APPENDIX

Appendix

1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Appendix5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 7, Appendix6.1

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 8
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9, Appendix4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Appendix4
Study characteristics	17	Cite each included study and present its characteristics.	Appendix5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Appendix13
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Appendix7-8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9-12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-12 and Appendix7-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 12 and Appendix9
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 13 and Appendix11
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 13 and

Section and Topic	Item #	Checklist item	Location where item is reported
			Appendix14
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 13-14 and Appendix15
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 14
	23b	Discuss any limitations of the evidence included in the review.	Page 17
	23c	Discuss any limitations of the review processes used.	Page 16
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14-16
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Appendix2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 8
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 3
Competing interests	26	Declare any competing interests of review authors.	Page 3
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 18

2 Protocol

A Network Meta-Analysis of Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia

Review question
To examine the efficacy, acceptability and tolerability of both first- and second-generation antipsychotic drugs for treatment-resistant schizophrenia patients of all ages by applying a network meta-analysis approach.

Searches
1. Electronic databases: We will search the Cochrane Schizophrenia Group's Study-Based Register of Trials with no date/time, language, document type, and publication status limitations. This register is compiled of regular searches in multiple electronic databases, ClinicalTrials.gov, WHO register of clinical trials and more. Details on the register can be found in (Shokraneh and Adams 2017, 2019, 2020, 2021).
2. Hand searching: The Cochrane Schizophrenia Group's Study-Based Register of Trials also includes hand searches. We will additionally inspect references in previous reviews on treatment-resistant schizophrenia, as well as previous reviews from our team [1-3].
3. Personal contact: We will contact via email the first and/or corresponding authors of each included study published in the last 20 years for missing information about their studies.

Types of study to be included
We will include all randomized trials (RCTs) comparing one antipsychotic drug with another antipsychotic agent or placebo in treatment-resistant schizophrenia, but open and single-blind RCTs will be excluded in a sensitivity analysis (see below the Analysis of subgroups or subsets). Trials in which antipsychotic drugs were used as an augmentation- or combination strategy will be excluded as well as studies with a high risk of bias in the randomization process, and studies from mainland China [4]. In the case of cross-over studies we will only use the first cross-over phase to avoid the problem of carry-over effects which are very likely in schizophrenia. We will include cluster-RCTs applying the appropriate correction of the unit of analysis, or if such a correction can be applied post-hoc. But we anticipate it could be a very rare case. The minimum duration of trials will be 3 weeks.

Condition or domain being studied
Schizophrenia

Participants/population
We will include participants with a treatment-resistant form of schizophrenia, schizophreniform disorder, or schizoaffective disorder (no age limit, any definition of treatment resistance, no restriction in diagnostic criteria, setting, gender, and ethnicity).

Intervention(s), exposure(s)
We will include all antipsychotic drugs that are available in at least one country, including first-generation ("typical", "conventional") antipsychotics as well as second-generation ("atypical") antipsychotics and placebo. We will include all these compounds at any dose and in any oral forms of administration (for example tablets, liquid) or as intramuscular depot formulations. If an antipsychotic is available in both oral and depot forms, both formulations will be used as separate interventions in the network.

Comparator(s)/control
In a network meta-analysis, any treatment can be a comparator as all antipsychotics and placebo will be used to compare with each other. Placebo will be used as reference for presentation.

Context
There are no restrictions in terms of setting, for example, we will include in- and outpatients.

Main outcome(s)

The primary outcome will be the overall symptoms of schizophrenia as measured by rating scales such as the Positive and Negative Syndrome Scale (PANSS) [5], the Brief Psychiatric Rating Scale (BPRS) [6] or of any other validated scale (e.g. the Manchester Scale [7]) for the assessment of overall schizophrenic symptomatology. As not all studies will have used the same scale, we will apply the following hierarchy: mean change of the PANSS total score from baseline to endpoint, if not available mean change of the BPRS, or if again not available the mean values at endpoint of the PANSS/ BPRS. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal, because it has been shown that unvalidated schizophrenia scales exaggerate differences [8].

Measures of effect
The effect size for the primary outcome will be the standardized mean difference (SMD), presented with their 95% CIs, because we expect different rating scales of schizophrenia symptomatology can be used in studies. We will give preference to the estimates based on imputation methods to handle missing data (used by the original authors) over completers' data.

Additional outcome(s)
1. Response to treatment. The following hierarchy of the response definitions will be applied: at least 20% reduction of the baseline score of the PANSS, 20% reduction of the BPRS or 20% reduction of any other global schizophrenia rating scale, at least "minimally improved" (score of 3) on the Clinical Global-Impressions-Improvement Scale (CGI). We choose this cutoff because even minimal improvement can be clinically important for treatment-resistant patients. If none of these definitions is available, we will use the original authors' primary definition [9].
2. Positive symptoms, measured by published rating scales.
3. Negative symptoms, measured by published rating scales.
4. Dropout due to any reason. Premature discontinuation due to any reason combines efficacy, tolerability, and other factors and can therefore be considered as a measure of "overall acceptability of treatment".
5. Dropout due to specific reasons. Dropout due to inefficacy of treatment will be considered as an additional outcome of the efficacy of treatment. Dropout due to the occurrence of adverse events will be used as a measure of overall tolerability.
6. Specific adverse events. We will focus on five most common adverse events, use of antiparkinson medication (dichotomous outcome), weight gain (kg, continuous outcome), sedation (dichotomous outcome), prolactin levels (ng/mL, continuous outcome) and QTc prolongation (ms, continuous outcome).
7. Quality of life. We will accept any published rating scale such as Heinrichs quality of life scale, Quality of Life Scale (QOLS), or any other published rating scale.
8. Functioning. Functioning will be measured by rating scales such as the Global Assessment of Functioning, the Psychosocial Performance Scale, or any other published rating scale.

Measures of effect
The effect size for continuous outcomes will be the standardized mean difference (SMD), presented with their 95% CIs, since we expect different rating scales of schizophrenia symptomatology, quality of life and functioning can be used in studies. Nevertheless, we will use mean differences (MD) for weight gain (kg), prolactin levels (ng/ml) and QTc prolongation (ms), since we can convert values of these outcomes into the same metric. We will give preference to the estimates based on imputation methods to handle missing data (used by the original authors) over completers' data.
The effect size for dichotomous outcomes will be the odds ratio (OR) and its 95% confidence intervals (CIs), because odds ratio has better mathematical properties. But we will convert back to relative risks (RRs) and percentages in treatment and control groups for presentation of the results.

Data extraction (selection and coding)
1. Selection of trials: Two reviewers will independently inspect all abstracts identified in the searches. Disagreement will be resolved by discussion, and where doubt still remains, we will acquire the full article for further inspection. Once the full articles are obtained, at least two reviewers will independently decide whether the studies meet the review criteria. If disagreement cannot be resolved by discussion, we will resolve it with a third reviewer or seek further information from the study authors.

2. Data extraction: At least two reviewers will independently extract data from all selected trials on specifically customized digital forms in the Microsoft Access database. Disagreement will be resolved by discussion with a third reviewer or by contacting the study authors.

Risk of bias (quality) assessment

Two independent reviewers will assess risk of bias of individual studies using the Cochrane Risk of Bias tool, RoB 2.0 [10].

Strategy for data synthesis

1. Two-step procedure. In a first step we will perform series of conventional pair-wise meta-analyses by combining studies that compared the same interventions. In a second step we will then perform network meta-analysis within a frequentist framework [11]. The analysis and presentation of results will be performed using R (meta and netmeta packages).
2. The heterogeneity (variability in relative treatment effects within the same treatment comparison) will be measured with the tau-squared (the variance of the random effects distribution). The heterogeneity variance will be assumed common across the various treatment comparisons and we will compare the empirical distribution with predictive distributions [12, 13]. Potential reasons for heterogeneity will be explored by subgroup analysis (see below the Analysis of subgroups or subsets).
3. Assessment of the transitivity. Intransitive networks can lead to misleading estimates. Therefore, we will assess the transitivity assumption by investigating the distribution of clinical and methodological variables that can act as effect modifiers across treatment comparisons. Potential effect modifiers are listed under "Analysis of subgroups or subsets "below. We will investigate if these variables are similarly distributed across studies grouped by comparison.
4. Network meta-analysis**.** We will conduct a random effects network meta-analysis to synthesize all evidence for each outcome, and obtain a comprehensive ranking of all treatments. Treatments will be ranked for each outcome using P-scores [14]. A key assumption is coherence, meaning the agreement between direct and indirect evidence. This will be assessed locally for each closed loop using the separating indirect from direct evidence approach, and globally for the whole network using a design-by-treatment interaction model. In case incoherence, we will investigate possible sources of it (mistakes in data entry, clear differences in study characteristics) and utilize analytical approaches [15]. If the requirements of network meta-analysis are not met (low likelihood of transitivity and/or large unexplained inconsistency) we will use pairwise meta-analysis for data synthesis.
5. Assessment of the confidence in the evidence. The confidence in the relative treatment effects for the primary outcome will be evaluated using the Confidence in Network Meta-Analysis framework [16, 17], implemented in the web application (http://cinema.ispm.ch/model/CINeMA_paper.pdf). This tool evaluates the credibility of the findings across the domains of within-study bias, across-study bias, indirectness, imprecision, heterogeneity and incoherence.

Analysis of subgroups or subsets

The following potential effect moderators of the primary outcome will be explored by subgroup analyses:
1. The criteria of treatment-resistant definitions
2. Mean participant age
3. Dose of the antipsychotics in chlorpromazine-equivalents according to Gardner et al. [18]
4. Publication date (to address the effect of possibly generally decreasing effect sizes over time)
5. Severity of illness at baseline (PANSS or BPRS score at baseline)
6. Study duration

Sensitivity analyses will be performed as follow:
1. Exclusion of non-double-blind studies (open and single-blind studies)
2. Exclusion of studies that presented only completer analyses
3. Exclusion of studies that did not use operationalized criteria to diagnose schizophrenia
4. Exclusion of studies with an overall assessment of high risk of bias
5. Exclusion of studies only included children and/or adolescents

Contact details for further information

Stefan Leucht

stefan.leucht@tum.de

Organisational affiliation of the review
Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany
https://www.tum.de/

Review team members and their organisational affiliations
Ms Shimeng Dong. Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany
Dr Johannes Schneider-Thoma. Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany
Mr Spyridon Siafis. Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany
Mr Dongfang Wang. Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany
Professor Stefan Leucht. Department of Psychiatry and Psychotherapy, School of Medicine, Technical University of Munich, Munich, Germany

Type and method of review
Network meta-analysis

Anticipated or actual start date
01 June 2021

Anticipated completion date
31 June 2022

Funding sources/sponsors
China Scholarship Council (CSC)

Language
English

Country
Germany

References
1. Huhn, M., et al., *Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis.* Lancet, 2019. **394**(10202): p. 939-951.
2. Samara, M.T., et al., *Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis.* JAMA Psychiatry, 2016. **73**(3): p. 199-210.
3. Krause, M., et al., *Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis.* Eur Neuropsychopharmacol, 2018. **28**(6): p. 659-674.
4. Wu, T., et al., *Randomized trials published in some Chinese journals: how many are randomized?* Trials, 2009. **10**: p. 46.
5. Kay, S.R., A. Fiszbein, and L.A. Opler, *The positive and negative syndrome scale (PANSS) for schizophrenia.* Schizophr Bull, 1987. **13**(2): p. 261-76.
6. Overall, J.E. and D.R. Gorham, *The Brief Psychiatric Rating Scale.* Psychological Reports, 1962. **10**(3): p. 799-812.
7. Krawiecka, M., D. Goldberg, and M. Vaughan, *A standardized psychiatric assessment scale for rating chronic psychotic patients.* Acta Psychiatr Scand, 1977. **55**(4): p. 299-308.

8. Marshall, M., et al., *Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia.* Br J Psychiatry, 2000. **176**: p. 249-52.
9. Leucht, S., et al., *Linking the PANSS, BPRS, and CGI: clinical implications.* Neuropsychopharmacology, 2006. **31**(10): p. 2318-25.
10. Sterne, J.A.C., et al., *RoB 2: a revised tool for assessing risk of bias in randomised trials.* BMJ, 2019. **366**: p. l4898.
11. Rücker, G., *Network meta-analysis, electrical networks and graph theory.* Res Synth Methods, 2012. **3**(4): p. 312-24.
12. Turner, R.M., et al., *Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews.* Int J Epidemiol, 2012. **41**(3): p. 818-27.
13. Rhodes, K.M., R.M. Turner, and J.P. Higgins, *Predictive distributions were developed for the extent of heterogeneity in meta-analyses of continuous outcome data.* J Clin Epidemiol, 2015. **68**(1): p. 52-60.
14. Rücker, G. and G. Schwarzer, *Ranking treatments in frequentist network meta-analysis works without resampling methods.* BMC Med Res Methodol, 2015. **15**: p. 58.
15. Salanti, G., *Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool.* Res Synth Methods, 2012. **3**(2): p. 80-97.
16. Nikolakopoulou, A., et al., *CINeMA: An approach for assessing confidence in the results of a network meta-analysis.* PLoS Med, 2020. **17**(4): p. e1003082.
17. Salanti, G., et al., *Evaluating the quality of evidence from a network meta-analysis.* PLoS One, 2014. **9**(7): p. e99682.
18. Gardner, D.M., et al., *International consensus study of antipsychotic dosing.* Am J Psychiatry, 2010. **167**(6): p. 686-93.

3 Search strategy

We searched the register of the Cochrane Schizophrenia Group.

Following the methods from Cochrane,[1] the Information Specialist compiles this register from systematic searches of major resources and their monthly updates (unless otherwise specified):

1. MEDLINE;
2. Embase;
3. Allied and Complementary Medicine (AMED);
4. Cumulative Index to Nursing and Allied Health Literature (CINAHL);
5. PsycINFO;
6. PubMed;
7. US National Institute of Health Ongoing Trials Register ClinicalTrials.gov;
8. World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp);
9. ProQuest Dissertations and Theses A&I and its quarterly update;
10. Chinese databases (Chinese Biomedical Literature Database, China Knowledge Resource Integrated Database, and Wanfang) and their annual updates until the end of 2016.

The register also includes hand searches and conference proceedings (see Group's website: http://schizophrenia.cochrane.org/register-trials). It does not place any limitations on language, date, document type or publication status. Further information about the register has been published by Shokraneh et al.[2–5]

The search strategy of the first search (27/04/2020) was:

((*Amisulpride* OR *Aripiprazole* OR *Asenapine* OR *Benperidol* OR *Brexpiprazole* OR *Cariprazine* OR *Chlorpromazine* OR *Clopenthixol* OR *Clozapine* OR *Flupentixol* OR *Fluphenazine* OR *Fluspirilene* OR *Haloperidol* OR *Iloperidone* OR *Levomepromazine* OR *Loxapine* OR *Lumateperone* OR *Lurasidone* OR *Molindone* OR *Olanzapine* OR *Paliperidone* OR *Penfluridol* OR *Perazine* OR *Perphenazine* OR *Pimozide* OR *Quetiapine* OR *Risperidone* OR *Sertindole* OR *Sulpiride* OR *Thioridazine* OR *Tiotixene* OR *Trifluoperazine* OR *Ziprasidone* OR *Zotepine* OR *Zuclopenthixol*) in Intervention Field of Study)

The second and the third update searches of the Cochrane Schizophrenia Group Register were made on September 19, 2021 and March 06, 2022, respectively. Both searches were not restricted to the antipsychotic drugs above, all controlled trials of schizophrenia were inspected. Apart from this all descriptions of the register etc. above applied.

The last update search was conducted in MEDLINE (20/01/2023) with the following search strategy:

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 20, 2023>

Search Strategy:

1 randomized controlled trial.pt. (584874)
2 controlled clinical trial.pt. (95158)
3 randomized.ab. (590240)
4 placebo.ab. (235122)
5 clinical trials as topic.sh. (200778)
6 randomly.ab. (400293)
7 trial.ab. (632640)
8 or/1-7 (1692527)
9 exp animals/ not humans.sh. (5084723)
10 8 not 9 (1552536)
11 exp SCHIZOPHRENIA/ (113837)
12 exp Paranoid Disorders/ (4248)
13 schizo$.mp. (187748)
14 hebephreni$.mp. (287)
15 oligophreni$.mp. (1146)
16 psychotic$.mp. (77111)
17 psychosis.mp. (45087)
18 psychoses.mp. (21437)
19 ((chronic$ or sever$) adj2 mental$ adj2 (ill$ or disorder$)).mp. (10531)
20 exp dyskinesia, drug-induced/ (7370)
21 exp psychomotor agitation/ (6916)
22 exp neuroleptic malignant syndrome/ (2143)
23 exp "diagnosis, dual (psychiatry)"/ (3725)
24 (tardiv$ adj dyskine$).mp. (4583)
25 akathisi$.mp. (3065)
26 acathisi$.mp. (14)
27 (neuroleptic$ and (malignant adj2 syndrome)).mp. (2883)
28 (neuroleptic$ and (movement and disorder$)).mp. (983)
29 parkinsoni$.mp. (34289)
30 neuroleptic-induc$.mp. (1276)
31 or/24-30 (44295)
32 31 not (parkinson's adj1 disease).ti. (36572)
33 or/11-23 (273796)
34 or/32-33 (300026)
35 and/10,34 (23251)

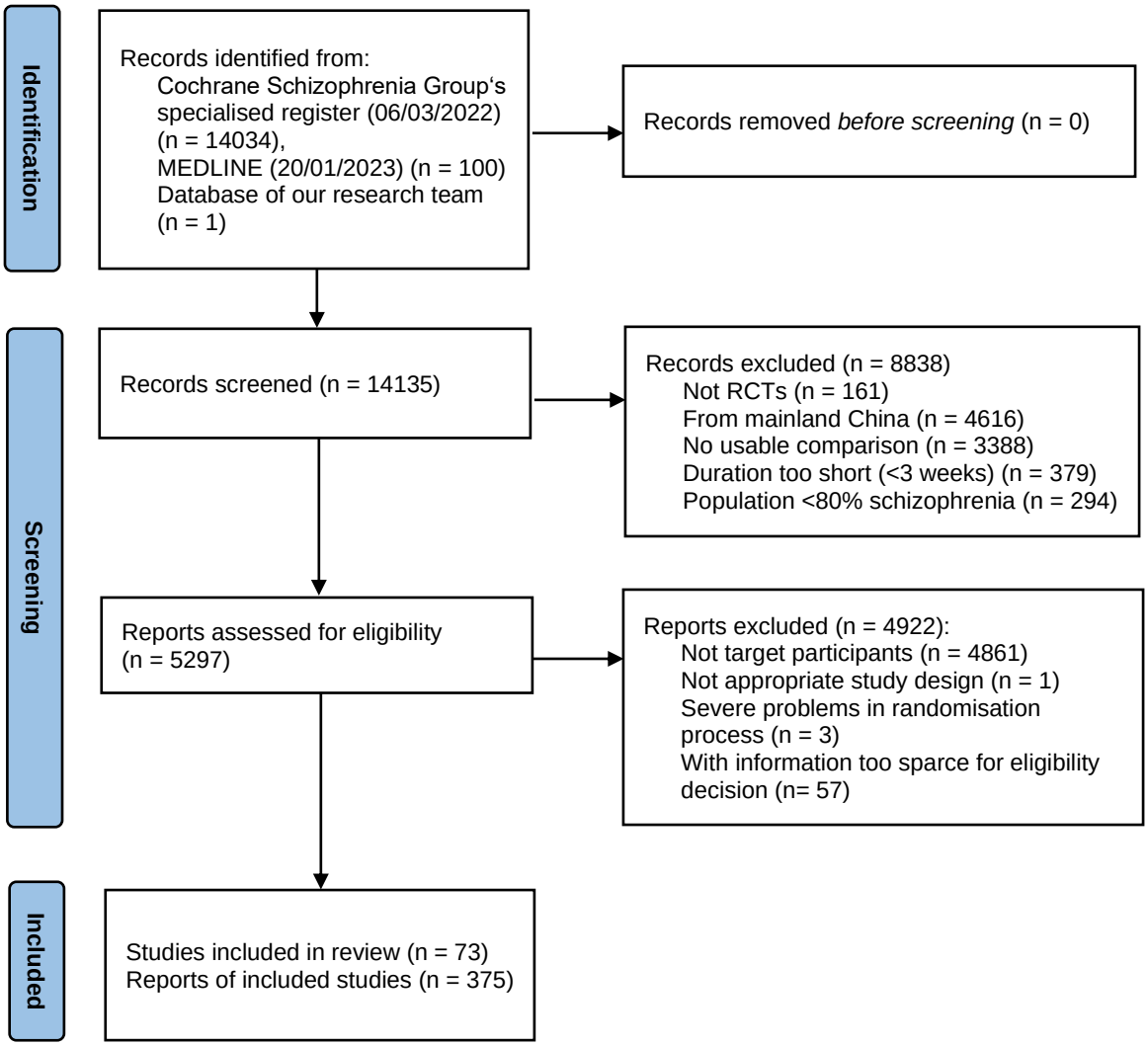
36 Amisulpride/ (792)
37 Aripiprazole/ (2818)
38 Asenapine.mp. (486)
39 Benperidol/ (799)
40 Brexpiprazole.mp. (316)
41 Cariprazine.mp. (360)
42 Chlorpromazine/ (17378)
43 Clopenthixol/ (408)
44 Clopenthixol/ (408)
45 Flupenthixol/ (927)
46 Fluphenazine/ (2427)
47 Fluspirilene/ (113)
48 Haloperidol/ (16016)
49 Iloperidone.mp. (234)

50 Methotrimeprazine/ or Levomepromazine.mp. (1031)
51 Loxapine/ (319)
52 Lumateperone.mp. (54)
53 Lurasidone Hydrochloride/ (344)
54 Molindone/ (145)
55 Olanzapine/ (6157)
56 Paliperidone Palmitate/ (1016)
57 Penfluridol/ (179)
58 Perazine/ (158)
59 Perphenazine/ (1593)
60 Pimozide/ (1741)
61 Quetiapine Fumarate/ (3107)
62 Risperidone/ (6709)
63 Sertindole.mp. (491)
64 Sulpiride/ (4029)
65 Thioridazine/ (2393)
66 Thiothixene/ (335)
67 Trifluoperazine/ (3614)
68 Ziprasidone.mp. (2135)
69 Zotepine.mp. (303)
70 Zuclopenthixol.mp. (313)
71 or/36-70 (64470)

72 limit 71 to yr="2022 - 2023" (928)
73 and/35,72 (100)

Although Pipotiazine was not part of our initial search strategy, we decided to include it in this study because it was a comparator in a three-armed trial.[6]

4 Flow chart



Reference from the database of our research team.[7] RCTs = randomized controlled trials.

