
Iranpour et al., 2016	Iran	8	DSM-IV-TR	inpatient	risperidone	8	pioglitazone	21	38.0 (8.9)	33.3
							placebo	21	37.0 (7.7)	26.6
Kaphzan et al., 2014	Israel	12	DSM-IV	md	mixed	8	entacapone	23	41.8 (2.7)	26
							placebo	22	43.8 (2.3)	27
Kardashev et al., 2018	Israel	8	DSM-IV	md	mixed	6	pregnenolone & L-theanine	18	32.2 (7.6)	11.1
							placebo	21	33.0 (6.7)	9.5
Kelly et al., 2015	USA	10	DSM-IV-TR	both	clozapine	24	minocycline	28	42.9 (14.2)	29
							placebo	23	42.3 (11.0)	22
Khodaie-Ardakani et al., 2014	Iran	8	DSM-IV-TR	outpatient	risperidone	8	minocycline	20	41.1 (7.47)	30
							placebo	20	38.9 (7.8)	25
Lane et al., 2006	Taiwan	6	DSM-IV	inpatient	clozapine	12	sarcosine	10	36.7 (10.1)	30
							placebo	10	35.5 (6.6)	30
Lane et al., 2010	Taiwan	6	DSM-IV	inpatient	mixed	12	sarcosine	20	30.4 (10.6)	40
							D-serine	20	30.7 (9.6)	40
							placebo	20	31.5 (7.9)	55
Lane et al., 2013	Taiwan	6	DSM-IV	md	mixed	12	sodium benzoate	25	38.4 (9.7)	56
							placebo	27	36.3 (7.9)	44.4
Lee et al., 2012	Republic of Korea	12	DSM-IV	inpatient	mixed	12	memantine	15	44.3 (4.3)	26.7
							placebo	11	43.4 (3.9)	54.5
Lerner et al., 2013	USA	6	DSM-IV-TR	both	mixed	6	bexarotene	45	41.2 (12.4)	9
							placebo	45	41.7 (10.0)	11
Lin et al., 2017	Taiwan	6	DSM-IV	inpatient	clozapine	12	sodium benzoate 1000 mg	20	44.3 (7.2)	30
							sodium benzoate 2000 mg	20	44.8 (8.1)	35
							placebo	20	47.0 (11.9)	30

(Table 1 continues on next page)

Study (First author, publication year)	Country	Trial duration (weeks)	Schizophrenia diagnostic	In/out patient	Baseline regime	Stable dose (weeks)	Treatment	Sample size	Age (sd)	Percentage of female
(Continued from previous page)										
Michalopoulou et al., 2015	UK	10	DSM-IV	outpatient	mixed	4	modafinil	24	37.2 (9.6)	29
							placebo	24	35.4 (9.9)	25
Mico et al., 2011	Italy	16	DSM-IV	outpatient	clozapine	4	duloxetine	20	35.9 (7.1)	35
							placebo	20	34.0 (6.8)	45
Miodownik et al., 2019	Israel	24	DSM-IV	inpatient	mixed	12	curcumin	20	54.1 (12.9)	30
							placebo	18	53.4 (4.9)	38.8
Moazen-zadeh et al., 2020	Iran	8	DSM5	inpatient	risperidone	8	vortioxetine	34	34.4 (5.8)	29.4
							placebo	34	32.9 (4.7)	32.4
Muscatello et al., 2014	Italy	16	DSM-IV	outpatient	clozapine	4	ziprasidone	20	36.5 (8.8)	75
							placebo	20	33.5 (5.6)	60
Niitsu et al., 2012	Japan	8	DSM-IV	outpatient	mixed	8	fluvoxamine	23	38.6 (9.5)	39
							placebo	24	36.3 (9.4)	37.5
Nikbakhat et al., 2016	Iran	8	DSM-IV	md	risperidone	8	duloxetine	32	33.9 (5.9)	34.3
							placebo	32	34.2 (5.8)	31.2
Noroozian et al., 2013	Iran	8	DSM-IV-TR	outpatient	risperidone	8	tropisetron	20	33.8 (7.0)	20
							placebo	20	33.7 (5.9)	25
Omranifard et al., 2017	Iran	12	DSM-IV-TR	inpatient	mixed	12	memantine	30	32.3 (9.9)	40
							placebo	30	34.2 (10.6)	53
Piškulić et al., 2009	Australia	6	DSM-IV	outpatient	mixed	8	buspirone	9	43.4 (10.3)	11
							placebo	9	37.2 (13.7)	33
Rezaei et al., 2013	Iran	8	DSM-IV-TR	outpatient	risperidone	8	memantine	20	33.5 (6.9)	40
							placebo	20	33.0 (6.9)	45
Roffman et al., 2018	USA	12	DSM-IV-TR	outpatient	mixed	6	L-methylfolate	29	46.3 (9.2)	17.2
							placebo	26	44.7 (12.9)	26.9
Salehi et al., 2022	Iran	8	DSM5	md	risperidone	8	palmitoylethanolamide	25	33.76 (6.9)	8
							placebo	25	36.8 (9.6)	16
Samaei et al., 2020	Iran	8	DSM5	outpatient	risperidone	8	resveratrol	26	34.73 (7.0)	38
							placebo	26	33.1 (5.5)	42
Sheikhmoonesi et al., 2015	Iran	6	DSM-IV-TR	inpatient	mixed	4	buspirone	25	46.7 (9.5)	20
							placebo	25	47.3 (10.6)	20
Shiloh et al., 1997	Israel	10	DSM-IV	inpatient	clozapine	12	sulpiride	16	40.3 (10.8)	31.25
							placebo	12	37.1 (12.3)	33.3
Tharoor et al., 2023	India	24	ICD-10	both	mixed	md	L-carnosine	50	32.1 (7.4)	30
							placebo	50	31.0 (5.8)	38
Veerman et al., 2016	The Netherlands	26	DSM-IV	outpatient	clozapine	12	memantine	26	42.4 (9.6)	25
							placebo	26		
Weiser et al., 2021	Romania	16	DSM-IV-TR	both	mixed	2	aspirin	100	42.2 (10.7)	51
							placebo	100	43.5 (9.7)	46
Xiao et al., 2011	China	8	DSM-IV	md	risperidone	4	sarsasapogenin	41	46.0 (17.2)	51.2
							placebo	39	55.2 (15.7)	51.3