5 Characteristics and references of included studies

5.1 Characteristics and references of specific studies with usable data

Study	Duration (weeks)	Study Design	Diagnosis	Definition of treatment-resistance	Intervention	Application, interval, mean dose in mg (range)	Randomized N	Mean age
Actrn12618001113246[8]	26	OL-RCT	Schizophrenia (DSM-V)	Unsuccessful treatment with 1 oral antipsychotic	Paliperidone	Depot, 4 weeks, n.i. (50-150)	36	46.4
					Paliperidone	Oral, daily, n.i. (6-12)	36	46.4
Ahlfors 1980[9]	26	DB-RCT	Schizophrenia (clinical diagnosis)	Unsatisfactory response to present neuroleptic treatment	Clopenthixol	Depot, 2 weeks, 280 (50-280)	87	n.i.
					Perphenazine	Depot, 2 weeks, 141 (20-600)	85	n.i.
Altamura 2002[10]	14	DB-RCT	Paranoid schizophrenia (DSM-IV)	partial response to previous treatments, at least 2 retrospective trials	Haloperidol	Oral, daily, 12.3 (5-20)	15	38.3
					Olanzapine	Oral, daily, 12.4 (10-20)	13	39.3
Alvarez 2006[11]	52	OL-RCT	Schizophrenia (DSM-IV)	Prominent negative symptoms and previously treated with conventional antipsychotics	Olanzapine	Oral, daily, 12.2 (10-n.i.)	124	37
					Risperidone	Oral, daily, 4.9 (3-n.i.)	123	35.5
AstraZeneca 5077IL/0031[12]	10	DB-RCT	Schizophrenia (DSM-IV)	Historical and prospective criteria of treatment-resistance	Quetiapine	Oral, daily, 571.2 (n.i. -750)	130	41
					Chlorpromazine	Oral, daily, 1040.4 (n.i. -1500)	130	40.8
AstraZeneca 5077IL/0054[13]	10	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective trials	Quetiapine	Oral, daily, 600 (600-600)	117	39
					Chlorpromazine	Oral, daily, 900 (900-900)	119	39
Azorin 2001[14]	12	DB-RCT	Schizophrenia (DSM-IV)	Poor response to previous treatment, at least 2 retrospective trials	Clozapine	Oral, daily, 642 (200-900)	138	38.2
					Risperidone	Oral, daily, 9 (2-15)	135	39.4
Bitter 2004[15]	18	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance or intolerance, at least 1 retrospective trial	Clozapine	Oral, daily, 216.2 (100-500)	72	37.4
					Olanzapine	Oral, daily, 17.2 (5-25)	75	37.6
Bondolfi 1998[16]	8	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance or intolerance, at least 2	Clozapine	Oral, daily, 291.2 (150-400)	43	36.2
					Risperidone	Oral, daily, 6.4 (3-10)	43	38.3

				retrospective trials				
Breier 1999a[17]	6	DB-RCT	Schizophrenia (DSM-IV)	Partial response to neuroleptics, at least 1 retrospective and 1 prospective trials	Clozapine	Oral, daily, 403.6 (200-600)	14	37.7
					Risperidone	Oral, daily, 5.9 (2-9)	15	32.4
Breier 1999b[18]	6	DB-RCT	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-III-R)	Treatment-resistance, at least 1 retrospective trial	Olanzapine	Oral, daily, 11.1 (5-20)	352	38.3
					Haloperidol	Oral, daily, 10 (5-20)	174	38.2
Browne 1988[19]	20	DB-RCT	Schizophrenia (Feighner's criteria, 1972)	Treatment-resistance, at least 1 retrospective trial	Haloperidol	Oral, daily, n.i. (10-160)	6	40.88
					Placebo	Oral, daily	5	40.88
Buchanan 1998[20]	10	DB-RCT	Schizophrenia or schizoaffective disorder (DSM-III-R)	Partial response to conventional neuroleptics, at least 2 retrospective and 1 prospective trials	Clozapine	Oral, daily, 415 (200-600)	38	41
					Haloperidol	Oral, daily, 25.2 (10-30)	37	40.1
Buchanan 2005[21]	16	DB-RCT	Schizophrenia or schizoaffective disorder (DSM-IV)	Partial response to conventional neuroleptics, at least 2 retrospective and 1 prospective trials	Haloperidol	Oral, daily, 18.3 (10-30)	34	46.4
					Olanzapine	Oral, daily, 20.3 (10-30)	29	41.9
Chen 2012[22]	8	SB-RCT	Schizophrenia (DSM-IV)	Inadequate response to only 1 line of first-generation antipsychotics, 1 retrospective trial	Olanzapine	Oral, daily, 17.8 (n.i. -20)	16	37.9
					Risperidone	Oral, daily, 4.3 (n.i. -6)	16	36.7
Chowdhury 1999[23]	16	n.i.	Schizophrenia and it subtypes (ICD-10)	Inadequate response, at least 1 retrospective trial	Clozapine	Oral, daily, 342.86 (200-500)	30	30.3
					Risperidone	Oral, daily, 5.8 (4-8)	30	32.43
Claus 1992[24]	12	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance, at least 1 retrospective trial	Haloperidol	Oral, daily, 10.3 (10.3-10.3)	22	39
					Risperidone	Oral, daily, 12 (12-12)	22	37.4
Conley 1998[25]	8	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance, at least 2 retrospective and 1 prospective trials	Chlorpromazine	Oral, daily, 1200 (1200-1200)	42	42.63
					Olanzapine	Oral, daily, 25 (25-25)	42	42.91

Conley 2003[26]	8	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective trials	Clozapine	Oral, daily, 390 (300-450)	5	40.26
					Olanzapine	Oral, daily, 50 (30-50)	8	35.91
Conley 2005[27]	12	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective and 1 prospective trials	Fluphenazine	Oral, daily, 13.2 (10-15)	13	44.2
					Quetiapine	Oral, daily, 463.6 (300-500)	12	43.7
					Risperidone	Oral, daily, 4.31 (3-5)	13	46.3
Daniel 1996[28]	6	SB-RCT	Schizophrenia or schizoaffective disorder (DSM-III-R)	Multiple past treatment failures or intolerance of conventional antipsychotic side effects	Clozapine	Oral, daily, n.i. (n.i. - n.i.)	10	33.8
					Risperidone	Oral, daily, n.i. (n.i. - n.i.)	10	33.8
Dean 1958[29]	15	DB-RCT	Schizophrenia (clinical diagnosis)	Fail to respond to previous treatment	Chlorpromazine	Oral, daily, n.i. (2000-3000)	9	37
					Placebo	Oral, daily	9	37
Emsley 2000[30]	8	DB-RCT	Schizophrenia (DSM-IV)	History of unsuccessful antipsychotic therapy, at least 1 retrospective and 1 prospective trials	Haloperidol	Oral, daily, 20 (20-20)	145	38.8
					Quetiapine	Oral, daily, 600 (600-600)	143	37.7
Hall 1968[31]	12	DB-RCT	Schizophrenia (clinical diagnosis)	Treatment-resistance, at least 2 retrospective trials	Haloperidol	Oral, daily, 6.95 (2-10)	25	45
					Fluphenazine	Oral, daily, 17.86 (5-25)	25	45
Hong 1997[32]	12	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective and 1 prospective trials	Clozapine	Oral, daily, 543 (100-900)	21	39.7
					Chlorpromazine	Oral, daily, 1163 (200-1800)	19	37.1
Honigfeld 1984[33]	4	DB-RCT	Schizophrenia (DSM-II)	Poor response to previous therapy or sensitivity to extra-pyramidal side effects, at least 2 retrospective trials	Clozapine	Oral, daily, 417 (150-900)	75	30
					Chlorpromazine	Oral, daily, 795 (300-1800)	76	30
Howard 1974[34]	12	DB-RCT	Chronic psychosis (clinical diagnosis)	Treatment-resistance	Haloperidol	Oral, daily, 61.57 (10-133.33)	17	46.6
					Placebo	Oral, daily	16	47.8
					Tiotixene	Oral, daily, 184.7 (30-400)	16	45.3
Kahn 2018[35]	6	DB-RCT	Schizophrenia, schizophreniform disorder, or schizoaffective disorder	Not in remission from 1 prospective trial	Amisulpride	Oral, daily, 590.9 (200-800)	47	24.9
					Olanzapine	Oral, daily, 15.6 (5-20)	46	24.6

			(DSM-IV)					
Kane 1988[36]	6	DB-RCT	Schizophrenia (DSM-III)	Treatment-resistance, at least 3 retrospective and 1 prospective trials	Clozapine	Oral, daily, 600 (500-900)	126	36.2
					Chlorpromazine	Oral, daily, 1200 (1000-1800)	142	35.6
Kane 2001[37]	29	DB-RCT	Schizophrenia or schizoaffective disorder (DSM-III-R)	Partial or poor response, at least 3 retrospective trials or 2 retrospective and 1 prospective trials	Clozapine	Oral, daily, 523 (200-800)	37	41
					Haloperidol	Oral, daily, 18.9 (4-16)	34	40
Kane 2006[38]	12	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance, at least 3 retrospective and 1 prospective trials	Chlorpromazine	Oral, daily, 743.6 (200-1200)	154	34.4
					Ziprasidone	Oral, daily, 153.8 (80-160)	152	35.6
Kane 2007[39]	6	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective and 1 prospective trials	Aripiprazole	Oral, daily, 28.8 (15-30)	154	42.6
					Perphenazine	Oral, daily, 39.1 (8-64)	146	41.6
Kane 2011[40]	12	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 1 retrospective and 1 prospective trials	Risperidone	Oral, daily, 9 (6-12)	105	38.8
					Sertindole	Oral, daily, 18.1 (12-24)	216	38.9
Kinon 1993b[41]	4	DB-RCT	Schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-III-R)	Treatment-resistance, non-response to 1 prospective trial	Haloperidol	Oral, daily, 20 (20-20)	13	n.i.
					Fluphenazine	Oral, daily, 48.24 (20-80)	34	n.i.
Kinon 2009[42]	12	DB-RCT	Schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-IV)	Treatment-resistance, non-response to 1 prospective trial	Risperidone	Oral, daily, n.i. (2-6)	192	41.87
					Olanzapine	Oral, daily, n.i. (10-20)	186	41.84
Kumra 1996[43]	6	DB-RCT	Schizophrenia (DSM-III-R)	Non-response or/and intolerance, at least 2 retrospective trials	Clozapine	Oral, daily, 176 (6.25-525)	10	14.4
					Haloperidol	Oral, daily, 16 (0.25-27)	11	13.73
Kumra 2007[44]	12	DB-RCT	Schizophrenia or	Treatment-resistance, at least 2 retrospective trials	Clozapine	Oral, daily, 403.1 (50-700)	18	15.8

			schizoaffective disorder (DSM-IV)		Olanzapine	Oral, daily, 26.2 (10-30)	21	15.5
Lal 2006[45]	15	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance, at least 3 retrospective and 1 prospective trials	Chlorpromazine	Oral, daily, 762 (600-1000)	19	39.4
					Levomepromazine	Oral, daily, 813 (600-1000)	19	38.5
Marjerrison 1964[46]	30	DB-RCT	Chronic psychosis (clinical diagnosis)	Treatment-resistance	Placebo	Oral, daily	34	47
					Trifluoperazine	Oral, daily, 28 (n.i. – n.i.)	16	49
McCreadie 1977[47]	12	DB-RCT	Schizophrenia (clinical diagnosis)	Treatment-resistance	Chlorpromazine	Oral, daily, 350 (100-600)	10	52
					Haloperidol	Oral, daily, 57.5 (15-100)	10	52
McEvoy 2006[48]	26	DB-RCT (Clozapine OL)	Schizophrenia (DSM-IV)	Non-response to prior atypical antipsychotic treatment	Olanzapine	Oral, daily, 23.4 (7.5-30)	19	44.3
					Quetiapine	Oral, daily, 642.9 (200-800)	15	37.1
					Risperidone	Oral, daily, 4.8 (1.5-6)	16	37.7
					Clozapine	Oral, daily, 332.1 (n.i. – n.i.)	49	39.4
Meltzer 2008[49]	26	DB-RCT	Schizophrenia or schizoaffective disorder (DSM-IV)	Treatment-resistance, at least 2 retrospective trials	Clozapine	Oral, daily, 564 (300-900)	21	37.2
					Olanzapine	Oral, daily, 33.6 (25-45)	19	36.4
Mercer 1997[50]	9	SB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance	Chlorpromazine	Oral, daily, 500 (50-850)	12	37.3
					Risperidone	Oral, daily, 8 (4-16)	15	42.5
Meyer-Lindenberg 1997[51]	6	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance or intolerance, at least 2 retrospective trials	Clozapine	Oral, daily, 300 (150-450)	25	33.2
					Zotepine	Oral, daily, 300 (150-450)	25	33.7
Moresco 2004[52]	8	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective trials	Clozapine	Oral, daily, 325.4 (300-400)	12	38.3
					Olanzapine	Oral, daily, 18.3 (15-20)	11	34.1
Naber 2005[53]	26	DB-RCT	Schizophrenia (DSM-IV)	Non-response or intolerance, at least 1 retrospective trial	Clozapine	Oral, daily, 209.4 (100-400)	57	35.2
					Olanzapine	Oral, daily, 16.2 (5-25)	57	32.9
Rosenheck 1997[54]	52	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance, at least 2 retrospective trials	Clozapine	Oral, daily, 552 (100-900)	205	43.2
					Haloperidol	Oral, daily, 28 (5-30)	218	43.9
Sacchetti 2009[55]	18	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance or/and intolerance, at least 3	Clozapine	Oral, daily, 345.7 (250-600)	74	38.3
					Ziprasidone	Oral, daily, 130.4 (80-160)	73	41.6

				retrospective trials				
Schiele 1961, 06602[56]	16	DB-RCT	Schizophrenia (clinical diagnosis)	Treatment-resistance	Chlorpromazine	Oral, daily, 894 (200-1000)	20	40.6
					Placebo	Oral, daily	20	40.6
					Thioridazine	Oral, daily, 958 (200-1000)	20	40.6
					Trifluoperazine	Oral, daily, 35 (10-50)	20	40.6
Schlosberg 1978[6]	52	DB-RCT	Schizophrenia (clinical diagnosis)	Treatment-resistance	Fluphenazine	Depot, 4 weeks, 27.5 (6.25-50)	30	43
					Pipotiazine	Depot, 4 weeks, 27.5 (6.25-50)	30	45
					Placebo	Depot	15	39.87
Schooler 2016[57]	29	DB-RCT	Schizophrenia or schizoaffective disorder (DSM-IV)	Partial or poor response, at least 2 retrospective trials	Clozapine	Oral, daily, 456.7 (500-800)	53	42
					Risperidone	Oral, daily, 6.8 (6-16)	54	42
See 1999[58]	5	DB-RCT	Schizophrenia (DSM-IV)	Partial response to typical antipsychotics, at least 1 retrospective and 1 prospective trials	Haloperidol	Oral, daily, n.i. (15-30)	10	37.7
					Risperidone	Oral, daily, n.i. (4-6)	10	33.5
Shalev 1993[59]	4	SB-RCT	Schizophrenia (DSM-III)	Treatment-resistance	Haloperidol	Oral, daily, 29.3 (n.i. – n.i.)	18	33
					Perphenazine	Oral, daily, 35.8 (n.i. – n.i.)	21	33
					Levomepromazine	Oral, daily, 379 (n.i. – n.i.)	21	33
Shaw 2006[60]	8	DB-RCT	Schizophrenia (DSM-IV)	Insufficient response, at least 2 retrospective trials	Clozapine	Oral, daily, 327 (150-500)	12	11.7
					Olanzapine	Oral, daily, 18.1 (5-20)	13	12.8
Sirota 2006[61]	12	SB-RCT	Schizophrenia (DSM-IV)	Inadequate response, at least 2 retrospective trials	Olanzapine	Oral, daily, 16 (5-20)	21	36.2
					Quetiapine	Oral, daily, 637.2 (200-800)	19	38.3
Smith 2001[62]	8	DB-RCT	Schizophrenia or schizoaffective psychosis (criteria n.i.)	Poor clinical response, at least 2 retrospective trials	Haloperidol	Oral, daily, 37.9 (5-40)	18	43
					Olanzapine	Oral, daily, 19.9 (5-20)	20	43
Suzuki 2007[63]	4	OL-RCT	Schizophrenia (DSM-IV)	Non-response to 1 prospective trial	Olanzapine	Oral, daily, n.i. (n.i. - 20)	15	44.9
					Quetiapine	Oral, daily, n.i. (n.i. - 750)	10	44.9
					Risperidone	Oral, daily, n.i. (n.i. - 12)	12	44.9

Tollefson 2001[64]	18	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective trials	Clozapine	Oral, daily, 303.6 (200-600)	90	38.6
					Olanzapine	Oral, daily, 20.5 (15-25)	90	38.6
Toru 1972[65]	8	DB-RCT	Schizophrenia (clinical diagnosis)	Non-response to conventional psychotropic	Chlorpromazine	Oral, daily, n.i. (150-600)	37	35
					Sulpiride	Oral, daily, n.i. (300-1200)	38	35
Volavka 2002[66]	14	DB-RCT	Schizophrenia or schizoaffective disorder (DSM-IV)	Suboptimal response, at least 1 retrospective trial	Clozapine	Oral, daily, 526.6 (200-800)	40	42.6
					Haloperidol	Oral, daily, 25.7 (10-30)	37	37.3
					Olanzapine	Oral, daily, 30.4 (10-40)	39	41
					Risperidone	Oral, daily, 11.6 (4-16)	41	42.9
Wahlbeck 2000[67]	10	SB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective and 1 prospective trials	Clozapine	Oral, daily, 385 (25-600)	11	35.7
					Risperidone	Oral, daily, 7.8 (2-10)	9	36.8
Wirshing 1999[68]	8	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance or intolerance, at least 3 retrospective trials	Haloperidol	Oral, daily, 19.4 (5-30)	33	40
					Risperidone	Oral, daily, 7.5 (3-15)	34	41