Table 1: **Characteristics of the included studies.**

presented in this network meta-analysis used a placebo as the reference. In summary, studies including patients treated with risperidone, mixed antipsychotics, or clozapine yielded different results.

The studies that included patients treated with risperidone mainly focused on patients with negative symptoms. The results of the network meta-analysis of patients taking risperidone indicated that tropisetron was the most effective treatment for negative symptoms, with a large effect size (ES) [–0.83; 95% confidence interval (95% CI) (–1.12 to –0.55); rank = 1]. The three drugs had moderate-to-large ES for negative symptoms: pioglitazone [–0.63; 95% CI (–0.94 to –0.30), rank = 2]; minocycline [–0.56; 95% CI (–0.72 to –0.39), rank = 3]; and memantine [–0.50; 95% CI (–0.66 to –0.32), rank = 4]. Palmitoylethanolamide had a small ES for negative symptoms [–0.28; 95% CI (–0.50 to –0.05), rank = 5] but a moderate-to-high effect on general

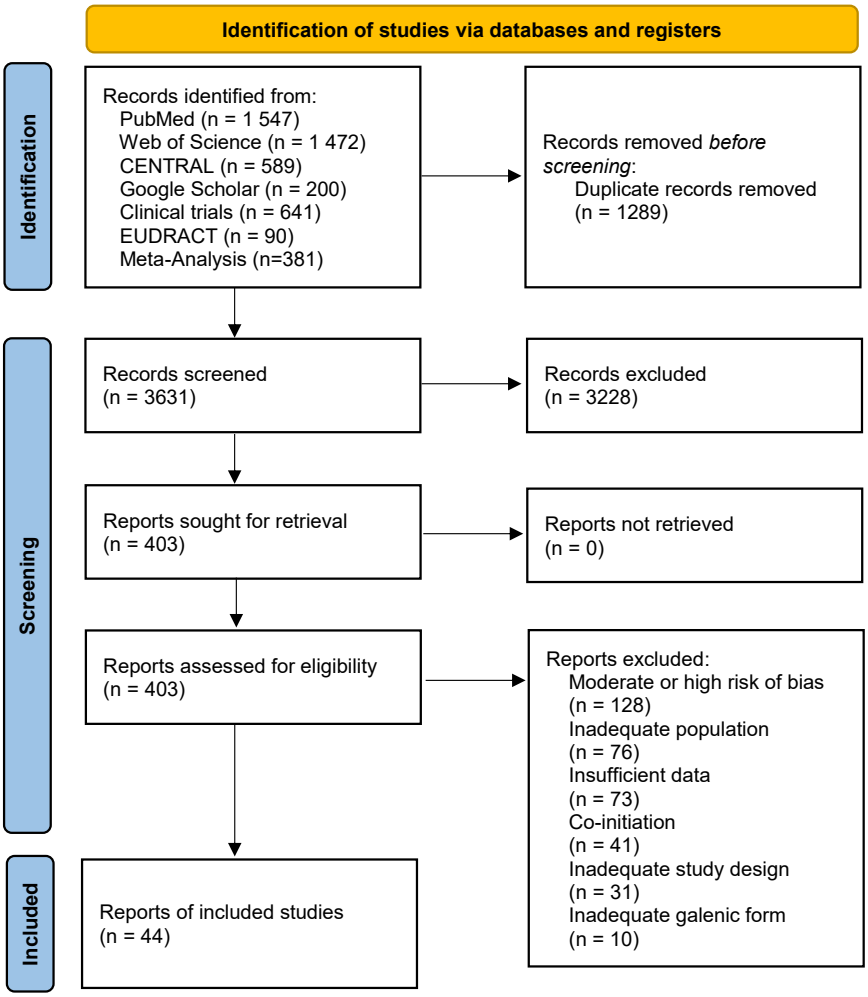

Fig. 1: Flow diagram.

psychopathology [–0.58; 95% CI (–0.84 to –0.32), rank = 1]. Duloxetine [–0.47; 95% CI (–0.59 to–0.35), rank = 5] and sarsasapogenin [–0.21 (–0.33 to –0.09, rank = 6] had small-to-moderate effects on total symptoms. The net graphs and forest plots of effect sizes with rankings for the risperidone group are shown in Supplementary Materials 3–8, respectively.

The results of the studies including patients treated with mixed antipsychotics yielded more modest ESs than did the studies involving patients treated with risperidone only. No augmentation drug yielded a large ES in any dimension. Only sarcosine yielded a moderate-to-large ES for total symptoms [–0.57; 95% CI (–0.90 to –0.27), rank = 1] and presented a small-to-moderate ES for negative symptoms [–0.35; 95% CI (–0.57 to –0.13), rank = 2]. The other drugs yielded small-to-moderate ES. Notably, two augmentation drugs had small-to-moderate ES for positive symptoms (sodium benzoate [–0.41; 95% CI (–0.60 to –0.21), rank = 1] and memantine [–0.23; 95% CI (–0.36 to –0.11), rank = 2]). Memantine also had a small-to-moderate ES for negative symptoms [–0.32; 95% CI (–0.45 to –0.19), rank = 1] and general psychopathology [–0.32; 95% CI (–0.44 to –0.20), rank = 1]. Additionally, sodium benzoate had a small-to-moderate ES for general psychopathology [–0.25; 95% CI (–0.44 to –0.07), rank = 3]. The combination of vitamin D + probiotics yielded a small-to-moderate ES for negative symptoms [–0.29; 95% CI (–0.50 to –0.08), rank = 3], and pregnenolone + L-theanine for general psychopathology [–0.31; 95% CI (–0.47 to –0.15), rank = 2]. D-serine and fluvoxamine yielded a small-to-moderate ES for total symptoms: [–0.33; 95% CI (–0.68 to –0.01), rank = 4] and [–0.22; 95% CI (–0.37 to –0.07), rank = 5]. The net graphs and forest plots of effect sizes with rankings for the mixed group are shown in Supplementary Materials 9–15, respectively.

In the studies including only patients with clozapine, duloxetine yielded the best ES (negative symptoms [–1.12; 95% CI (–1.30 to –0.91), rank = 1], a moderate-to-large effect for depressive symptoms [–0.52; 95% CI

Baseline regimen	Drug	Dose(mg/d)	Duration (Weeks)	Positive	Negative	Depressive	General psychopathology	Total	k RCTs	N subjects
Risperidone	tropisetron	10	8	–	1	N/A	3	1	1	20
	minocycline	200	8	–	3	–	4	3	1	20
	palmitoylethanolamide	1200	8	–	5	N/A	1	4	1	25
	pioglitazone	30	8	–	2	–	–	2	1	21
	memantine	20	8	–	4	N/A	2	–	1	20
	duloxetine	60	8	–	–	N/A	–	5	1	32
	sarsapogenin	200	8	–	–	N/A	N/A	6	1	41
Mixed	memantine	20	12	2	1	–	1	2	2	45
	sodium benzoate	1000	6	1	–	–	3	3	1	25
	sarcosine	2000	6	N/A	2	N/A	N/A	1	1	20
	pregnelonone/L-theanine	50/400	8	N/A	4	N/A	2	N/A	1	18
	vitamin D/probiotics	50,000 UI/2weeks 8 × 10^9 CFU/d	12	–	3	N/A	–	–	1	30
	D-serine	2000	6	N/A	–	N/A	N/A	4	1	20
	fluvoxamine	150	8	N/A	–	–	N/A	5	1	23
Clozapine	duloxetine	60	12	–	1	1	1	1	1	20
	sodium benzoate	1000	6	2	3	–	3	2	1	20
	ziprasidone	80	16	–	2	–	4	4	1	20
	sulpiride	600	10	–	–	2	N/A	5	1	16
	risperidone	4	6	–	–	–	2	3	1	11
	sodium benzoate	2000	6	1	–	–	–	–	1	20
	minocycline	200	10	–	–	–	N/A	6	1	28

The drug's rank according to the symptom is noted in the boxes only for significant effects. The number of subjects (N subjects) represents the number of subjects receiving the active treatment, not the entire sample size, including patients treated with a placebo. "Total" means "Total symptomatology score"; "–" means "non-significant result"; "N/A" means "non applicable"(not tested); "k RCTs" means "number of randomised controlled trials". Only low-risk-of-bias randomised controlled trials (RCTs) have been included, which accounts for the low number of studies for each molecule.

Table 2: **Efficacy of 16 augmentation drugs demonstrating significant effects in at least one symptom domain of schizophrenia.**

(–0.63 to –0.40), rank = 1], small-to-moderate effect for total symptoms [–0.46; 95% CI (–0.63 to –0.30), rank = 1] and for general psychopathology [–0.45; 95% CI (–0.54 to –0.34), rank = 1] but no significant ES for positive symptoms). The other strategies yielded small-to-moderate ES. A dose-dependent effect was observed for sodium benzoate on positive symptoms (1000 mg/d [–0.27; 95% CI (–0.55 to –0.01), rank = 2] and 2000 mg/d [–0.32; 95% CI (–0.59 to –0.08)], rank = 1). Sodium benzoate (1000 mg/d) was also effective for treating negative symptoms with a small-to-moderate ES [–0.21; 95% CI (–0.38 to –0.02), rank = 4]. Minocycline yielded a small-to-moderate ESs for total symptoms [–0.21; 95% CI (–0.37 to –0.04), rank = 6].

The studies combining clozapine with other antipsychotics yielded small-to-moderate ESs (ziprasidone for negative symptoms [–0.27; 95% CI (–0.36 to –0.18), rank = 2] and general psychopathology [–0.21; 95% CI (–0.33 to –0.10), rank = 4]; sulpiride for depressive symptoms [–0.25; 95% CI (–0.36 to –0.12), rank = 2]; and risperidone for general psychopathology symptoms [–0.25; 95% CI (–0.46 to –0.04), rank = 2], while aripiprazole yielded no significant results. The net graphs and forest plots of effect sizes with rankings for the clozapine group are shown in Supplementary Materials 16–21, respectively.

Serious adverse events

Serious adverse events are presented in Supplementary Material 22. None of the augmentation drugs that showed efficacy were associated with a significant increase in serious adverse events.