5.2 Characteristics and references of specific studies without usable data

Study	Duration (weeks)	Study Design	Diagnosis	Definition of treatment-resistant	Intervention	Application, interval, mean dose in mg (range)	Randomized N	Mean age
Addington 1996[69]	6	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance	Risperidone	Oral, daily, n.i. (6-10)	n.i.	n.i.
					Haloperidol	Oral, daily, n.i. (10-15)	n.i.	n.i.
Byerly 1999[70]	12	SB-RCT	Schizophrenia (criteria n.i.)	Non-response to olanzapine or risperidone	Clozapine	Oral, daily, 300 (300-300)	n.i.	n.i.
					Quetiapine	Oral, daily, 400 (400-400)	n.i.	n.i.
Estrella 1996[71]	104	OL-RCT	schizophrenic patients	Treatment-resistance	Clozapine	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	n.i.
					Risperidone	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	n.i.
Green 2004[72]	104	OL-RCT	Schizophrenia or schizoaffective disorder (criteria n.i.)	Treatment-resistance to 2 trials of typical neuroleptics or 1 trial of atypical antipsychotic	Clozapine	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	n.i.
					Olanzapine	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	n.i.
Hamilton 1960[73]	8	DB-RCT	Schizophrenia (clinical diagnosis)	Treatment-resistance	Chlorpromazine	Oral, daily, 300 (300-300)	18	38
					Placebo	Oral, daily	18	38
Heres 2022[74]	6	DB-RCT	schizophrenia, schizoaffective disorder or schizophreniform disorder (DSM-IV)	Not in remission from 1 prospective trial	Amisulpride	Oral, daily, n.i. (600-800)	n.i.	n.i.
					Olanzapine	Oral, daily, n.i. (15-20)	n.i.	n.i.
Heylen 1988[75]	8	DB-RCT	Chronic psychosis (clinical diagnosis)	Treatment-resistance	Risperidone	Oral, daily, n.i. (2-20)	n.i.	n.i.
					Haloperidol	Oral, daily, n.i. (2-20)	n.i.	n.i.
Mergl 1999[76]	6	DB-RCT	Schizophrenia (criteria n.i.)	Non-response to typical neuroleptics	Olanzapine	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	n.i.
					Clozapine	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	n.i.
Oliemeulen 2000[77]	8	n.i.	Schizophrenia (DSM-IV)	Treatment-resistance or intolerance	Olanzapine	Oral, n.i., n.i. (n.i. - n.i.)	21	n.i.
					Clozapine	Oral, n.i., n.i. (n.i. - n.i.)	15	n.i.
Salganik 1998[78]	10	DB-RCT	Schizophrenia (DSM-III-R)	Treatment-resistance	Clozapine	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	66.6
					Haloperidol	Oral, n.i., n.i. (n.i. - n.i.)	n.i.	66.6

Teja 1975[7]	20	DB-RCT	Schizophrenia (DSM-II)	Non-response to the various treatments	Chlorpromazine	Oral, daily, n.i. (100-1080)	14	38.01
					Haloperidol	Oral, daily, n.i. (2-45)	13	38.01
					Placebo	Oral, daily	10	38.01

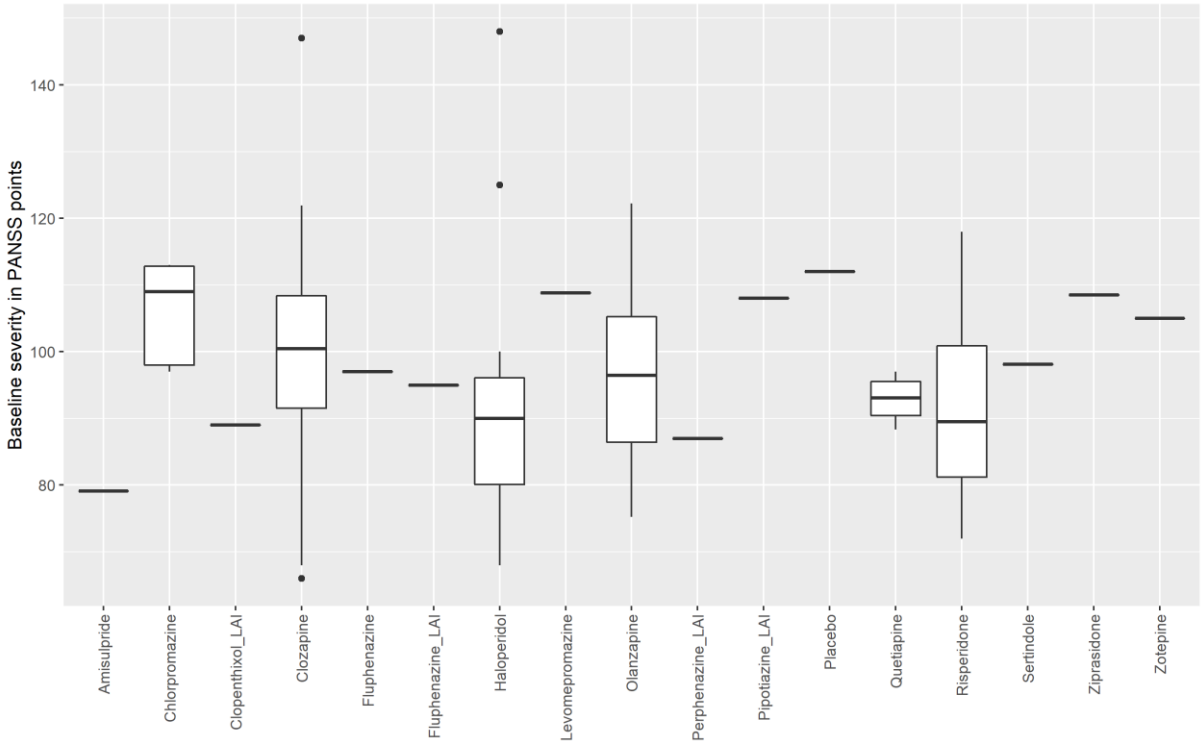
DB-RCT: double blind randomized controlled trial; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Statistical Classification of Diseases and Related Health Problems; n.i.: not indicated; OL-RCT: open label randomized controlled trial; SB-RCT: single blind randomized controlled trial.

6 Transitivity assessment

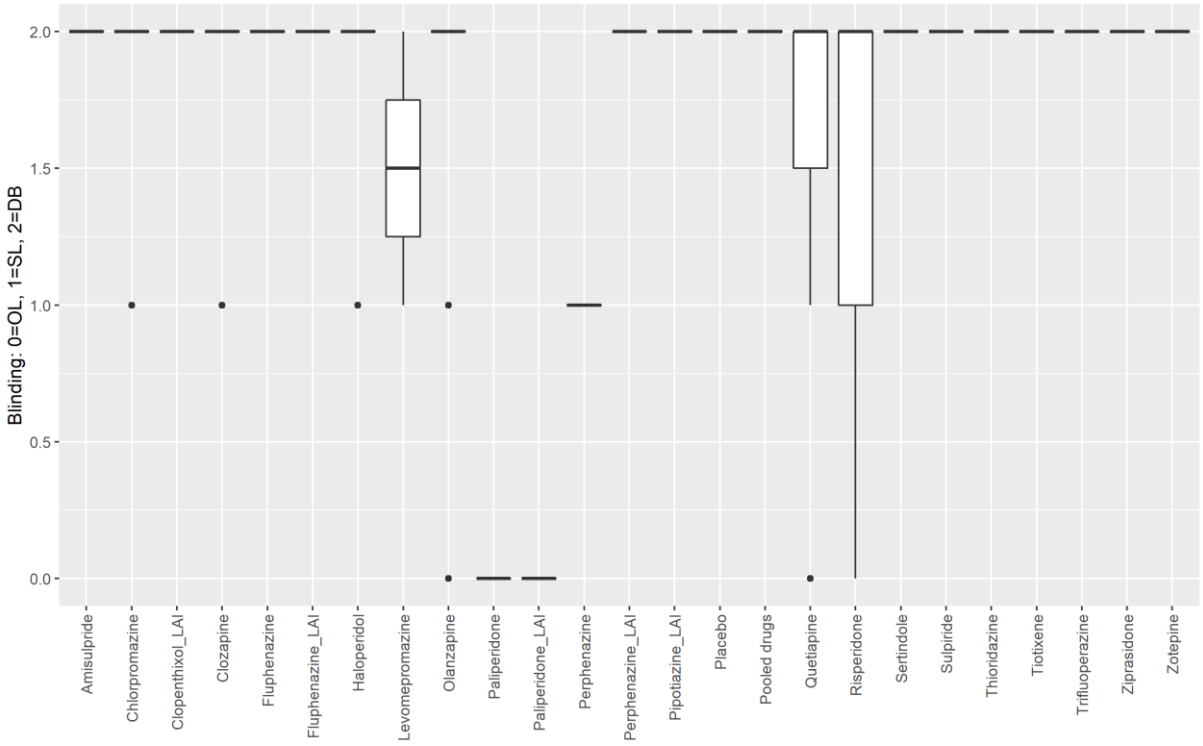
Following the recommendations of Cochrane handbook,[79] we visually inspected the distribution of potential effect modifiers across antipsychotics based on all included studies with at least one available data.

6.1 Baseline severity

We converted BPRS-18 baseline scores of studies to PANSS equivalents based on Leucht 2013[80]. Baseline severity ranges from a minimal of 66 in PANSS equivalents to a maximum of 148. However, the PANSS equivalents could be problematic as BPRS versions were not indicated clearly in studies when converting from BPRS to PANSS.

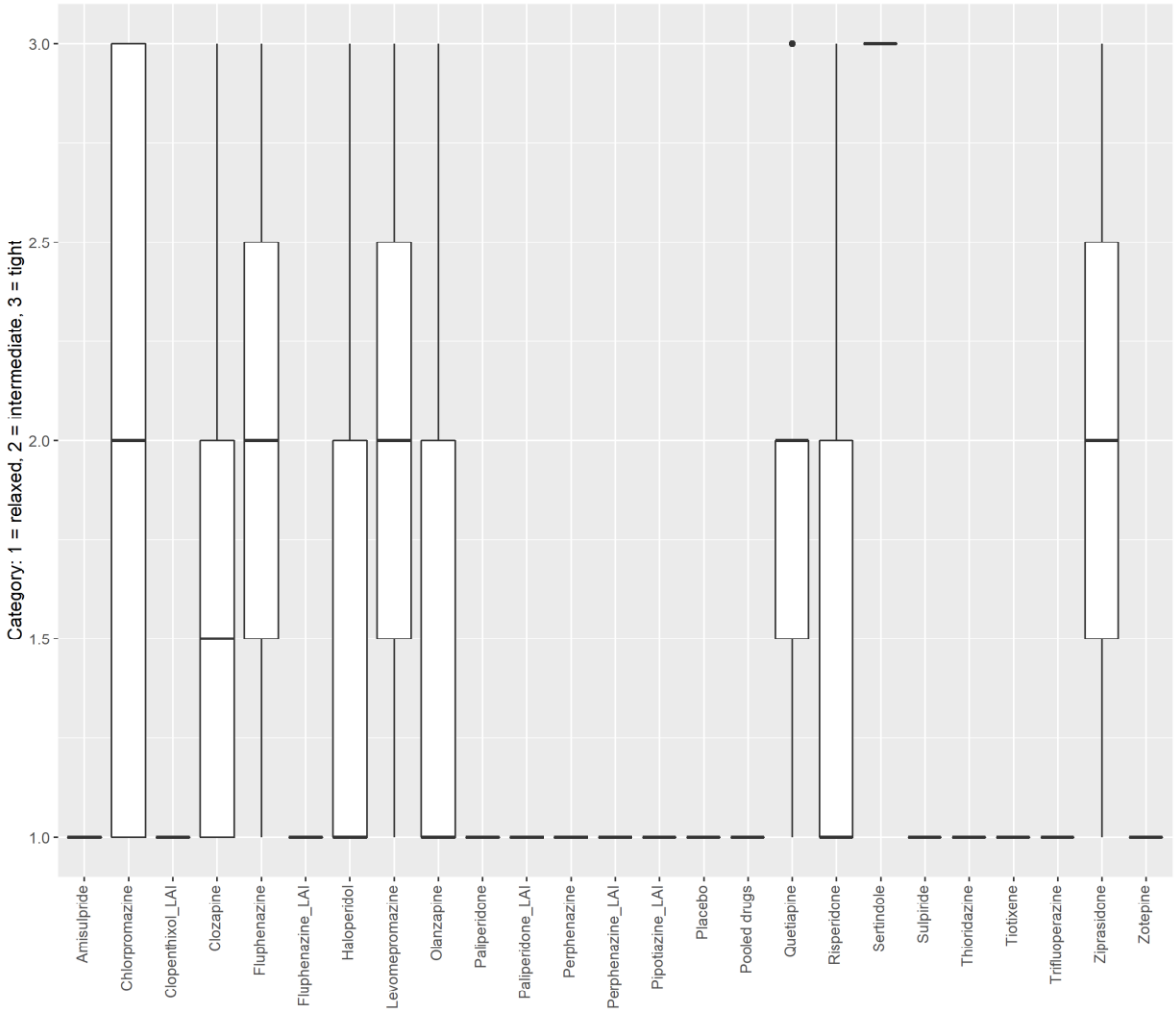


6.2 Blinding of outcome assessor



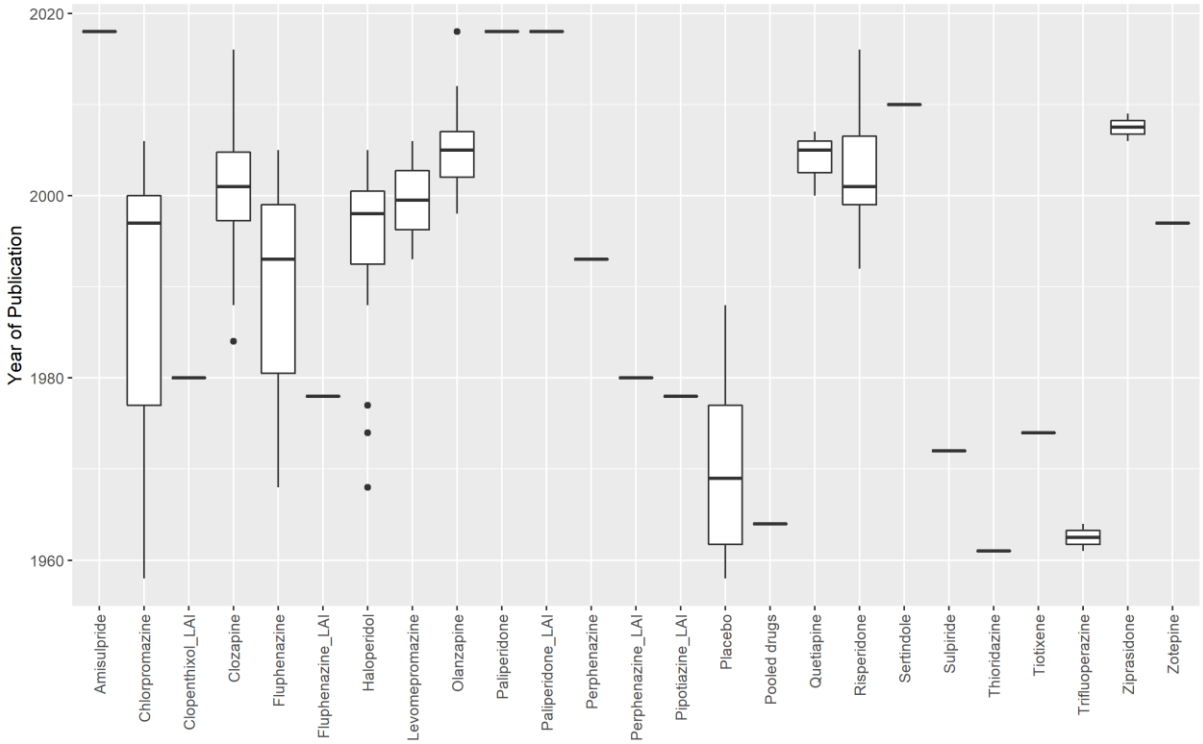
OL=open-label study; SL=single-blind study; DB=double-blind study

6.3 Treatment-resistance definition

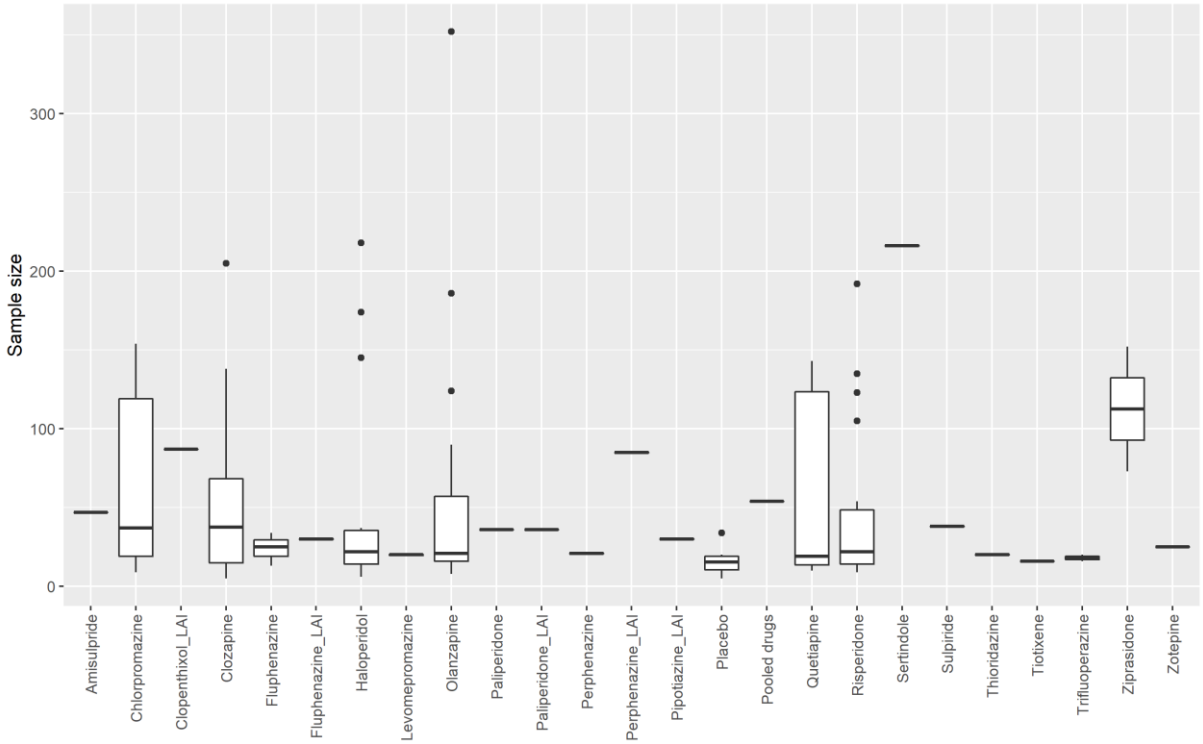


Criteria of treatment-resistance definition is presented in Appendix 12.1.1.

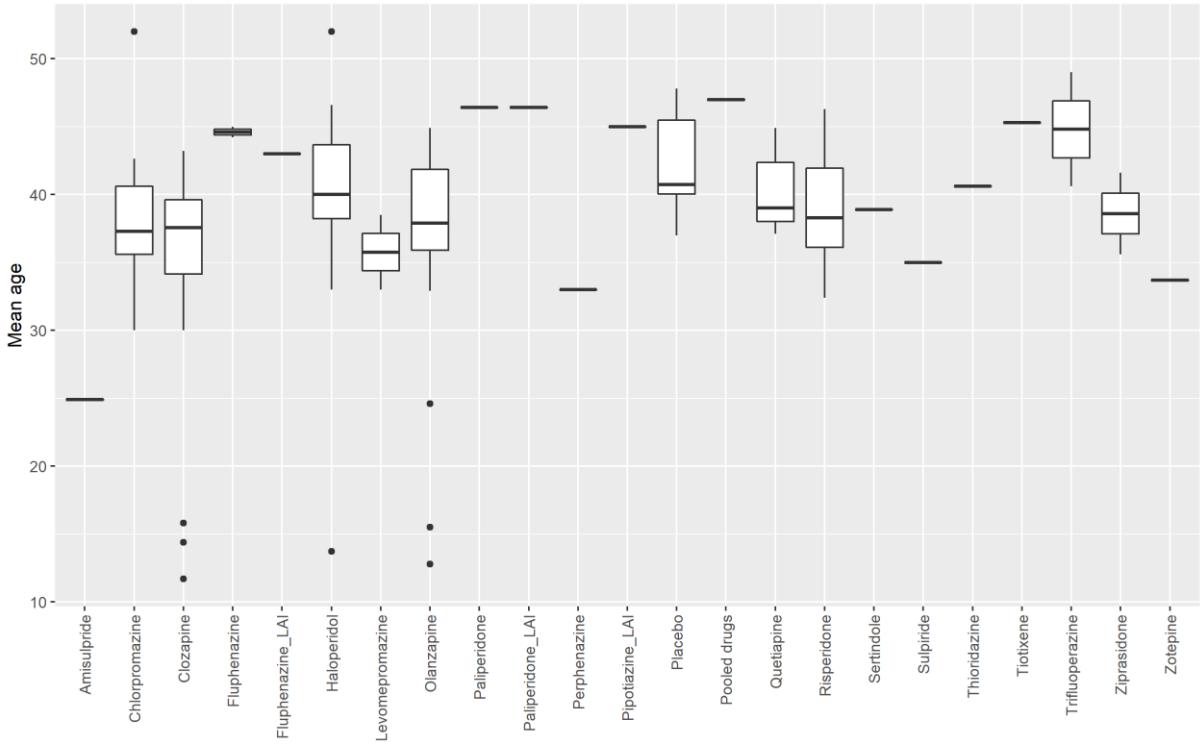
6.4 Publication year



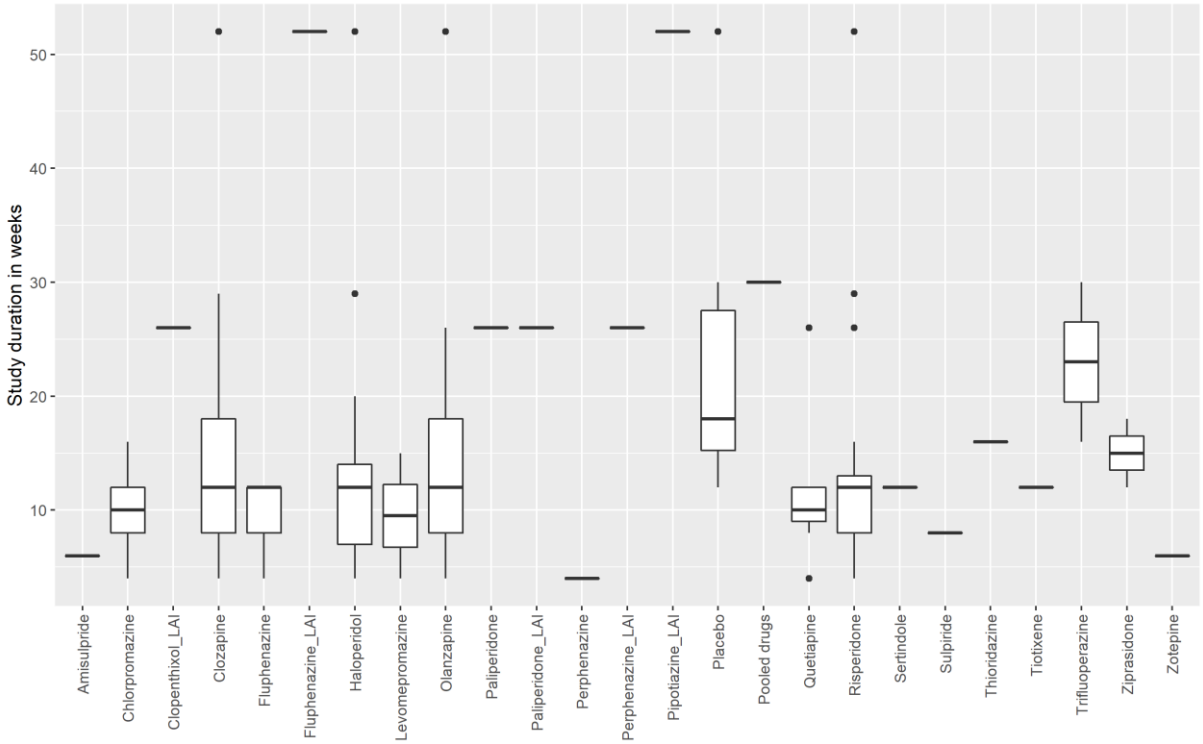
6.5 Sample size



6.6 Mean age

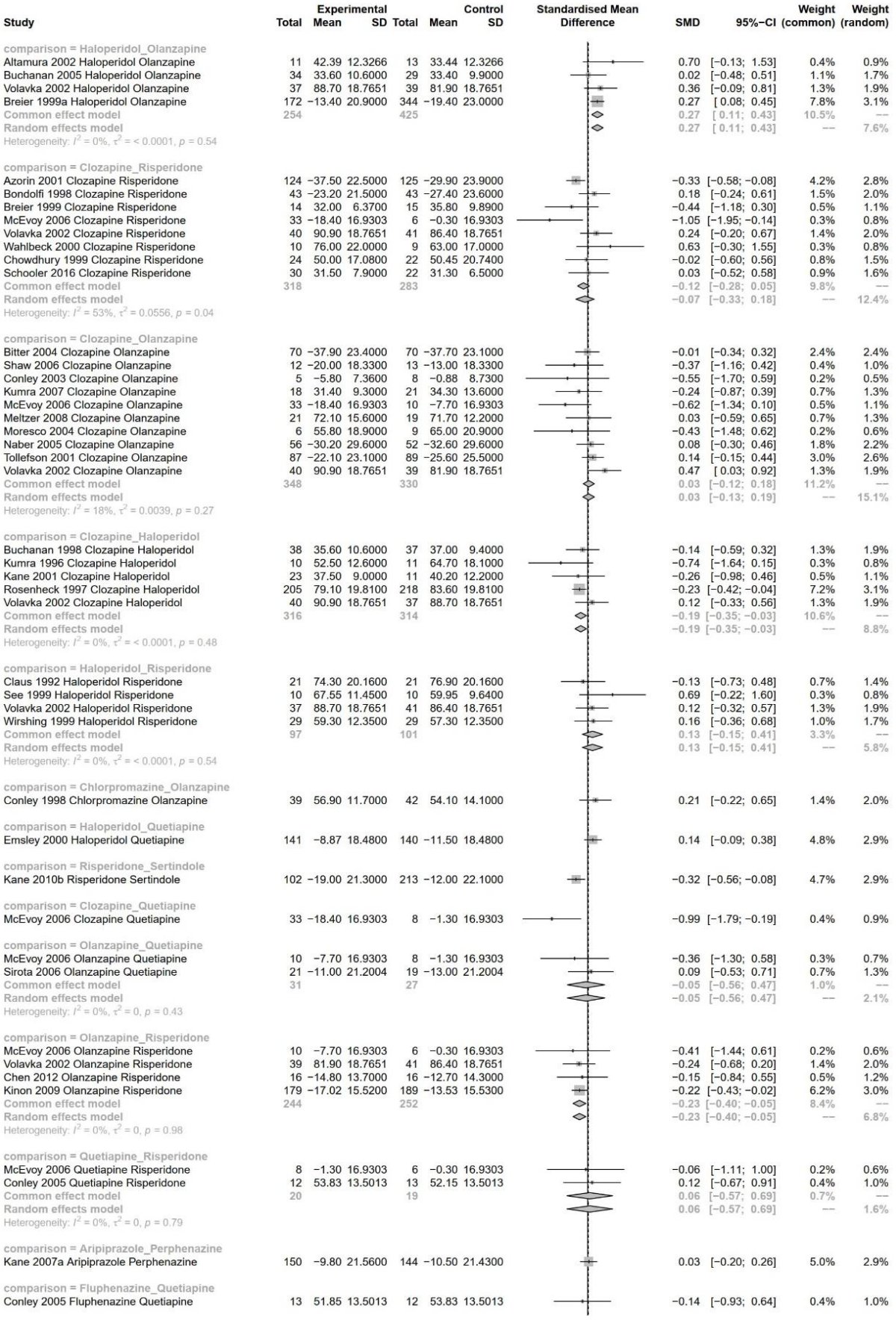


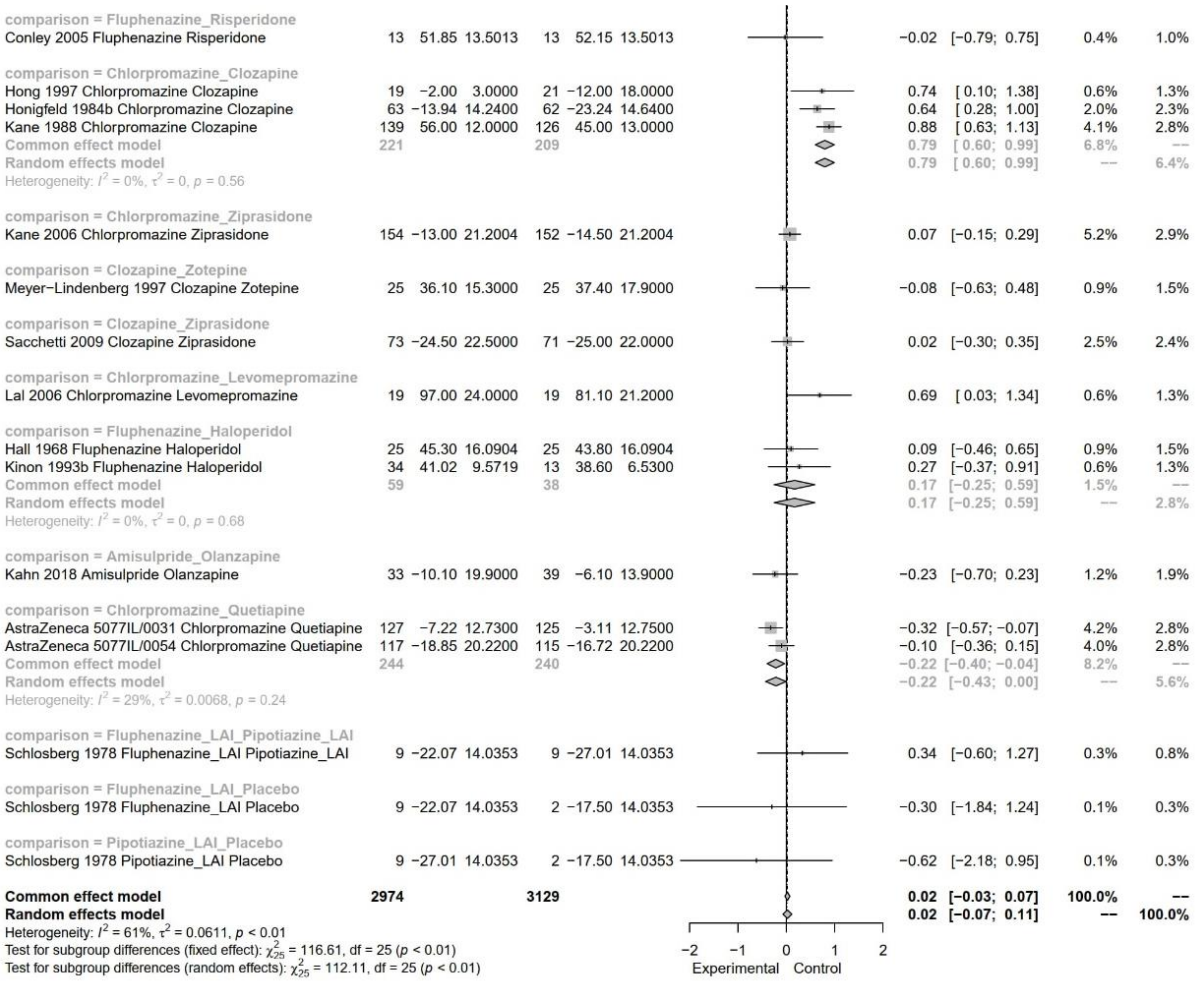
6.7 Study duration



7 Forest plots of pairwise meta-analyses of the primary outcome

7.1 Pairwise meta-analysis of all antipsychotics

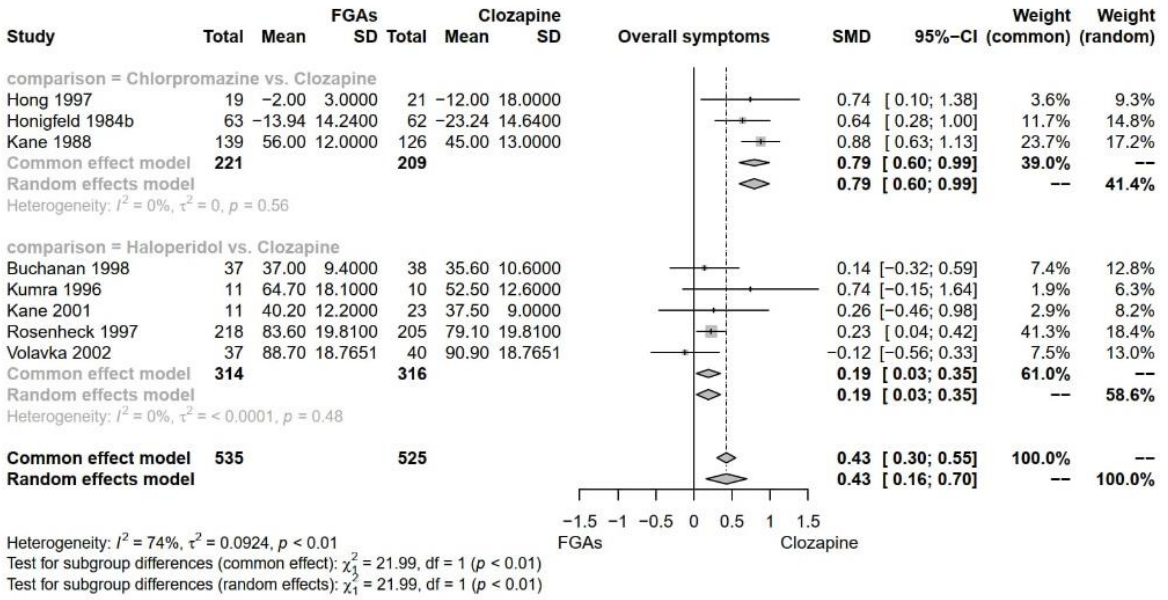




A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is standardized mean difference (SMD).

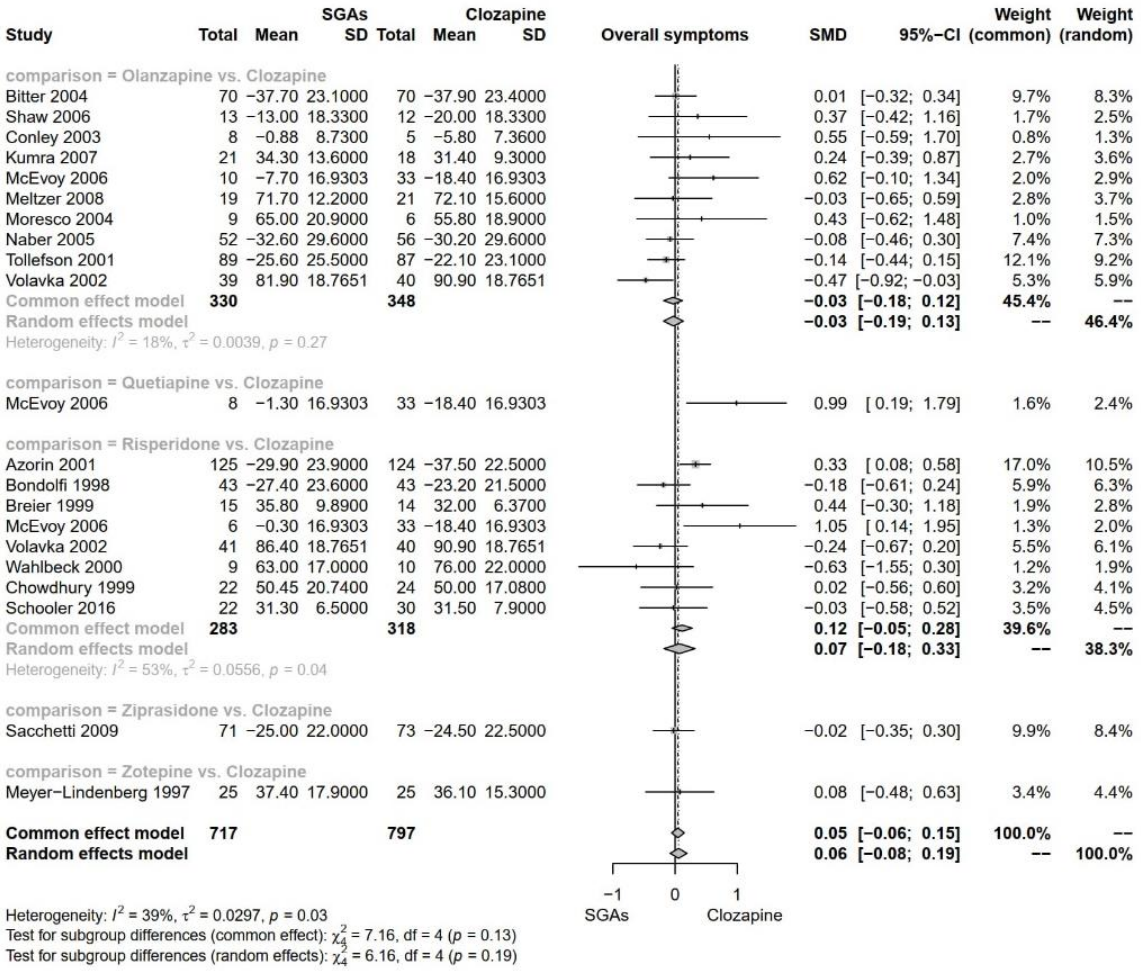
7.2 Post-hoc pairwise meta-analysis of first-generation antipsychotics (FGAs) vs. clozapine

Clozapine is better only as FGAs as a group but not as SGAs as a group.



7.3 Post-hoc pairwise meta-analysis of second-generation antipsychotics (SGAs) vs. clozapine

Clozapine is better only as FGAs as a group but not as SGAs as a group.



8 Results of the network meta-analyses of the secondary outcomes

Each outcome is presented in the order:

- Network plot
- Forest plot of results of network meta-analysis (clozapine as reference)
- League table
- Forest plot of results of pairwise meta-analysis

For the effect size of dichotomous outcomes, we performed the statistical analysis using odds ratios (OR) and not risk ratios (RR), because OR provide more stable estimates of treatment effects across study-conditions with different baseline risks. Therefore, it is recommended for (network-)meta-analysis. However, OR are more difficult to interpret than RR. For specific situations/patients with specific (assumed or known) baseline risks, OR can be transformed to RR or presented as exposure-event-rates (EER) versus control-event-rates (CER).

Formula for the transformations:

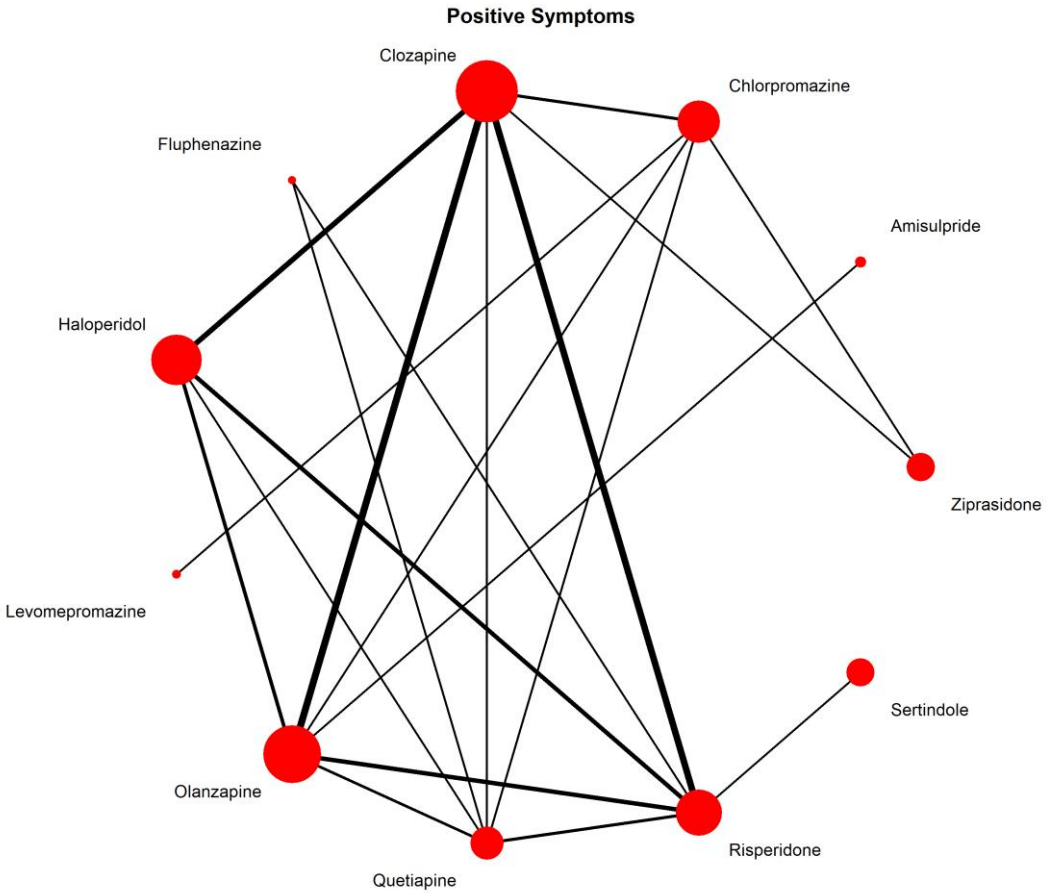
RR= OR/[(1-CER) +(OR*CER)]

EER= RR*CER

We present forests plots and league tables with the original results in OR, RR and EER vs. CER below (EER vs. CER in the forest plot only).