Risk of bias evaluation

According to the inclusion criteria, only studies with a low risk of bias were considered. The plot and table concerning the risk of bias v2 assessment are available in Supplementary Materials 23 and 24.

GRADE evaluation

With respect to the GRADE evaluation, we only included studies with a low risk of bias and no significant methodological limitations. The risk-of-bias assessment was therefore not downgraded. The only studies comparing two different augmentation drugs were three-arm studies with placebo as the reference. Since clinical trials are internally consistent, the loops formed by these studies were not checked for inconsistency. Furthermore, the network structure of this star network, which compares each drug to that of the placebo, prevents direct and indirect estimates from being compared. To ensure transitivity, the studies involved comparable populations (patients with chronic

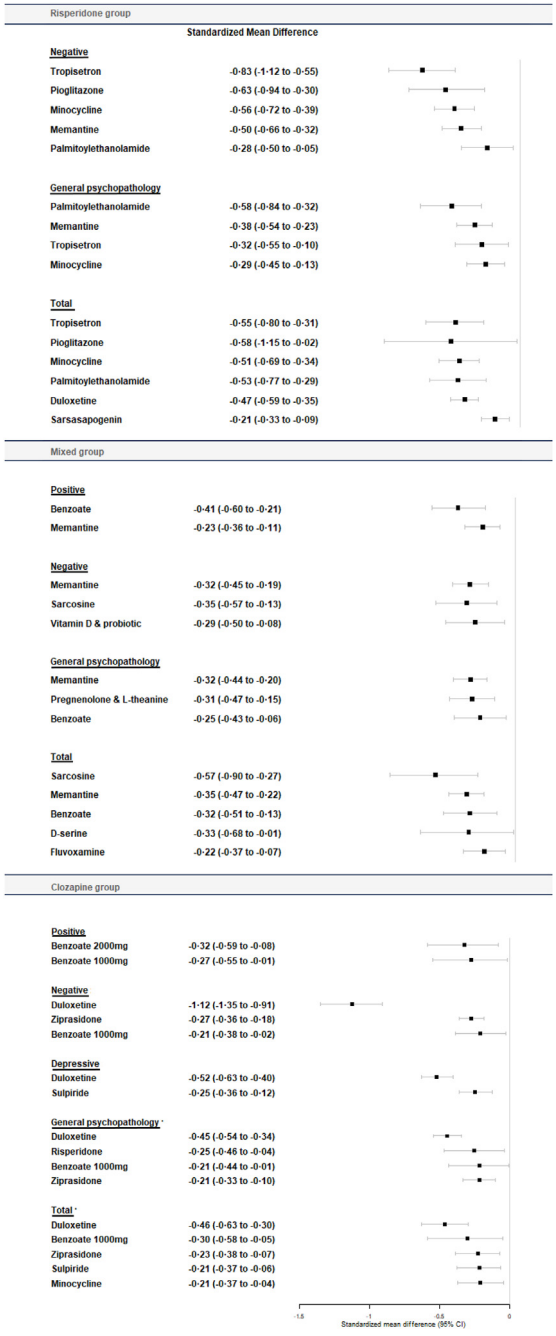

Fig. 2: Forest plots of drugs providing a statistically significant effect on at least one symptom dimension. 95% CI: 95% confidence interval.

schizophrenia treated with stable antipsychotics), the same interventions (augmentation strategies involving oral tablets/capsules compared with placebo indistinguishable from orally active compounds or another active drug), and comparable measurement scales, with the results presented in comparison to those of the placebo. These findings reinforce the applicability of the evidence generated for this population and ensure a low degree of indirectness for all the studies. Therefore, there was no significant indirectness, and the rating was not downgraded in the indirectness assessment. Since there are only one or two studies per tested drug, it is not possible to investigate publication bias, so this factor cannot be assessed. The imprecision is presented in Supplementary Material 25, in which a decrease of one level of imprecision is observed for each drug due to the limited number of participants, which does not allow the optimal information size to be achieved. Additionally, imprecision is further reduced when the drug's confidence interval includes zero. Therefore, the certainty of evidence is rated as "moderate" for each statistically significant drug and "low" for each nonsignificant drug based on the GRADE assessment.

Discussion

To our knowledge, this is the first network meta-analysis exploring the efficacy of augmentation drugs in patients with schizophrenia. Tropisetron (10 mg/d), memantine (20 mg/d) and minocycline (200 mg/d) may improve the negative symptoms of patients treated with risperidone with moderate-to-large ES (and large ES for tropisetron). Pioglitazone at a dosage of 30 mg/day has also been demonstrated to be effective; however, it is associated with safety concerns, particularly regarding bladder cancer.[70] Therefore, its use is not recommended. Palmitoylethanolamide (1200 mg/d) has also yielded a moderate-to-large ES for the persistent general psychopathology symptoms of patients treated with risperidone. These drugs should be further explored in patients treated with other antipsychotics. The studies including mixed antipsychotics yielded more disappointing results, probably due to increased heterogeneity in the baseline groups. However, sodium benzoate (1000 mg/d) and memantine (20 mg/d) have yielded small-to-moderate ES for positive symptoms. Memantine also yielded a small-to-moderate ES for negative symptoms and general psychopathology, as did sodium benzoate for general psychopathology. Studies including only patients treated with clozapine (i.e., the most resistant form of schizophrenia) have shown that 60 mg/d duloxetine yielded the best results, with a large ES for negative symptoms and a moderate-to-large ES for depressive symptoms. Sodium benzoate is the only drug that yielded a small-to-moderate ES for positive symptoms in patients treated with clozapine. Antipsychotic combination strategies with clozapine yielded more disappointing results, as indicated by the small-to-moderate ES for ziprasidone 80 mg/d in individuals with negative and general psychopathology, sulpiride 600 mg/d in individuals with depressive symptoms, and risperidone 4 mg/d in individuals with general psychopathology. Aripiprazole yielded nonsignificant results.