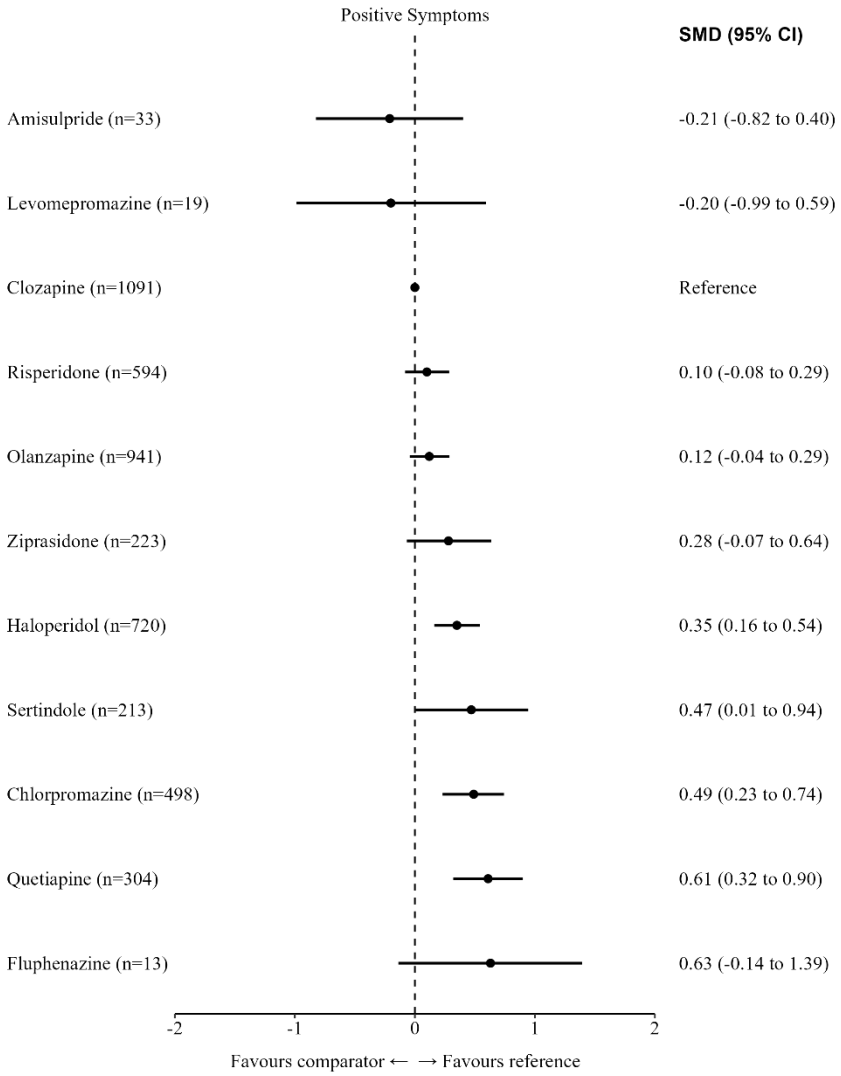
8.1 Positive symptoms

Network plot



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.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



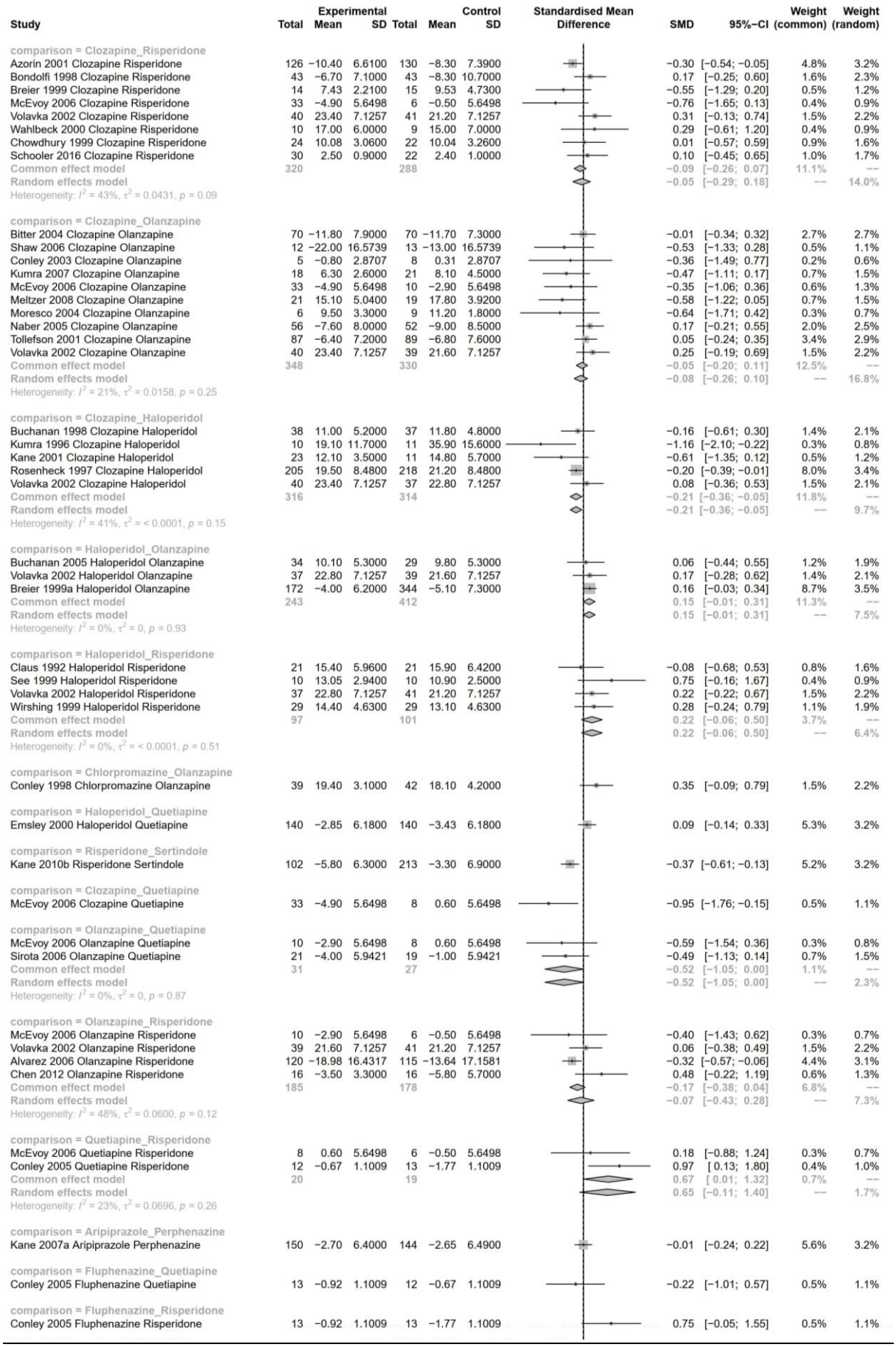
Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

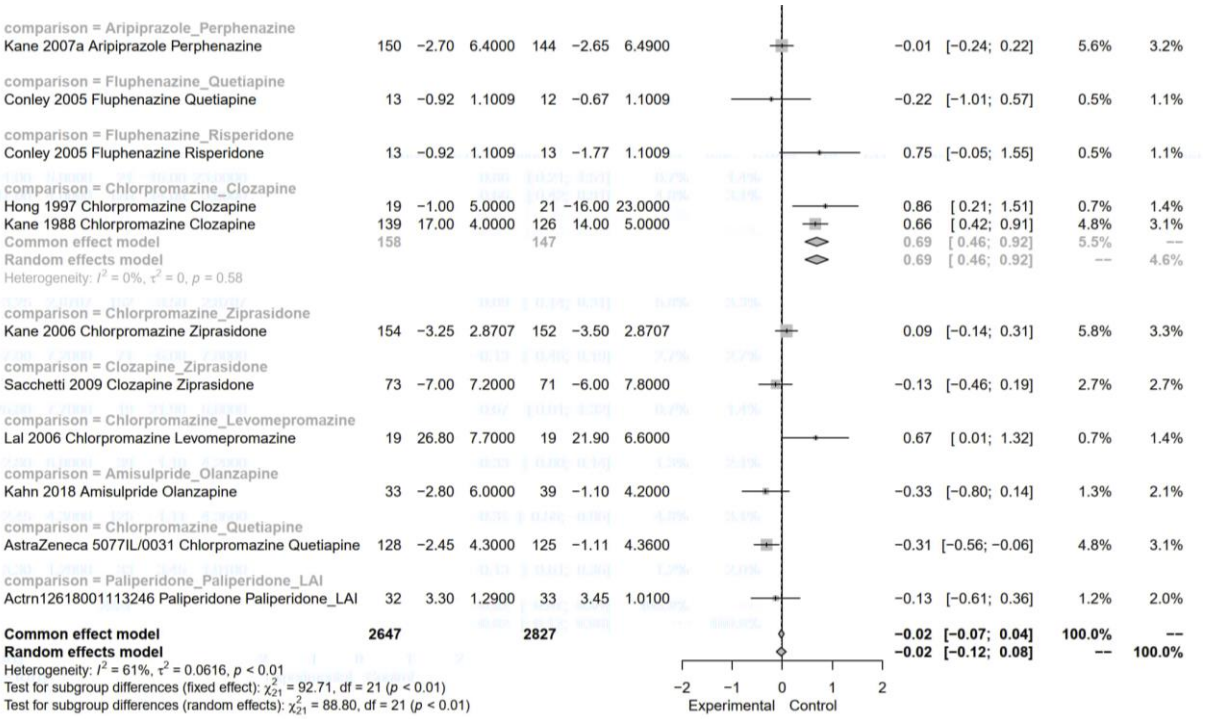
League table for the outcome: Positive symptoms

Amisulpride	NA	NA	NA	-0.33 (-0.92 to 0.26)	NA	NA	NA	NA	NA	NA
-0.01 (-1.01 to 0.98)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	-0.68 (-1.43 to 0.06)	NA	NA
-0.21 (-0.82 to 0.40)	-0.20 (-0.99 to 0.59)	**Clozapine**	-0.06 (-0.28 to 0.17)	-0.11 (-0.31 to 0.10)	-0.13 (-0.62 to 0.35)	-0.25 (-0.51 to 0.02)	NA	**-0.72 (-1.10 to -0.34)**	NA	**-0.97 (-1.84 to -0.10)**
-0.31 (-0.94 to 0.31)	-0.30 (-1.10 to 0.51)	-0.10 (-0.29 to 0.08)	**Risperidone**	0.10 (-0.21 to 0.40)	NA	-0.24 (-0.58 to 0.10)	-0.37 (-0.80 to 0.06)	NA	-0.77 (-1.64 to 0.09)	-0.69 (-1.38 to 0.01)
-0.33 (-0.92 to 0.26)	-0.32 (-1.12 to 0.48)	-0.12 (-0.29 to 0.04)	-0.02 (-0.22 to 0.19)	**Olanzapine**	NA	-0.14 (-0.43 to 0.15)	NA	-0.35 (-0.92 to 0.22)	NA	-0.54 (-1.13 to 0.04)
-0.50 (-1.20 to 0.20)	-0.48 (-1.30 to 0.34)	-0.28 (-0.64 to 0.07)	-0.18 (-0.57 to 0.21)	-0.16 (-0.54 to 0.21)	**Ziprasidone**	NA	NA	-0.09 (-0.51 to 0.34)	NA	NA
-0.56 (-1.19 to 0.06)	-0.55 (-1.35 to 0.25)	**-0.35 (-0.54 to -0.16)**	**-0.25 (-0.47 to -0.03)**	**-0.23 (-0.43 to -0.03)**	-0.07 (-0.46 to 0.32)	**Haloperidol**	NA	NA	NA	0.09 (-0.34 to 0.52)
-0.69 (-1.45 to 0.07)	-0.67 (-1.59 to 0.24)	**-0.47 (-0.94 to -0.01)**	-0.37 (-0.80 to 0.06)	-0.35 (-0.83 to 0.13)	-0.19 (-0.77 to 0.39)	-0.12 (-0.61 to 0.36)	**Sertindole**	NA	NA	NA
-0.70 (-1.35 to -0.05)	-0.68 (-1.43 to 0.06)	**-0.49 (-0.74 to -0.23)**	**-0.38 (-0.68 to -0.08)**	**-0.36 (-0.64 to -0.09)**	-0.20 (-0.54 to 0.14)	-0.13 (-0.43 to 0.16)	-0.01 (-0.54 to 0.51)	**Chlorpromazine**	NA	-0.31 (-0.75 to 0.13)
-0.84 (-1.81 to 0.13)	-0.82 (-1.91 to 0.26)	-0.63 (-1.39 to 0.14)	-0.53 (-1.28 to 0.23)	-0.51 (-1.27 to 0.26)	-0.34 (-1.17 to 0.49)	-0.28 (-1.05 to 0.49)	-0.15 (-1.03 to 0.72)	-0.14 (-0.93 to 0.65)	**Fluphenazine**	-0.23 (-1.09 to 0.64)
-0.82 (-1.48 to -0.16)	-0.81 (-1.62 to 0.00)	**-0.61 (-0.90 to -0.32)**	**-0.51 (-0.82 to -0.20)**	**-0.49 (-0.78 to -0.19)**	-0.33 (-0.75 to 0.10)	-0.26 (-0.55 to 0.03)	-0.13 (-0.67 to 0.40)	-0.12 (-0.43 to 0.19)	0.02 (-0.74 to 0.78)	**Quetiapine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses

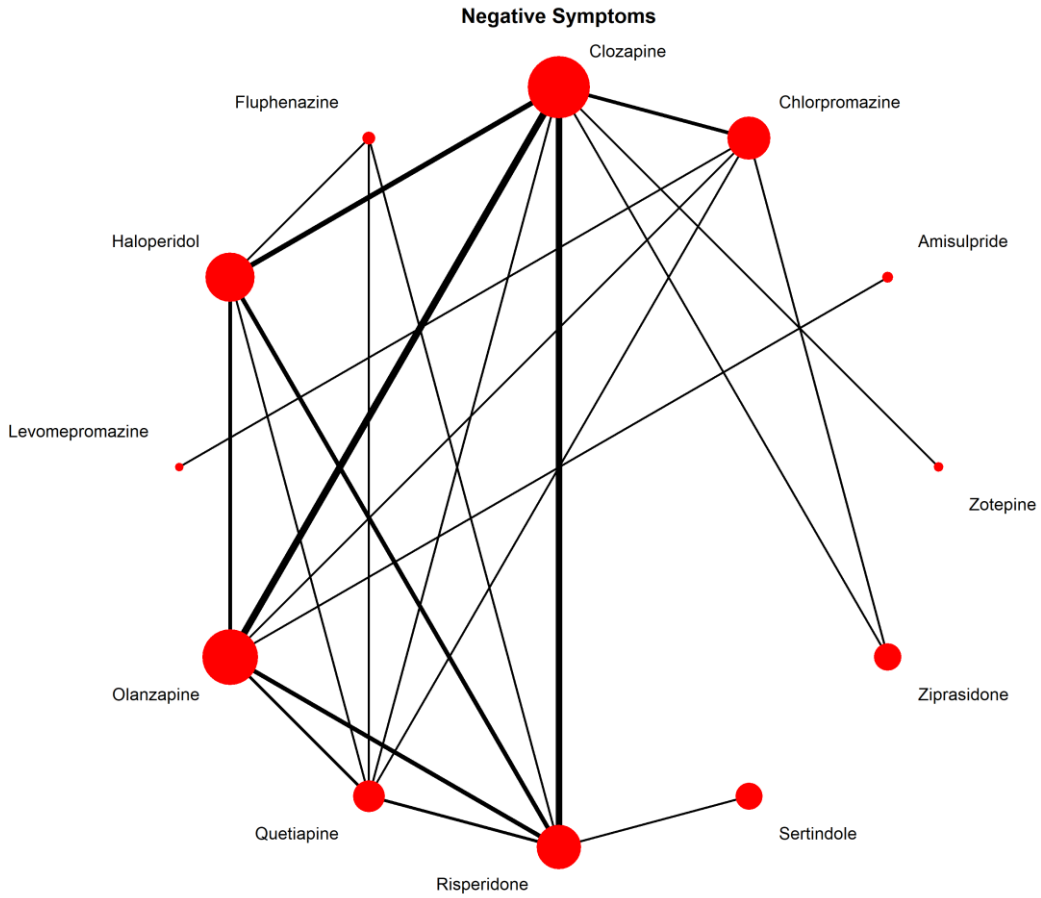




A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is standardized mean difference (SMD).

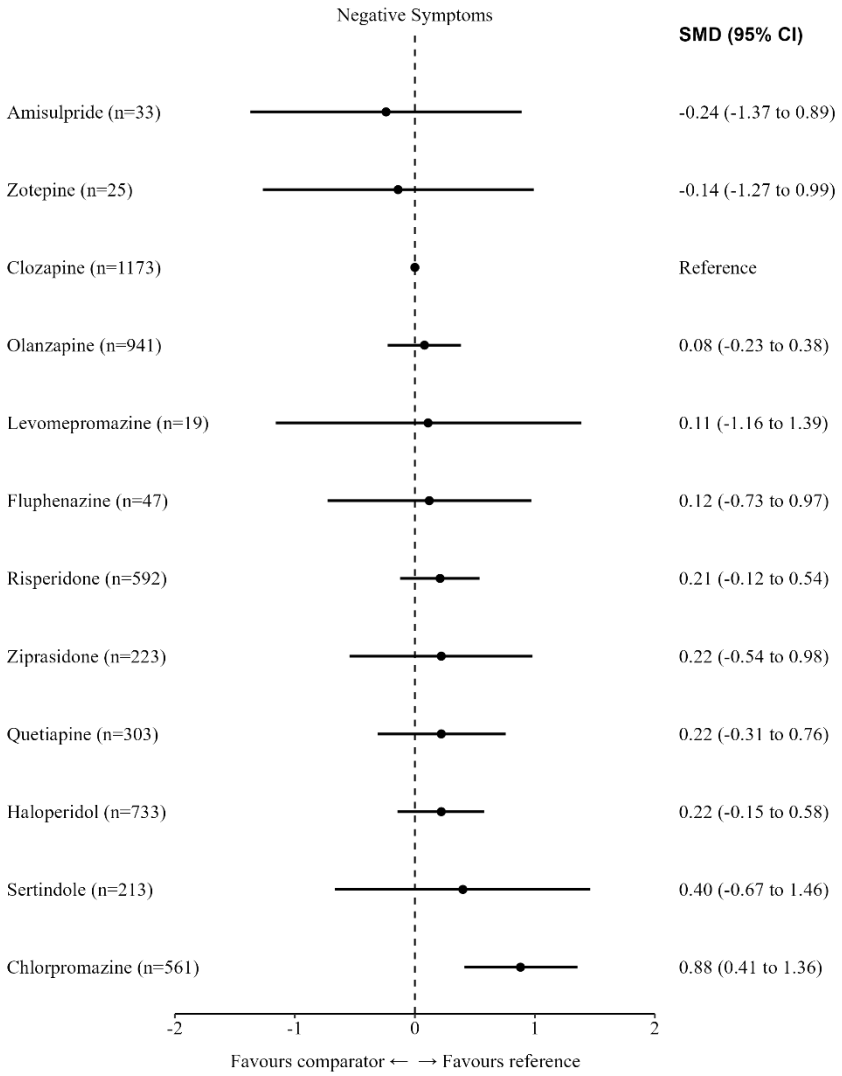
8.2 Negative symptoms

Network plot



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.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



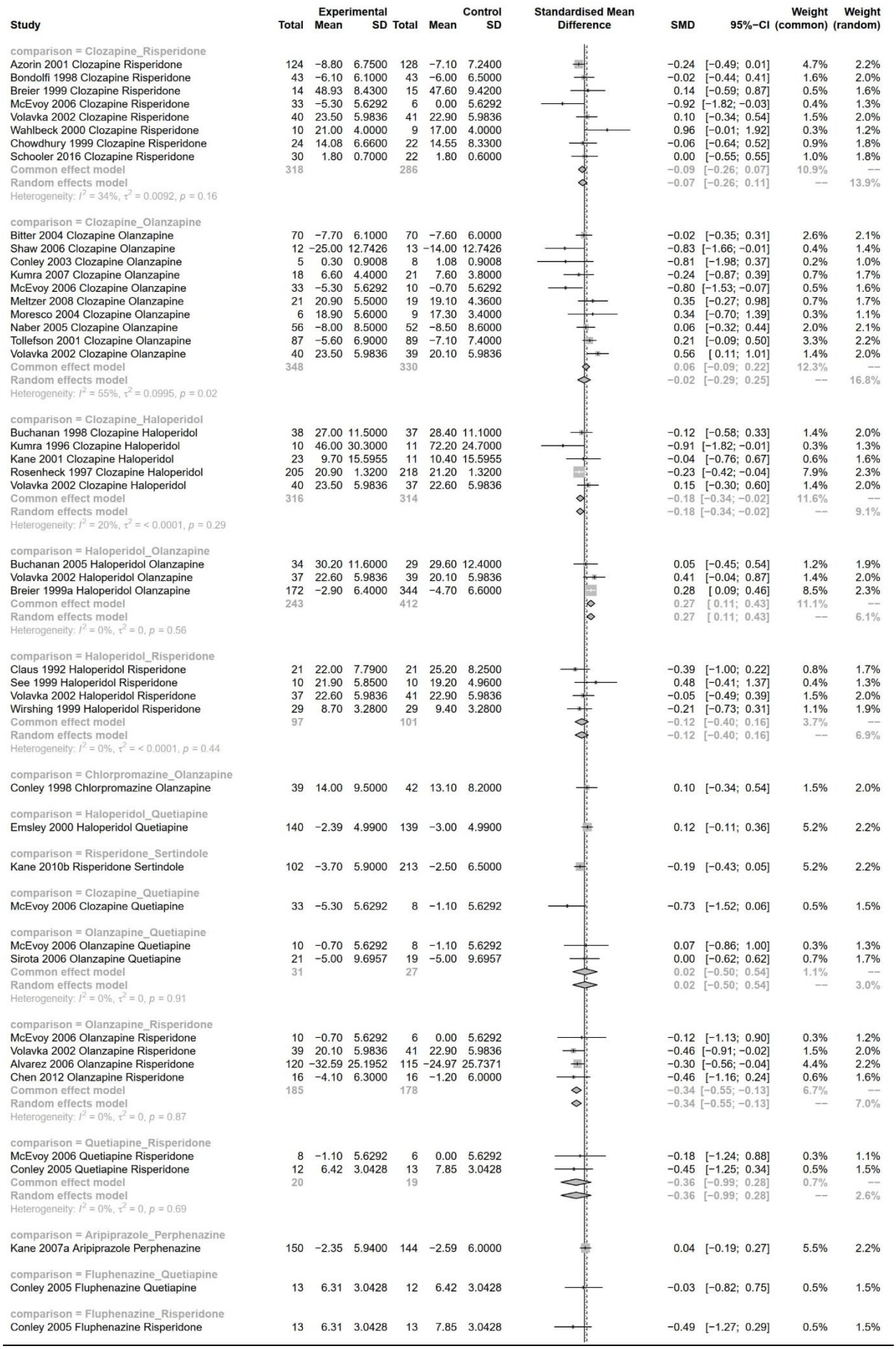
Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