We observed larger effect sizes for negative symptoms than for positive symptoms. However, this does not necessarily imply that augmentation drugs targeting negative symptoms are more effective. This difference in effect sizes can be attributed to the fact that antipsychotics generally exhibit greater efficacy in treating positive symptoms than in treating negative symptoms. Consequently, the baseline severity of positive symptoms was lower than that of negative symptoms, leading to artificially inflated effect sizes for negative symptoms. Moreover, most studies including risperidone as a baseline treatment have focused on negative symptoms. The use of mixed antipsychotics may have induced heterogeneity between groups, resulting in lower effect sizes.

We identified two augmentation drugs (sodium benzoate and memantine) that appear to be effective for persistent positive symptoms, exhibiting small-to-moderate effect sizes. Among these drugs, NMDA modulation seems to be the most likely shared mechanism of action. However, it is important to emphasise that the clinical relevance of these drugs may be subject to scrutiny, considering the small-to-moderate effect sizes. Effect sizes represent averages, and no definitive conclusions can be drawn about efficacy for individual patients.[71] It is also possible that more pronounced effects are observed with longer treatment durations. To address the question of treatment duration, our statistical analysis included the duration of the study and each measurement at every visit. However, not all durations were explored in the included trials, and most were limited to six or eight weeks.

Studies exploring the augmentation of clozapine with other antipsychotics have provided poor results, with small-to-moderate effect sizes for ziprasidone, sulpiride and risperidone and no significant effects for aripiprazole, suggesting that antipsychotic augmentation may not be the best strategy for improving psychotic symptomatology in stabilised patients. The combination of antipsychotics may increase the risk of side effects, including akathisia, resulting in a poor benefit/risk ratio. In contrast, duloxetine augmentation appears to be the best augmentation strategy for patients treated with clozapine with persistent negative symptoms or general psychopathology. Duloxetine selectively inhibits the reuptake of serotonin and norepinephrine and thus causes an increase in dopamine in the prefrontal cortex. This mechanism of action could account for its efficacy in addressing various symptoms. Other hypothesised mechanisms of action of the augmentation drugs that have shown significant efficacy are presented in Supplementary Material 26.

These results should be interpreted with caution. We achieved a moderate level of confidence in our grading evaluation, primarily due to the limited number of studies included. For instance, both the tropisetron and duloxetine results were supported by only one trial each; therefore, these findings warrant replication to confirm their preliminary nature. This limited sample size is mainly due to the augmentation design of the included trials, which makes them less common. Only high-quality trials with a low risk of bias were included in order to account for the small number of trials for each drug. Several studies were not included in our work due to methodological issues. In accordance with the RoB2 guidelines, regarding the randomization process, we found that simple statements such as "We carried out a random allocation" or "We used a random allocation plan" were insufficient to ensure that the allocation sequence was genuinely random. To address these randomization issues, clear and precise information must be provided.[72] Various methods can be employed, such as restricted randomization, stratified randomization, or a combination of both methods, known as minimization. Furthermore, these studies did not provide any evidence of the adequate generation of random sequences. To ensure the proper generation of random sequences, methods such as the use of sequentially numbered opaque sealed envelopes and block randomization can be employed.[73] This explains why we have a significantly smaller number of randomised controlled trials than the systematic overview of meta-analysis by Correll et al.[7] or why compounds that appeared to be effective previously, such as mirtazapine, lamotrigine, or N-acetyl-cysteine, were not examined herein.[12] Additionally, several crossover studies were not included, as the results were not presented after the first period, thus leading to potential carry-over bias.[10] One other limitation of our study could be the potential for differences between placebo arms across trials, particularly due to the star-like network structures with placebo at the centre. Such discrepancies could bias the estimates. To address this, we implemented a four-step strategy to minimise heterogeneity in the placebo arms. First, our focus was exclusively on studies with similar dosage forms (oral tablets/capsules), excluding intranasal/intravenous drug studies. Second, we identified background antipsychotic therapies as a major source of between-trial heterogeneity that could influence efficacy and safety profiles. Consequently, we performed separate analyses for networks involving risperidone, mixed antipsychotics, and clozapine as background therapies. Third, to acknowledge the potential for residual heterogeneity, we used a random effects model for data pooling to better manage this uncertainty. Finally, our initial plan to analyse differences in specific baseline variables was limited by the insufficient number of trials for consistent comparisons within each network.

The original data may face criticism due to the potential exclusion of certain patient groups, such as those with suicidal ideations, addiction issues, or physical comorbidities, as randomised controlled trials tend to favour specific patient characteristics.[74] Most of the RCTs conducted on the risperidone group were conducted by the same team and focused primarily on

negative symptoms. This emphasis may explain why more drugs were associated with a greater ES for negative symptoms in these studies. In the case of clozapine studies, the daily dose of clozapine varied from 275 mg/d to 503 mg/d. However, there are inadequate reports on clozapine blood levels, which can significantly vary depending on factors such as sex, smoking status, and CYP1A2 metabolism. These variables were not adequately addressed in the studies. Therefore, it is crucial to investigate the role of CYP1A2 in the observed results, particularly considering that duloxetine, which demonstrated efficacy in these studies, is metabolised by this enzyme. Combining the current findings with those from meta-analyses is recommended to provide comprehensive information for clinical practice. Despite these limitations, the present results may have important implications for clinical practice. Some of the treatments that have shown efficacy in our study may exhibit synergistic effects, such as the combination of memantine and galantamine.[75] Future guidelines for the treatment of schizophrenia should include these data in an algorithm to choose the best treatment option according to the clinician experience and the patient's preference in shared decision-making. Overall, these limitations underscore the complexity of assessing the efficacy of combination therapies in schizophrenia patients. The identification of biomarkers would likely assist clinicians in selecting the most appropriate augmentation drugs. Additional RCTs with a low risk of bias are needed to confirm the present findings and test combinations, as well as real-world data, to validate the effectiveness and safety of these methods.

The findings of this network meta-analysis indicate that sodium benzoate and memantine may be effective at relieving persistent positive symptoms, with effect sizes ranging from small to moderate. For patients treated with risperidone, tropisetron, pioglitazone, minocycline and memantine demonstrated efficacy in reducing negative symptoms, with effect sizes ranging from moderate to large. Augmentation of clozapine with antipsychotics had small-to-moderate effect sizes, while duloxetine had a large effect on reducing negative symptoms in patients treated with clozapine. Many factors remain to be explored to guide clinical practice.

Contributors

Damien Etchecopar-Etchart, Laurent Boyer and Guillaume Fond were responsible for conceptualization, data curation, formal analysis, methodology, supervision, validation, verification of the underlying data, writing-original draft, and writing-review and editing. Piotr Wojciechowski, Samuel Aballea and Mondher Toumi were responsible for the formal analysis, validation, and writing–review & editing. Dong Keon Yon was responsible for writing the original draft and writing, reviewing and editing the manuscript. All the authors confirm that they had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Data sharing statement

The data are available upon reasonable request to the authors.

Declaration of interests

No author reports any conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102473.

References

1 Huhn M, Nikolakopoulou A, Schneider-Thoma 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;394:939–951.
2 Organization WH. *WHO model list of essential medicines–22nd list, 2021*. Geneva: WHO; 2021.
3 Siskind D, Orr S, Sinha S, et al. Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. *Br J Psychiatry*. 2022;220:115–120.
4 Schennach R, Riedel M, Obermeier M, et al. What are residual symptoms in schizophrenia spectrum disorder? Clinical description and 1-year persistence within a naturalistic trial. *Eur Arch Psychiatry Clin Neurosci*. 2015;265:107–116.
5 Etchecopar-Etchart D, Korchia T, Loundou A, et al. Comorbid major depressive disorder in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2021;47:298–308.
6 Helfer B, Samara MT, Huhn M, et al. Efficacy and safety of antidepressants added to antipsychotics for schizophrenia: a systematic review and meta-analysis. *Am J Psychiatry*. 2016;173:876–886.
7 Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmacologic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: systematic overview and quality appraisal of the meta-analytic evidence. *JAMA Psychiatry*. 2017;74:675.
8 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
9 Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
10 Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31:140–149.
11 Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Syst Rev*. 2017;6:245.
12 Grover S, Sarkar S, Sahoo S. Augmentation strategies for clozapine resistance: a systematic review and meta-analysis. *Acta Neuropsychiatr*. 2023;35:65–75.
13 Pedder H, Dias S, Bennetts M, Boucher M, Welton NJ. Modelling time-course relationships with multiple treatments: model-based network meta-analysis for continuous summary outcomes. *Res Synth Methods*. 2019;10:1351.
14 Team RC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2016.
15 Izcovich A, Chu DK, Mustafa RA, Guyatt G, Brignardello-Petersen R. A guide and pragmatic considerations for applying GRADE to network meta-analysis. *BMJ*. 2023;381:e074495.
16 Higgins JP, Thomas J, Chandler J, et al. *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons; 2019.
17 Cohen J. *Statistical power analysis for the behavioral sciences | Jacob Cohen |*; 1988. https://www.taylorfrancis.com/books/mono/10.4324/9780203771587/statistical-power-analysis-behavioral-sciences-jacob-cohen. Accessed August 21, 2023.
18 Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network meta-analysis for decision making, 1st ed. *Wiley*. 2018. https://doi.org/10.1002/9781118951651.