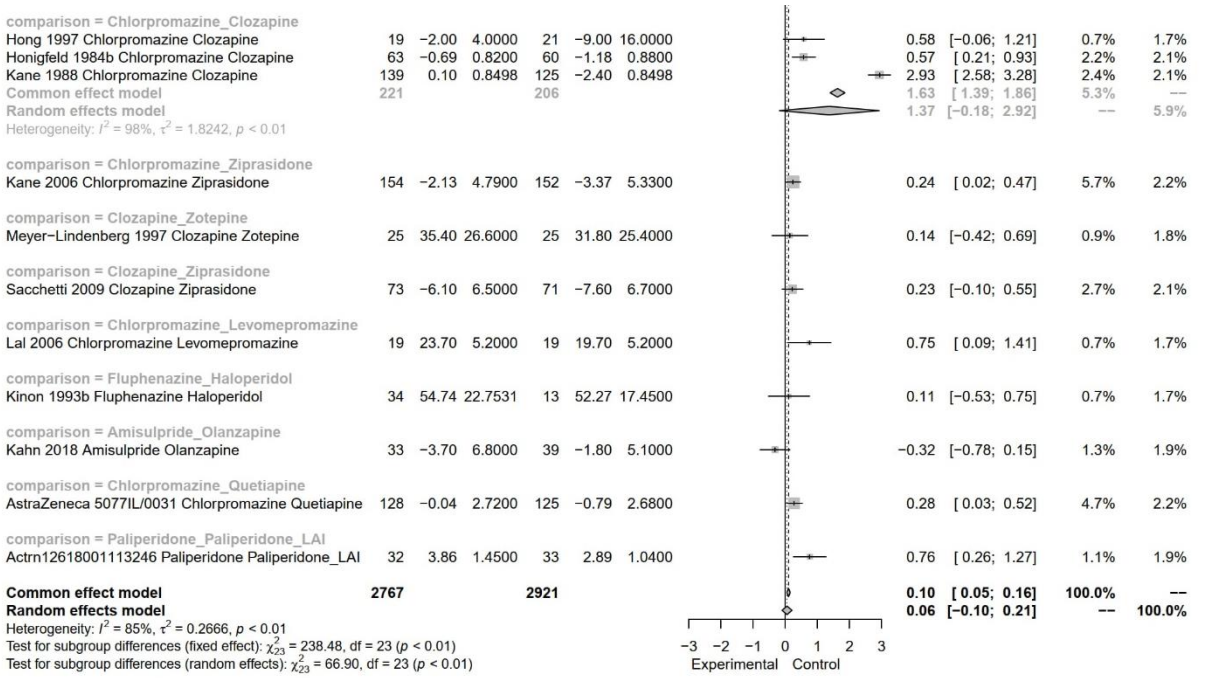
League table for the outcome: Negative symptoms

Amisulpride	NA	NA	-0.32 (-1.41 to 0.77)	NA	NA	NA	NA	NA	NA	NA	NA
-0.24 (-1.37 to 0.89)	**Clozapine**	0.14 (-0.99 to 1.27)	-0.06 (-0.43 to 0.31)	NA	NA	0.23 (-0.81 to 1.26)	-0.75 (-2.00 to 0.51)	-0.02 (-0.43 to 0.39)	-0.19 (-0.70 to 0.31)	NA	**-1.43 (-2.05 to -0.80)**
-0.10 (-1.70 to 1.49)	0.14 (-0.99 to 1.27)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA	NA	NA
-0.32 (-1.41 to 0.77)	-0.08 (-0.38 to 0.23)	-0.22 (-1.39 to 0.95)	**Olanzapine**	NA	NA	NA	0.03 (-0.85 to 0.91)	-0.36 (-0.93 to 0.22)	-0.25 (-0.86 to 0.36)	NA	-0.10 (-1.18 to 0.97)
-0.36 (-1.75 to 1.02)	-0.12 (-0.97 to 0.73)	-0.26 (-1.67 to 1.15)	-0.04 (-0.90 to 0.82)	**Fluphenazine**	NA	NA	-0.04 (-1.29 to 1.22)	-0.51 (-1.76 to 0.75)	0.12 (-1.06 to 1.29)	NA	NA
-0.36 (-2.04 to 1.33)	-0.11 (-1.39 to 1.16)	-0.25 (-1.95 to 1.45)	-0.04 (-1.33 to 1.25)	0.01 (-1.50 to 1.52)	**Levomepromazine**	NA	NA	NA	NA	NA	-0.77 (-1.95 to 0.41)
-0.46 (-1.81 to 0.89)	-0.22 (-0.98 to 0.54)	-0.36 (-1.72 to 1.01)	-0.14 (-0.94 to 0.67)	-0.10 (-1.22 to 1.03)	-0.10 (-1.51 to 1.30)	**Ziprasidone**	NA	NA	NA	NA	-0.24 (-1.25 to 0.76)
-0.46 (-1.68 to 0.75)	-0.22 (-0.76 to 0.31)	-0.36 (-1.61 to 0.89)	-0.14 (-0.68 to 0.40)	-0.10 (-0.98 to 0.78)	-0.11 (-1.44 to 1.22)	-0.01 (-0.90 to 0.89)	**Quetiapine**	-0.35 (-1.30 to 0.60)	-0.12 (-1.13 to 0.89)	NA	-0.28 (-1.29 to 0.74)
-0.45 (-1.60 to 0.70)	-0.21 (-0.54 to 0.12)	-0.35 (-1.52 to 0.83)	-0.13 (-0.50 to 0.25)	-0.09 (-0.93 to 0.76)	-0.09 (-1.40 to 1.21)	0.01 (-0.81 to 0.83)	0.02 (-0.54 to 0.57)	**Risperidone**	0.08 (-0.50 to 0.66)	-0.19 (-1.20 to 0.82)	NA
-0.46 (-1.61 to 0.70)	-0.22 (-0.58 to 0.15)	-0.35 (-1.54 to 0.83)	-0.14 (-0.53 to 0.25)	-0.09 (-0.92 to 0.73)	-0.10 (-1.41 to 1.21)	0.00 (-0.83 to 0.83)	0.01 (-0.54 to 0.56)	-0.01 (-0.40 to 0.38)	**Haloperidol**	NA	NA
-0.64 (-2.17 to 0.89)	-0.40 (-1.46 to 0.67)	-0.54 (-2.09 to 1.02)	-0.32 (-1.40 to 0.76)	-0.28 (-1.59 to 1.04)	-0.28 (-1.93 to 1.37)	-0.18 (-1.48 to 1.12)	-0.17 (-1.33 to 0.98)	-0.19 (-1.20 to 0.82)	-0.18 (-1.27 to 0.90)	**Sertindole**	NA
-1.13 (-2.33 to 0.08)	**-0.88 (-1.36 to -0.41)**	-1.02 (-2.25 to 0.20)	**-0.81 (-1.32 to -0.29)**	-0.76 (-1.70 to 0.18)	-0.77 (-1.95 to 0.41)	-0.67 (-1.42 to 0.09)	**-0.66 (-1.28 to -0.05)**	**-0.68 (-1.23 to -0.12)**	**-0.67 (-1.23 to -0.10)**	-0.49 (-1.64 to 0.67)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses





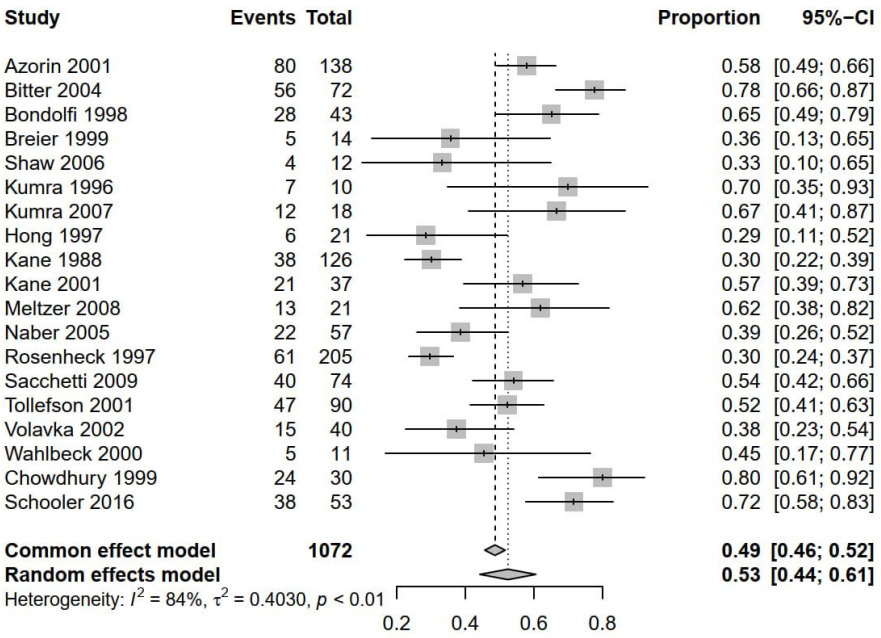
A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is standardized mean difference (SMD).

8.3 Response

The following hierarchy of the response definitions were applied: at least 20% reduction of the baseline score of the PANSS, 20% reduction of the BPRS or 20% reduction of any other global schizophrenia rating scale, at least “minimally improved” (score of 3) on the Clinical Global-Impressions-Improvement Scale (CGI). We chose this cutoff because even minimal improvement can be clinically important for patients with treatment-resistant schizophrenia. If none of these definitions was available, we used the original authors’ primary definition.

We transformed the original ORs to RRs and EERs vs. CER assuming the baseline response rate with clozapine of 49% (namely CER). 49% was the average response rate with clozapine across all clozapine-arms in the network meta-analysis, as estimated by a single-arm meta-analysis of proportions (see below).

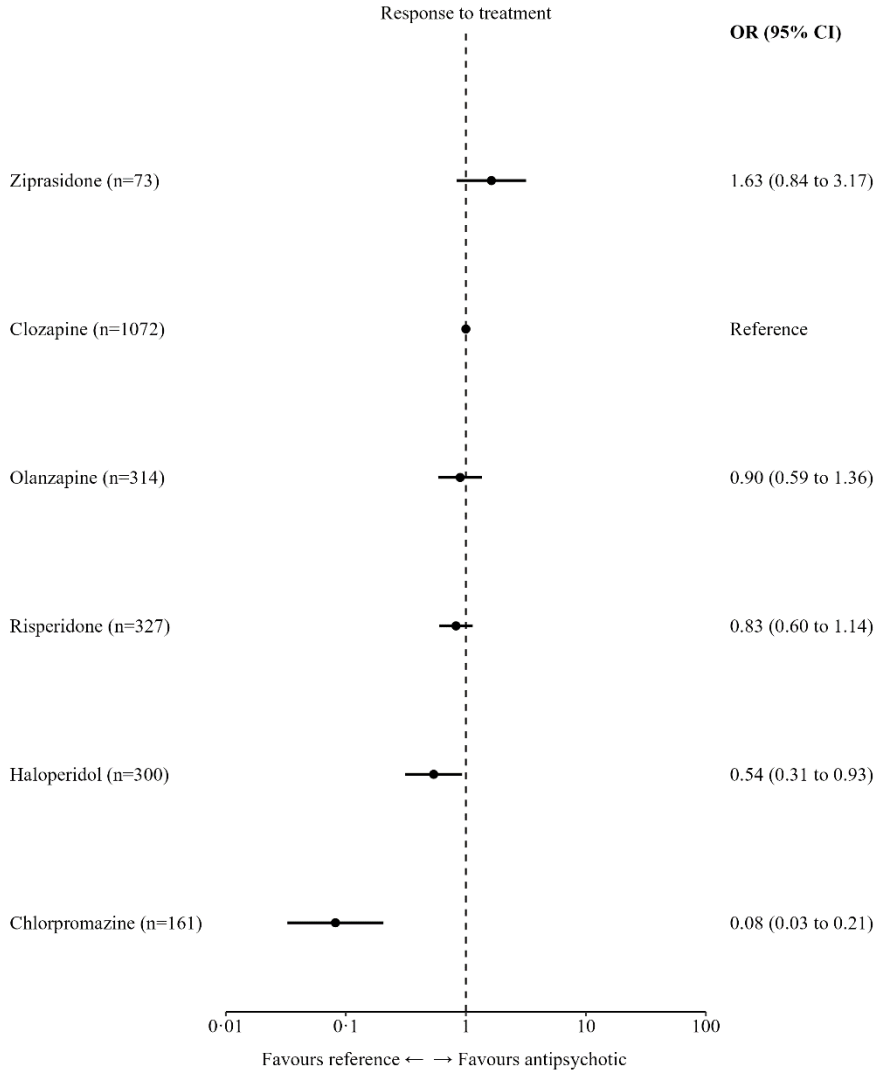
Forest plot of the single arm meta-analysis of response in the clozapine-arm



Forest plot of response in all clozapine-arms included in the network meta-analysis. The summary effect size is from a single-arm meta-analysis of proportions.

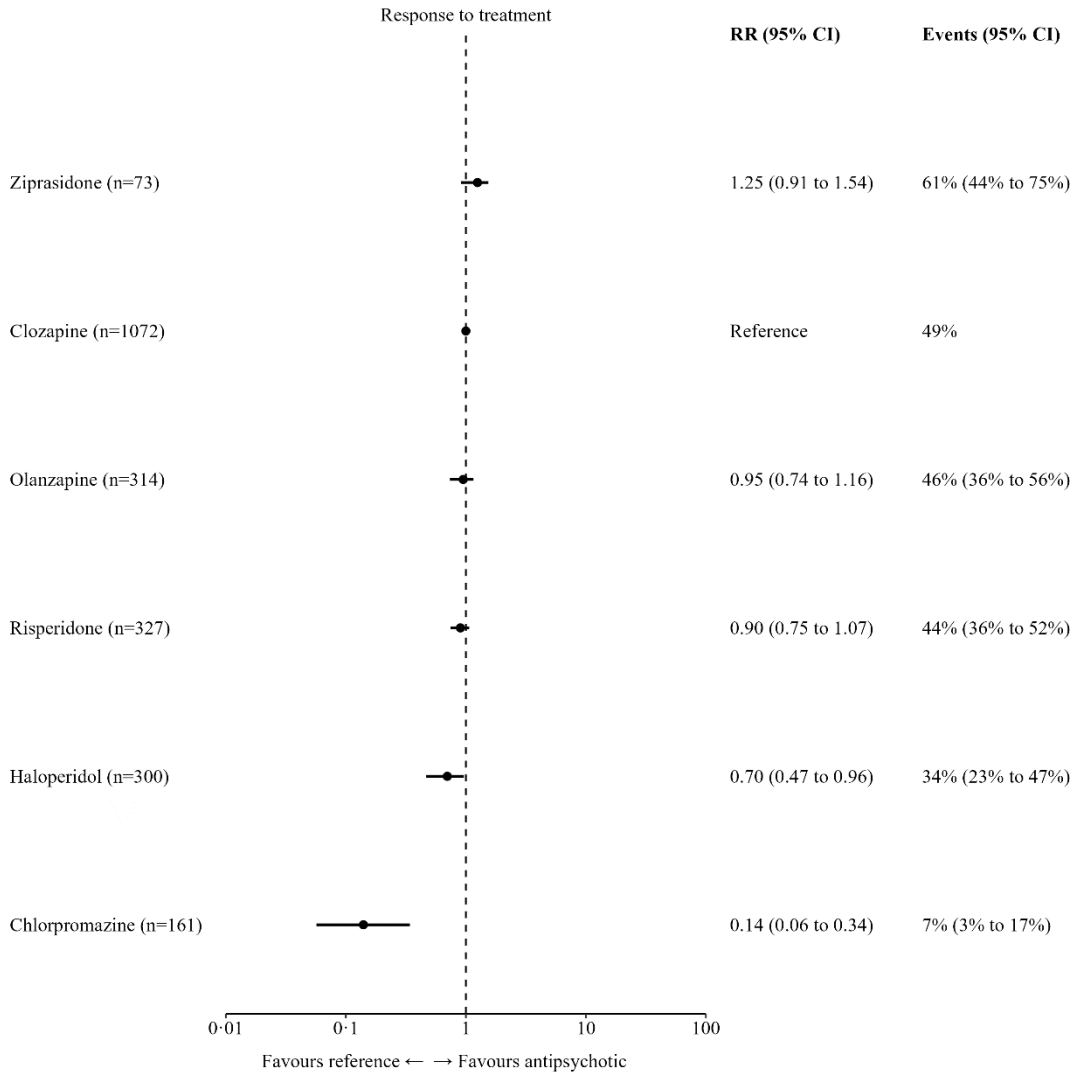
Because inconsistency of the network was high for response to treatment (12.9% inconsistent comparisons, design-by-treatment interaction test p=0.0194), we conducted a pairwise meta-analysis of active antipsychotics versus clozapine and present the results below.