19 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med*. 2004;23:3105–3124.
20 Kincaid C. Guidelines for selecting the covariance structure in mixed model analysis. In: *Proceedings of the thirtieth annual SAS users group international conference*. SAS Institute Inc Cary NC; 2005.
21 Plummer M. Penalized loss functions for Bayesian model comparison. *Biostatistics*. 2008;9:523–539.
22 Spiegelhalter DJ, Best NG, Carlin BP, Van Der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B Stat Methodol*. 2002;64:583–639.
23 Plummer M. *JAGS Version 3.3. 0 user manual*. Lyon: France; 2012.
24 Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Syst Rev*. 2017;6:79.
25 Brignardello-Petersen R, Guyatt GH, Mustafa RA, et al. GRADE guidelines 33: addressing imprecision in a network meta-analysis. *J Clin Epidemiol*. 2021;139:49–56.
26 Moazen-Zadeh E, Bayanati S, Ziafat K, Rezaei F, Mesgarpour B, Akhondzadeh S. Vortioxetine as adjunctive therapy to risperidone for treatment of patients with chronic schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol*. 2020;34:506–513.
27 Xiao S-F, Xue H-B, Li X, et al. A double-blind, placebo-controlled study of traditional Chinese medicine sarsasapogenin added to risperidone in patients with negative symptoms dominated schizophrenia. *Neurosci Bull*. 2011;27:258–268.
28 Noroozian M, Ghasemi S, Hosseini S-M-R, et al. A placebo-controlled study of tropisetron added to risperidone for the treatment of negative symptoms in chronic and stable schizophrenia. *Psychopharmacology (Berl)*. 2013;228:595–602.
29 Chengappa KNR, Turkin SR, DeSanti S, et al. A preliminary, randomized, double-blind, placebo-controlled trial of l-carnosine to improve cognition in schizophrenia. *Schizophr Res*. 2012;142:145–152.
30 Lane H-Y, Lin C-H, Huang Y-J, Liao C-H, Chang Y-C, Tsai GE. A randomized, double-blind, placebo-controlled comparison study of sarcosine (N-methylglycine) and d-serine add-on treatment for schizophrenia. *Int J Neuropsychopharmacol*. 2010;13:451.
31 Niitsu T, Fujisaki M, Shiina A, et al. A randomized, double-blind, placebo-controlled trial of fluvoxamine in patients with schizophrenia: a preliminary study. *J Clin Psychopharmacol*. 2012;32:593–601.
32 Sheikhmoonesi F, Zarghami M, Saravi SFB, Khalilian A, Ala S. A triple-blinded, randomized, placebo-controlled trial to examine the efficacy of buspirone added to typical antipsychotic drugs in patients with chronic schizophrenia. *J Res Med Sci*. 2015;20:140.
33 Kardashev A, Ratner Y, Ritsner MS. Add-on pregnenolone with L-theanine to antipsychotic therapy relieves negative and anxiety symptoms of schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. *Clin Schizophr Relat Psychoses*. 2018;12:31–41.
34 Lane H-Y, Lin C-H, Green MF, et al. Add-on treatment of benzoate for schizophrenia: a randomized, double-blind, placebo-controlled trial of d -amino acid oxidase inhibitor. *JAMA Psychiatry*. 2013;70:1267.
35 Weiser M, Zamora D, Levi L, et al. Adjunctive aspirin vs placebo in patients with schizophrenia: results of two randomized controlled trials. *Schizophr Bull*. 2021;47:1077–1087.
36 Lee JG, Lee SW, Lee BJ, Park SW, Kim GM, Kim YH. Adjunctive memantine therapy for cognitive impairment in chronic schizophrenia: a placebo-controlled pilot study. *Psychiatry Investig*. 2012;9:166.
37 Kelly DL, Sullivan KM, McEvoy JP, et al. Adjunctive minocycline in clozapine-treated schizophrenia patients with persistent symptoms. *J Clin Psychopharmacol*. 2015;35:374–381.
38 Salehi A, Namaei P, TaghaviZanjani F, et al. Adjuvant palmitoylethanolamide therapy with risperidone improves negative symptoms in patients with schizophrenia: a randomized, double-blinded, placebo-controlled trial. *Psychiatry Res*. 2022;316:114737.
39 Chang JS. Aripiprazole augmentation in clozapine-treated patients with refractory schizophrenia: an 8-week, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2008;69:720.
40 Muscatello MRA, Pandolfo G, Micò U, et al. Augmentation of clozapine with ziprasidone in refractory schizophrenia: a double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2014;34:129–133.
41 Roffman JL, Petruzzi LJ, Tanner AS, et al. Biochemical, physiological and clinical effects of l-methylfolate in schizophrenia: a randomized controlled trial. *Mol Psychiatry*. 2018;23:316–322.
42 Bugarski-Kirola D, Blaettler T, Arango C, et al. Bitopertin in negative symptoms of schizophrenia—results from the phase III FlashLyte and DayLyte studies. *Biol Psychiatry*. 2017;82:8–16.
43 Ghajar A, Gholamian F, Tabatabei-Motlagh M, et al. Citicoline (CDP-choline) add-on therapy to risperidone for treatment of negative symptoms in patients with stable schizophrenia: a double-blind, randomized placebo-controlled trial. *Hum Psychopharmacol Clin Exp*. 2018;33:e2662.
44 Ghaderi A, Banafshe HR, Mirhosseini N, et al. Clinical and metabolic response to vitamin D plus probiotic in schizophrenia patients. *BMC Psychiatry*. 2019;19:77.
45 Tharoor H, Maran S, Chandan AK, Pari M, Rao S, Durairaj J. Cognitive and negative symptoms in schizophrenia with L-Carnosine adjuvant therapy – a randomized double-blind placebo-controlled study. *Pharmacol Res Perspect*. 2023;11:e01074.
46 Miodownik C, Lerner V, Kudkaeva N, et al. Curcumin as add-on to antipsychotic treatment in patients with chronic schizophrenia: a randomized, double-blind, placebo-controlled study. *Clin Neuropharmacol*. 2019;42:117–122.
47 Nikbakhat M-R, Arabzadeh S, Zeinoddini A, et al. Duloxetine add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: randomized double-blind placebo-controlled study. *Pharmacopsychiatry*. 2016;49:162–169.
48 Mico' U, Bruno A, Pandolfo G, et al. Duloxetine as adjunctive treatment to clozapine in patients with schizophrenia: a randomized, placebo-controlled trial. *Int Clin Psychopharmacol*. 2011;26:303–310.
49 Bugarski-Kirola D, Bitter I, Liu I-Y, Abbs B, Stankovic S. ENHANCE: phase 3, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin for schizophrenia in patients with an inadequate response to antipsychotic treatment. *Schizophr Bull Open*. 2022;3:sgac006.
50 Kaphzan H, Ben-Shachar D, Klein E. Entacapone augmentation of antipsychotic treatment in schizophrenic patients with negative symptoms; a double-blind placebo-controlled study. *Int J Neuropsychopharmacol*. 2014;17:337–340.
51 Iancu I, Tschernihovsky E, Bodner E, Piconne AS, Lowengrub K. Escitalopram in the treatment of negative symptoms in patients with chronic schizophrenia: a randomized double-blind placebo-controlled trial. *Psychiatry Res*. 2010;179:19–23.
52 Lane H-Y, Huang C-L, Wu P-L, et al. Glycine transporter I inhibitor, N-methylglycine (sarcosine), added to clozapine for the treatment of schizophrenia. *Biol Psychiatry*. 2006;60:645–649.
53 Chen EYH, Hui CLM. HT1001, A proprietary north American ginseng extract, improves working memory in schizophrenia: a double-blind, placebo-controlled study: HT1001 improves memory in schizophrenia. *Phytother Res*. 2012;26:1166–1172.
54 Rezaei F, Mohammad-karimi M, Seddighi S, et al. Memantine add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2013;33:336–342.
55 Veerman SRT, Schulte PFJ, Smith JD, De Haan L. Memantine augmentation in clozapine-refractory schizophrenia: a randomized, double-blind, placebo-controlled crossover study. *Psychol Med*. 2016;46:1909–1921.
56 Khodaie-Ardakani M-R, Mirshafiee O, Farokhnia M, et al. Minocycline add-on to risperidone for treatment of negative symptoms in patients with stable schizophrenia: randomized double-blind placebo-controlled study. *Psychiatry Res*. 2014;215:540–546.
57 Michalopoulou PG, Lewis SW, Drake RJ, et al. Modafinil combined with cognitive training: pharmacological augmentation of cognitive training in schizophrenia. *Eur Neuropsychopharmacol*. 2015;25:1178–1189.
58 Berk M, Copolov D, Dean O, et al. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biol Psychiatry*. 2008;64:361–368.
59 Goff D, Cather C, Gottlieb J, et al. Once-weekly d-cycloserine effects on negative symptoms and cognition in schizophrenia: an exploratory study. *Schizophr Res*. 2008;106:320–327.
60 Buchanan RW, Weiner E, Kelly DL, et al. Rasagiline in the treatment of the persistent negative symptoms of schizophrenia. *Schizophr Bull*. 2015;41:900–908.
61 Samaei A, Moradi K, Bagheri S, et al. Resveratrol adjunct therapy for negative symptoms in patients with stable schizophrenia: a double-blind, randomized placebo-controlled trial. *Int J Neuropsychopharmacol*. 2020;23:775–782.
62 Freudenreich O, Henderson DC, Walsh JP, Culhane MA, Goff DC. Risperidone augmentation for schizophrenia partially responsive to

clozapine: a double-blind, placebo-controlled trial. *Schizophr Res*. 2007;92:90–94.
63 Lin C-H, Lin C-H, Chang Y-C, et al. Sodium benzoate, a D-amino acid oxidase inhibitor, added to clozapine for the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Biol Psychiatry*. 2018;84:422–432.
64 Shiloh R, Zemishlany Z, Aizenberg D, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine: a double-blind, placebo-controlled study. *Br J Psychiatry*. 1997; 171:569–573.
65 Omranifard V, Rajabi F, Mohammadian-Sichani M, Maracy MR. The effect of add-on memantine on positive, negative and depressive symptoms of schizophrenia: a doubleblind, randomized, controlled trial. *Actas Esp Psiquiatr*. 2017;45:108–115.
66 Bobo WV, Woodward ND, Sim MY, Jayathilake K, Meltzer HY. The effect of adjunctive armodafinil on cognitive performance and psychopathology in antipsychotic-treated patients with schizophrenia/schizoaffective disorder: a randomized, double-blind, placebo-controlled trial. *Schizophr Res*. 2011;130:106–113.
67 Iranpour N, Zandifar A, Farokhnia M, et al. The effects of pioglitazone adjuvant therapy on negative symptoms of patients with chronic schizophrenia: a double-blind and placebo-controlled trial: pioglitazone in Treatment of Schizophrenia. *Hum Psychopharmacol Clin Exp*. 2016;31:103–112.
68 Lerner V, Miodownik C, Gibel A, et al. The retinoid X receptor agonist bexarotene relieves positive symptoms of schizophrenia: a 6-week, randomized, double-blind, placebo-controlled multicenter trial. *J Clin Psychiatry*. 2013;74:1224–1232.
69 Piškulić D, Olver JS, Maruff P, Norman TR. Treatment of cognitive dysfunction in chronic schizophrenia by augmentation of atypical antipsychotics with buspirone, a partial 5-HT $_{1A}$ receptor agonist. *Hum Psychopharmacol Clin Exp*. 2009;24:437–446.
70 Korhonen P, Heintjes EM, Williams R, et al. Pioglitazone use and risk of bladder cancer in patients with type 2 diabetes: retrospective cohort study using datasets from four European countries. *BMJ*. 2016;354:i3903.
71 Cahan A, Cimino JJ. Improving precision medicine using individual patient data from trials. *Can Med Assoc J*. 2017;189:E204–E207.
72 Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emerg Med J*. 2003;20:164–168.
73 Clark L, Fairhurst C, Torgerson DJ. Allocation concealment in randomised controlled trials: are we getting better?: table 1. *BMJ*. 2016;355:i5663.
74 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;79:210–218.
75 Bai MY, Lovejoy DB, Guillemin GJ, Kozak R, Stone TW, Koola MM. Galantamine-memantine combination and kynurenine pathway enzyme inhibitors in the treatment of neuropsychiatric disorders. *Complex Psychiatry*. 2021;7:19–33.