Forest-plot of results of pairwise meta-analysis for antipsychotic drugs versus clozapine with OR



Effect sizes, measured as odds ratio (OR), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

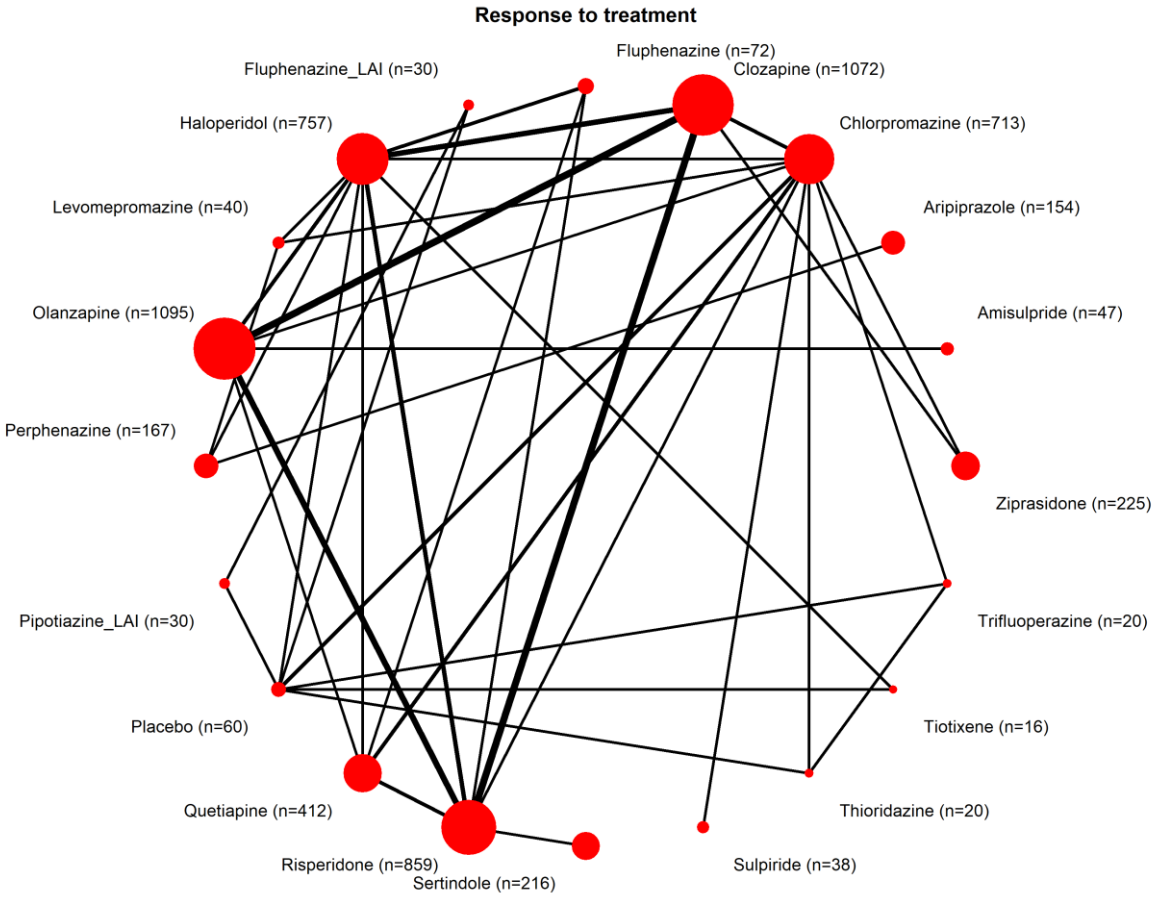
Forest-plot of results of pairwise meta-analysis for antipsychotic drugs versus clozapine with RR



For this forest plot, we transformed the original OR to RR and exposure events rates (EER, called "events" in the forest plot) using the formula indicated above. Therefore, we used an average response rate with clozapine of 49% as the control event rate (CER).
Effect sizes are from the pairwise meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

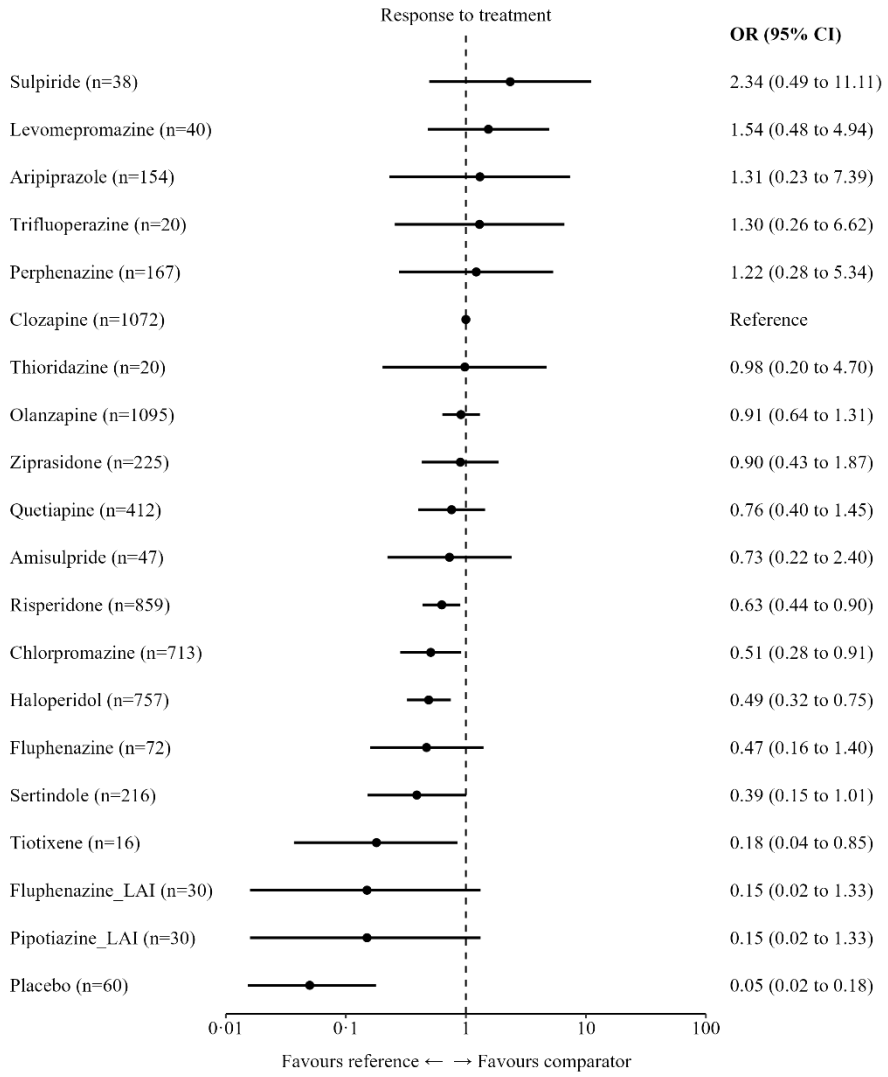
We additionally present the results of the network meta-analysis below, which agree with the results of the pairwise meta-analysis, but it should be emphasized that differences between antipsychotics need to be interpreted with caution due to the observed inconsistency.

Network plot



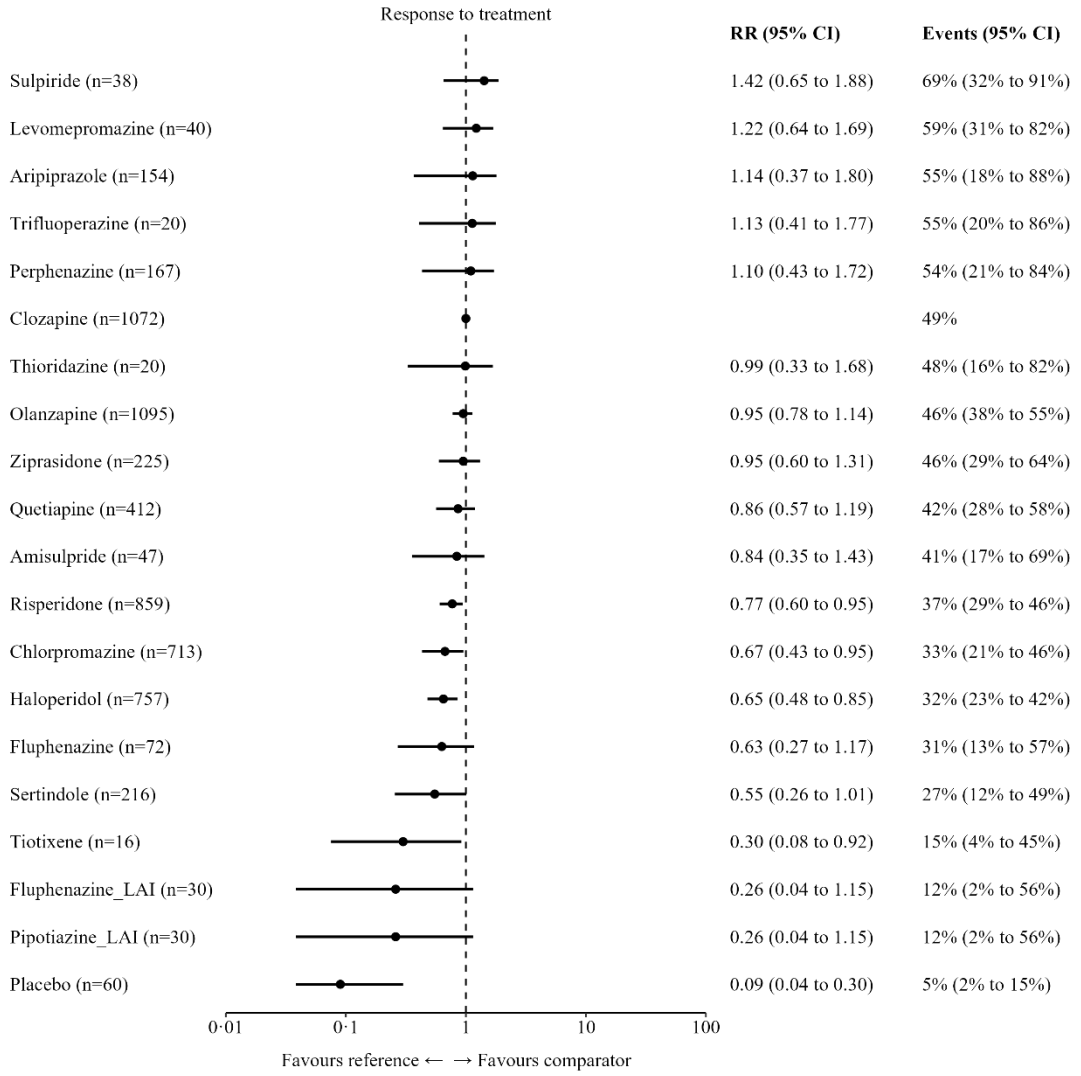
Lines link treatments with direct comparisons in trials; thickness of lines corresponds to the number of trials evaluating the comparison; size of the nodes corresponds to the number of participants assigned to the treatment.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as odds ratio (OR), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

Forest plot with RR and EER versus CER



For this forest plot, we transformed the original OR to RR and exposure events rates (EER, called "events" in the forest plot) using the formula indicated above. Therefore, we used an average response rate with clozapine of 49% as the control event rate (CER).
Effect sizes are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table for the outcome: Response to treatment (OR)

Sulpiride	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**4.60 (1.09 to 19.47)**	NA	NA	NA	NA	NA	NA	NA
1.52 (0.24 to 9.46)	**Levomepromazine**	NA	NA	1.28 (0.27 to 6.13)	NA	NA	NA	NA	NA	NA	NA	2.98 (0.65 to 13.64)	3.20 (0.68 to 15.12)	NA	NA	NA	NA	NA	NA
1.79 (0.19 to 17.31)	1.18 (0.21 to 6.59)	**Aripiprazole**	NA	1.07 (0.43 to 2.65)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.80 (0.22 to 14.90)	1.19 (0.18 to 7.92)	1.01 (0.10 to 10.19)	**Trifluoperazine**	NA	NA	1.33 (0.25 to 7.05)	NA	NA	NA	NA	NA	2.15 (0.43 to 10.78)	NA	NA	NA	NA	NA	NA	**36.00 (5.02 to 258.37)**
1.92 (0.24 to 15.37)	1.27 (0.29 to 5.46)	1.07 (0.43 to 2.65)	1.07 (0.13 to 8.99)	**Perphenazine**	NA	NA	NA	NA	NA	NA	NA	NA	2.50 (0.55 to 11.39)	NA	NA	NA	NA	NA	NA
2.34 (0.49 to 11.11)	1.54 (0.48 to 4.94)	1.31 (0.23 to 7.39)	1.30 (0.26 to 6.62)	1.22 (0.28 to 5.34)	**Clozapine**	NA	1.14 (0.72 to 1.80)	0.61 (0.23 to 1.66)	NA	NA	1.25 (0.79 to 1.99)	**12.37 (3.98 to 38.43)**	**1.88 (1.05 to 3.39)**	NA	NA	NA	NA	NA	NA
2.40 (0.30 to 19.04)	1.58 (0.25 to 10.08)	1.34 (0.14 to 13.08)	1.33 (0.25 to 7.05)	1.25 (0.15 to 10.11)	1.03 (0.21 to 4.94)	**Thioridazine**	NA	NA	NA	NA	NA	1.62 (0.34 to 7.65)	NA	NA	NA	NA	NA	NA	**27.00 (3.94 to 185.22)**
2.57 (0.53 to 12.40)	1.69 (0.52 to 5.51)	1.43 (0.25 to 8.18)	1.42 (0.28 to 7.37)	1.34 (0.30 to 5.92)	1.10 (0.76 to 1.57)	1.07 (0.22 to 5.24)	**Olanzapine**	NA	0.67 (0.11 to 3.94)	1.25 (0.40 to 3.88)	**1.68 (1.02 to 2.78)**	7.53 (0.34 to 164.72)	**2.04 (1.02 to 4.06)**	NA	NA	NA	NA	NA	NA
2.62 (0.53 to 13.00)	1.72 (0.48 to 6.22)	1.46 (0.23 to 9.17)	1.45 (0.27 to 7.83)	1.36 (0.27 to 6.74)	1.12 (0.54 to 2.33)	1.09 (0.21 to 5.57)	1.02 (0.46 to 2.25)	**Ziprasidone**	NA	NA	NA	1.12 (0.47 to 2.66)	NA	NA	NA	NA	NA	NA	NA
3.07 (0.64 to 14.65)	2.03 (0.61 to 6.76)	1.71 (0.29 to 10.11)	1.70 (0.33 to 8.79)	1.60 (0.35 to 7.35)	1.31 (0.69 to 2.49)	1.28 (0.26 to 6.24)	1.20 (0.62 to 2.32)	1.18 (0.50 to 2.76)	**Quetiapine**	NA	1.84 (0.46 to 7.38)	1.17 (0.55 to 2.49)	1.76 (0.73 to 4.23)	1.83 (0.22 to 15.39)	NA	NA	NA	NA	NA
3.21 (0.46 to 22.35)	2.12 (0.41 to 10.87)	1.79 (0.22 to 14.31)	1.78 (0.24 to 13.12)	1.67 (0.26 to 10.84)	1.37 (0.42 to 4.50)	1.34 (0.19 to 9.41)	1.25 (0.40 to 3.88)	1.23 (0.31 to 4.89)	1.05 (0.28 to 3.89)	**Amisulpride**	NA	NA	NA	NA	NA	NA	NA	NA	NA
3.75 (0.78 to 18.04)	2.47 (0.76 to 8.04)	2.09 (0.37 to 11.94)	2.08 (0.40 to 10.73)	1.95 (0.44 to 8.64)	**1.60 (1.11 to 2.30)**	1.56 (0.32 to 7.62)	1.46 (0.99 to 2.14)	1.43 (0.65 to 3.16)	1.22 (0.63 to 2.35)	1.17 (0.35 to 3.86)	**Risperidone**	0.18 (0.03 to 1.15)	1.30 (0.59 to 2.87)	1.65 (0.20 to 13.71)	1.60 (0.67 to 3.86)	NA	NA	NA	NA
4.60 (1.09 to 19.47)	3.03 (0.98 to 9.35)	2.57 (0.45 to 14.77)	2.55 (0.55 to 11.95)	2.39 (0.54 to 10.69)	**1.96 (1.09 to 3.53)**	1.92 (0.43 to 8.45)	1.79 (0.95 to 3.37)	1.76 (0.87 to 3.55)	1.50 (0.82 to 2.73)	1.43 (0.39 to 5.25)	1.23 (0.66 to 2.30)	**Chlorpromazine**	0.25 (0.03 to 2.08)	NA	NA	NA	NA	NA	**19.76 (4.22 to 92.52)**
4.77 (1.00 to 22.73)	**3.14 (1.01 to 9.71)**	2.66 (0.49 to 14.47)	2.64 (0.52 to 13.43)	2.48 (0.59 to 10.38)	**2.03 (1.33 to 3.10)**	1.98 (0.41 to 9.53)	**1.86 (1.18 to 2.91)**	1.82 (0.83 to 4.02)	1.55 (0.85 to 2.84)	1.48 (0.44 to 5.02)	1.27 (0.80 to 2.01)	1.03 (0.57 to 1.89)	**Haloperidol**	0.96 (0.29 to 3.26)	NA	1.96 (0.39 to 9.73)	NA	NA	3.85 (0.68 to 21.98)
4.95 (0.78 to 31.46)	3.26 (0.72 to 14.84)	2.76 (0.38 to 19.95)	2.75 (0.41 to 18.47)	2.57 (0.44 to 14.94)	2.11 (0.71 to 6.26)	2.06 (0.32 to 13.22)	1.93 (0.64 to 5.78)	1.89 (0.53 to 6.75)	1.61 (0.52 to 5.03)	1.54 (0.32 to 7.47)	1.32 (0.44 to 3.93)	1.08 (0.34 to 3.42)	1.04 (0.37 to 2.91)	**Fluphenazine**	NA	NA	NA	NA	NA
6.00 (0.99 to 36.34)	3.96 (0.91 to 17.23)	3.35 (0.48 to 23.57)	3.33 (0.52 to 21.44)	3.12 (0.55 to 17.59)	2.56 (0.99 to 6.62)	2.50 (0.41 to 15.33)	2.34 (0.90 to 6.10)	2.30 (0.70 to 7.48)	1.95 (0.65 to 5.85)	1.87 (0.42 to 8.25)	1.60 (0.67 to 3.86)	1.30 (0.44 to 3.83)	1.26 (0.47 to 3.39)	1.21 (0.30 to 4.92)	**Sertindole**	NA	NA	NA	NA
13.22 (1.54 to 113.29)	**8.71 (1.33 to 56.98)**	7.37 (0.76 to 71.55)	7.33 (0.88 to 61.29)	6.87 (0.85 to 55.28)	**5.64 (1.17 to 27.13)**	5.50 (0.69 to 44.08)	**5.15 (1.06 to 25.01)**	5.05 (0.93 to 27.35)	4.30 (0.85 to 21.69)	4.11 (0.59 to 28.79)	3.53 (0.72 to 17.18)	2.87 (0.58 to 14.12)	2.77 (0.60 to 12.78)	2.67 (0.43 to 16.77)	2.20 (0.36 to 13.45)	**Tiotixene**	NA	NA	1.97 (0.33 to 11.93)
16.15 (1.18 to 221.59)	10.64 (0.94 to 120.56)	9.00 (0.57 to 141.77)	8.96 (0.73 to 109.56)	8.40 (0.62 to 113.45)	6.89 (0.75 to 62.90)	6.72 (0.57 to 79.31)	6.29 (0.68 to 57.96)	6.17 (0.64 to 60.02)	5.25 (0.56 to 48.97)	5.03 (0.42 to 60.86)	4.31 (0.47 to 39.74)	3.51 (0.39 to 31.23)	3.39 (0.38 to 30.47)	3.26 (0.29 to 36.56)	2.69 (0.25 to 29.30)	1.22 (0.10 to 14.24)	**Fluphenazine_LAI**	1.00 (0.26 to 3.78)	2.79 (0.44 to 17.49)
16.15 (1.18 to 221.59)	10.64 (0.94 to 120.56)	9.00 (0.57 to 141.77)	8.96 (0.73 to 109.56)	8.40 (0.62 to 113.45)	6.89 (0.75 to 62.90)	6.72 (0.57 to 79.31)	6.29 (0.68 to 57.96)	6.17 (0.64 to 60.02)	5.25 (0.56 to 48.97)	5.03 (0.42 to 60.86)	4.31 (0.47 to 39.74)	3.51 (0.39 to 31.23)	3.39 (0.38 to 30.47)	3.26 (0.29 to 36.56)	2.69 (0.25 to 29.30)	1.22 (0.10 to 14.24)	1.00 (0.26 to 3.78)	**Pipotiazine_LAI**	2.79 (0.44 to 17.49)
44.99 (6.96 to 290.82)	**29.64 (6.07 to 144.83)**	**25.08 (3.21 to 195.81)**	**24.95 (4.55 to 136.76)**	**23.39 (3.70 to 147.96)**	**19.19 (5.61 to 65.72)**	**18.71 (3.60 to 97.32)**	**17.51 (5.03 to 61.03)**	**17.20 (4.50 to 65.72)**	**14.64 (4.12 to 52.01)**	**14.01 (2.59 to 75.60)**	**12.01 (3.45 to 41.84)**	**9.77 (2.99 to 31.96)**	**9.44 (2.83 to 31.45)**	**9.09 (1.89 to 43.67)**	**7.49 (1.63 to 34.45)**	3.40 (0.67 to 17.35)	2.79 (0.44 to 17.49)	2.79 (0.44 to 17.49)	**Placebo**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is odd ratio (OR). Bold results indicate 95% CI excluding no effect. NA=not available.

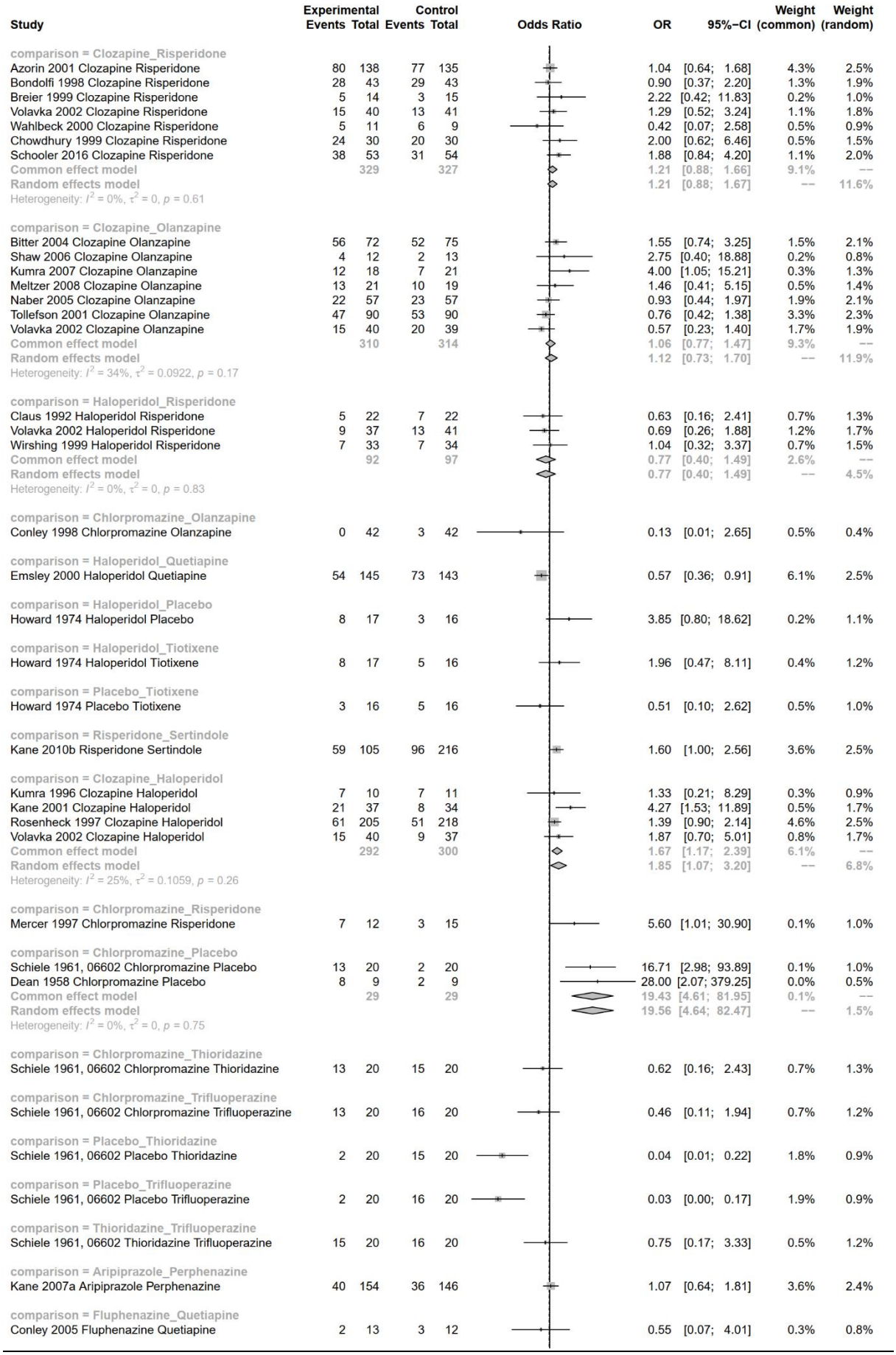
League table for the outcome: Response to treatment (RR)

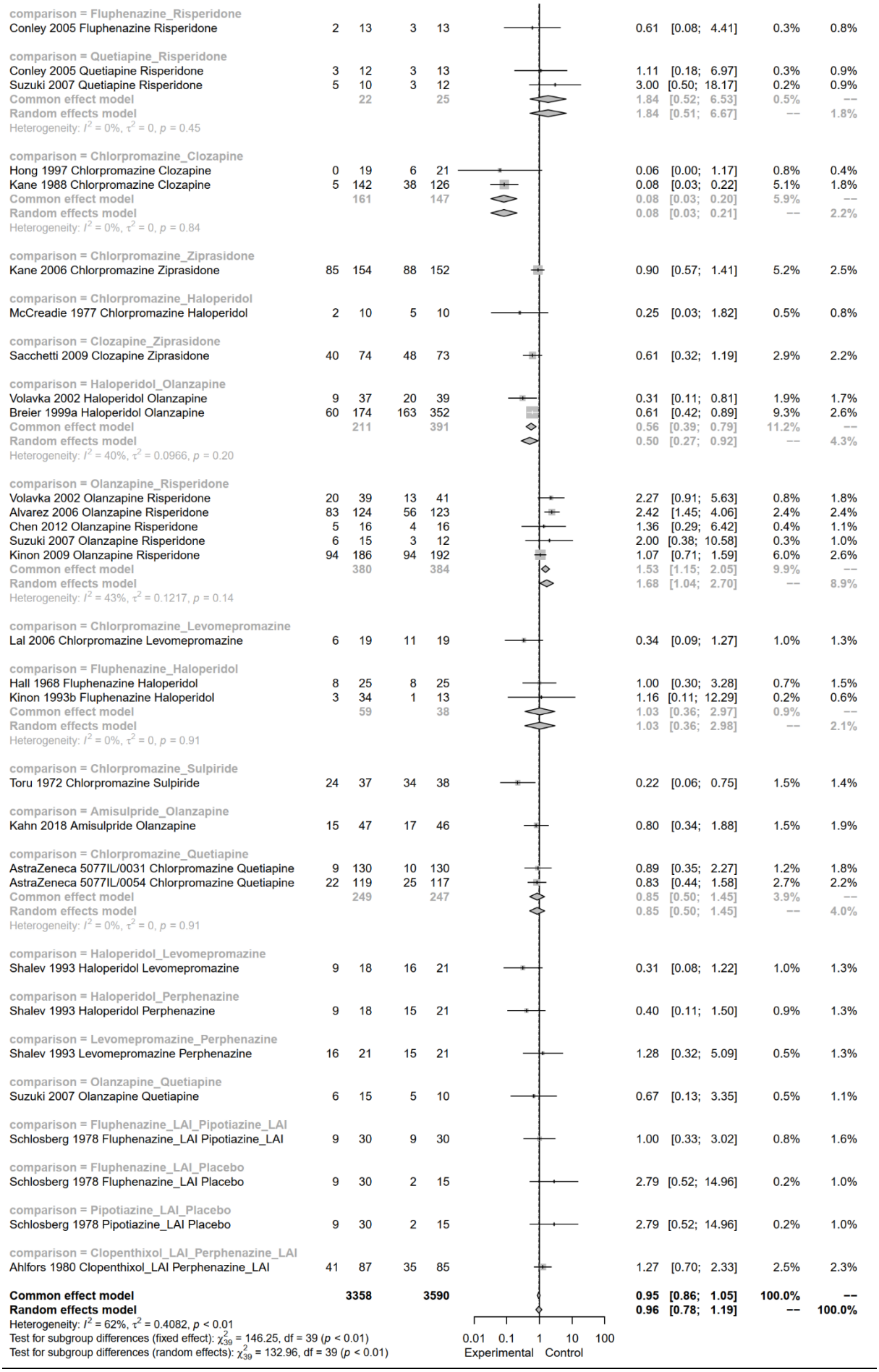
Sulpiride	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**2.16 (1.06 to 2.87)**	NA	NA	NA	NA	NA	NA	NA
1.17 (0.43 to 1.6)	**Levomepromazine**	NA	NA	1.12 (0.44 to 1.66)	NA	NA	NA	NA	NA	NA	NA	1.84 (0.73 to 2.75)	1.91 (0.75 to 2.84)	NA	NA	NA	NA	NA	NA
1.25 (0.34 to 1.76)	1.08 (0.37 to 1.64)	**Aripiprazole**	NA	1.03 (0.61 to 1.42)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.26 (0.38 to 1.76)	1.08 (0.32 to 1.68)	1 (0.19 to 1.71)	**Trifluoperazine**	NA	NA	1.15 (0.38 to 1.84)	NA	NA	NA	NA	NA	1.58 (0.52 to 2.66)	NA	NA	NA	NA	NA	NA	**14.03 (4.26 to 20.65)**
1.3 (0.4 to 1.81)	1.11 (0.46 to 1.64)	1.03 (0.61 to 1.42)	1.03 (0.24 to 1.74)	**Perphenazine**	NA	NA	NA	NA	NA	NA	NA	NA	1.71 (0.64 to 2.72)	NA	NA	NA	NA	NA	NA
1.43 (0.65 to 1.92)	1.23 (0.64 to 1.73)	1.14 (0.36 to 1.84)	1.14 (0.4 to 1.81)	1.11 (0.42 to 1.75)	**Clozapine**	NA	1.07 (0.82 to 1.32)	0.74 (0.35 to 1.28)	NA	NA	1.15 (0.85 to 1.47)	**2.71 (2.06 to 3.02)**	**1.48 (1.03 to 1.96)**	NA	NA	NA	NA	NA	NA
1.45 (0.45 to 2.02)	1.24 (0.38 to 1.92)	1.16 (0.23 to 1.97)	1.15 (0.38 to 1.84)	1.12 (0.25 to 1.93)	1.02 (0.33 to 1.74)	**Thioridazine**	NA	NA	NA	NA	NA	1.36 (0.43 to 2.48)	NA	NA	NA	NA	NA	NA	**12.48 (3.48 to 20.05)**
1.5 (0.67 to 2.02)	1.29 (0.66 to 1.82)	1.2 (0.38 to 1.93)	1.19 (0.41 to 1.9)	1.16 (0.44 to 1.84)	1.05 (0.85 to 1.25)	1.04 (0.34 to 1.8)	**Olanzapine**	NA	0.77 (0.17 to 1.79)	1.14 (0.52 to 1.81)	**1.35 (1.01 to 1.7)**	2.47 (0.43 to 3.15)	**1.55 (1.01 to 2.1)**	NA	NA	NA	NA	NA	NA
1.52 (0.67 to 2.05)	1.3 (0.62 to 1.87)	1.21 (0.35 to 1.98)	1.21 (0.4 to 1.94)	1.17 (0.4 to 1.89)	1.06 (0.68 to 1.46)	1.05 (0.32 to 1.83)	1.01 (0.61 to 1.44)	**Ziprasidone**	NA	NA	NA	1.08 (0.56 to 1.75)	NA	NA	NA	NA	NA	NA	NA
1.67 (0.75 to 2.24)	1.43 (0.72 to 2.02)	1.33 (0.41 to 2.15)	1.32 (0.45 to 2.11)	1.29 (0.48 to 2.05)	1.16 (0.79 to 1.55)	1.15 (0.37 to 1.99)	1.11 (0.73 to 1.51)	1.1 (0.63 to 1.61)	**Quetiapine**	NA	1.41 (0.57 to 2.24)	1.11 (0.64 to 1.7)	1.43 (0.8 to 2.13)	1.47 (0.29 to 2.91)	NA	NA	NA	NA	NA
1.71 (0.58 to 2.37)	1.47 (0.53 to 2.22)	1.36 (0.32 to 2.28)	1.36 (0.34 to 2.27)	1.32 (0.37 to 2.22)	1.2 (0.54 to 1.89)	1.18 (0.28 to 2.18)	1.14 (0.52 to 1.81)	1.13 (0.43 to 1.93)	1.03 (0.39 to 1.82)	**Amisulpride**	NA	NA	NA	NA	NA	NA	NA	NA	NA
1.89 (0.85 to 2.53)	1.62 (0.83 to 2.28)	1.5 (0.48 to 2.42)	1.5 (0.51 to 2.39)	1.45 (0.55 to 2.31)	**1.32 (1.07 to 1.57)**	1.3 (0.42 to 2.25)	1.25 (0.99 to 1.52)	1.24 (0.74 to 1.78)	1.13 (0.73 to 1.58)	1.1 (0.46 to 1.9)	**Risperidone**	0.24 (0.04 to 1.1)	1.19 (0.67 to 1.82)	1.38 (0.26 to 2.86)	1.38 (0.73 to 2.22)	NA	NA	NA	NA
2.16 (1.06 to 2.87)	1.85 (0.99 to 2.59)	1.72 (0.54 to 2.78)	1.72 (0.64 to 2.7)	1.67 (0.63 to 2.65)	**1.51 (1.06 to 1.97)**	1.49 (0.52 to 2.54)	1.44 (0.97 to 1.94)	1.42 (0.91 to 1.97)	1.3 (0.87 to 1.77)	1.26 (0.48 to 2.25)	1.15 (0.74 to 1.64)	**Chlorpromazine**	0.32 (0.04 to 1.56)	NA	NA	NA	NA	NA	**10.75 (3.69 to 18.17)**
2.21 (1 to 2.97)	**1.9 (1.01 to 2.65)**	1.76 (0.58 to 2.82)	1.76 (0.61 to 2.79)	1.71 (0.67 to 2.68)	**1.54 (1.21 to 1.89)**	1.52 (0.5 to 2.64)	**1.47 (1.12 to 1.84)**	1.45 (0.88 to 2.09)	1.33 (0.89 to 1.82)	1.29 (0.53 to 2.25)	1.17 (0.85 to 1.53)	1.02 (0.66 to 1.48)	**Haloperidol**	0.97 (0.37 to 1.95)	NA	1.73 (0.43 to 4.42)	NA	NA	3.41 (0.69 to 11.34)
2.27 (0.83 to 3.12)	1.95 (0.79 to 2.89)	1.81 (0.47 to 3)	1.81 (0.5 to 2.97)	1.75 (0.53 to 2.9)	1.59 (0.78 to 2.44)	1.57 (0.4 to 2.85)	1.51 (0.72 to 2.38)	1.49 (0.62 to 2.49)	1.36 (0.61 to 2.28)	1.33 (0.4 to 2.55)	1.21 (0.53 to 2.1)	1.05 (0.42 to 1.99)	1.03 (0.46 to 1.85)	**Fluphenazine**	NA	NA	NA	NA	NA
2.61 (0.99 to 3.57)	2.24 (0.93 to 3.3)	2.08 (0.55 to 3.44)	2.07 (0.59 to 3.4)	2.01 (0.62 to 3.31)	1.82 (0.99 to 2.69)	1.8 (0.48 to 3.25)	1.74 (0.92 to 2.62)	1.72 (0.76 to 2.79)	1.56 (0.71 to 2.59)	1.53 (0.49 to 2.86)	1.38 (0.73 to 2.22)	1.21 (0.51 to 2.21)	1.18 (0.55 to 2.09)	1.15 (0.37 to 2.44)	**Sertindole**	NA	NA	NA	NA
4.93 (1.43 to 6.89)	**4.23 (1.27 to 6.55)**	3.93 (0.79 to 6.68)	3.92 (0.89 to 6.59)	3.8 (0.87 to 6.53)	**3.44 (1.14 to 5.9)**	3.4 (0.72 to 6.36)	**3.28 (1.05 to 5.81)**	3.24 (0.94 to 5.91)	2.96 (0.87 to 5.64)	2.88 (0.63 to 5.97)	2.62 (0.75 to 5.33)	2.28 (0.62 to 5.03)	2.23 (0.63 to 4.88)	2.17 (0.47 to 5.29)	1.89 (0.39 to 4.96)	**Tiotixene**	NA	NA	1.89 (0.34 to 8.01)
5.88 (1.16 to 8.38)	5.04 (0.95 to 8.15)	4.68 (0.6 to 8.23)	4.67 (0.75 to 8.1)	4.53 (0.65 to 8.12)	4.1 (0.77 to 7.73)	4.05 (0.6 to 7.91)	3.91 (0.71 to 7.66)	3.87 (0.67 to 7.69)	3.52 (0.59 to 7.5)	3.43 (0.45 to 7.7)	3.12 (0.5 to 7.27)	2.72 (0.42 to 6.96)	2.66 (0.41 to 6.93)	2.59 (0.32 to 7.17)	2.25 (0.27 to 6.87)	1.19 (0.11 to 5.64)	**Fluphenazine_LAI**	1 (0.28 to 2.86)	2.58 (0.45 to 10.07)
5.88 (1.16 to 8.38)	5.04 (0.95 to 8.15)	4.68 (0.6 to 8.23)	4.67 (0.75 to 8.1)	4.53 (0.65 to 8.12)	4.1 (0.77 to 7.73)	4.05 (0.6 to 7.91)	3.91 (0.71 to 7.66)	3.87 (0.67 to 7.69)	3.52 (0.59 to 7.5)	3.43 (0.45 to 7.7)	3.12 (0.5 to 7.27)	2.72 (0.42 to 6.96)	2.66 (0.41 to 6.93)	2.59 (0.32 to 7.17)	2.25 (0.27 to 6.87)	1.19 (0.11 to 5.64)	1 (0.28 to 2.86)	**Pipotiazine_LAI**	2.58 (0.45 to 10.07)
15.16 (5.5 to 20.83)	**13 (4.95 to 19.49)**	**12.08 (2.92 to 20.16)**	**12.05 (3.93 to 19.34)**	**11.69 (3.3 to 19.54)**	**10.58 (4.65 to 16.88)**	**10.44 (3.23 to 18.34)**	**10.07 (4.26 to 16.56)**	**9.97 (3.89 to 16.88)**	**9.09 (3.62 to 15.85)**	**8.86 (2.42 to 17.44)**	**8.05 (3.11 to 14.8)**	**7.02 (2.75 to 13.4)**	**6.85 (2.62 to 13.32)**	**6.68 (1.82 to 15.02)**	**5.81 (1.59 to 13.8)**	3.07 (0.68 to 10.02)	2.58 (0.45 to 10.07)	2.58 (0.45 to 10.07)	**Placebo**

The original results given in OR (and their 95% CI) are transformed to RR (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column) using the formula described above. For this transformation, we assumed a response rate with clozapine of 49% as the control event rate (CER) for all comparisons of active antipsychotic versus clozapine.

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses



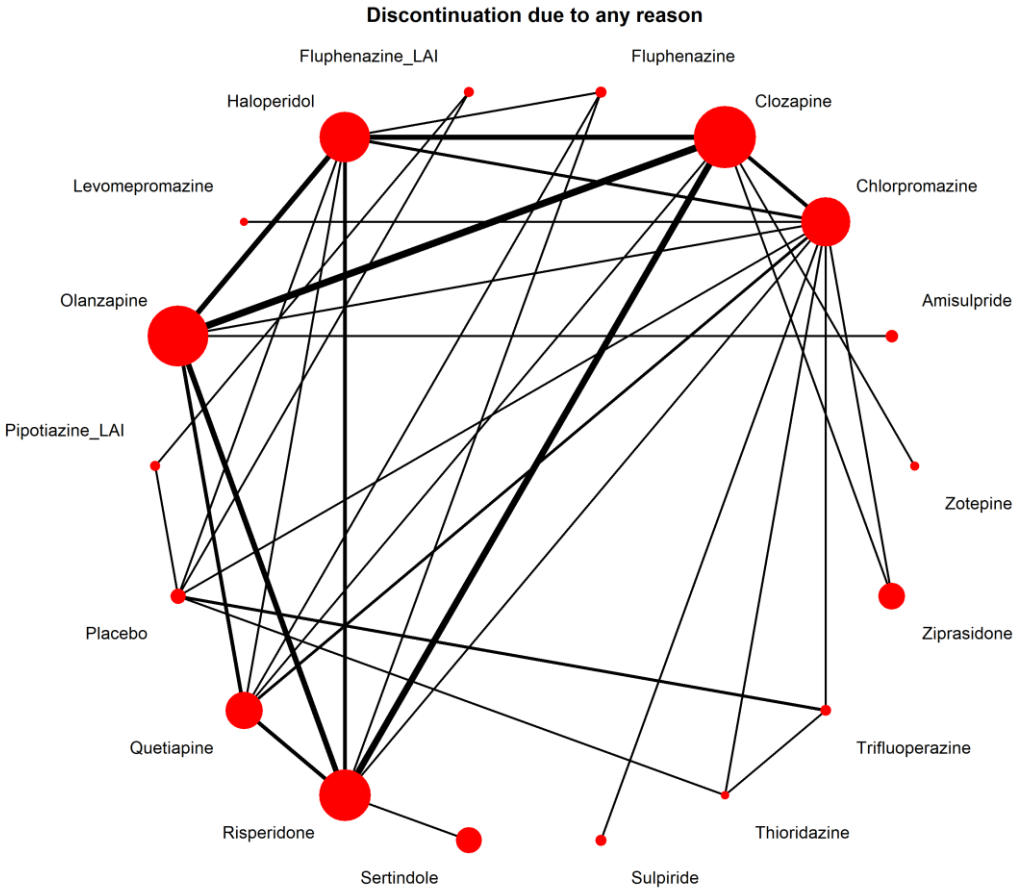

comparison = Fluphenazine_Risperidone
Conley 2005 Fluphenazine Risperidone 2 13 3 13 0.61 [0.08; 4.41] 0.3% 0.8%
comparison = Quetiapine_Risperidone
Conley 2005 Quetiapine Risperidone 3 12 3 13 1.11 [0.18; 6.97] 0.3% 0.9%
Suzuki 2007 Quetiapine Risperidone 5 10 3 12 3.00 [0.50; 18.17] 0.2% 0.9%
Common effect model 22 25 1.84 [0.52; 6.53] 0.5% --
Random effects model 1.84 [0.51; 6.67] -- 1.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.45
comparison = Chlorpromazine_Clozapine
Hong 1997 Chlorpromazine Clozapine 0 19 6 21 0.06 [0.00; 1.17] 0.8% 0.4%
Kane 1988 Chlorpromazine Clozapine 5 142 38 126 0.08 [0.03; 0.22] 5.1% 1.8%
Common effect model 161 147 0.08 [0.03; 0.20] 5.9% --
Random effects model 0.08 [0.03; 0.21] -- 2.2%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.84
comparison = Chlorpromazine_Ziprasidone
Kane 2006 Chlorpromazine Ziprasidone 85 154 88 152 0.90 [0.57; 1.41] 5.2% 2.5%
comparison = Chlorpromazine_Haloperidol
McCreadie 1977 Chlorpromazine Haloperidol 2 10 5 10 0.25 [0.03; 1.82] 0.5% 0.8%
comparison = Clozapine_Ziprasidone
Sacchetti 2009 Clozapine Ziprasidone 40 74 48 73 0.61 [0.32; 1.19] 2.9% 2.2%
comparison = Haloperidol_Olanzapine
Volavka 2002 Haloperidol Olanzapine 9 37 20 39 0.31 [0.11; 0.81] 1.9% 1.7%
Breier 1999a Haloperidol Olanzapine 60 174 163 352 0.61 [0.42; 0.89] 9.3% 2.6%
Common effect model 211 391 0.56 [0.39; 0.79] 11.2% --
Random effects model 0.50 [0.27; 0.92] -- 4.3%
Heterogeneity: I^2 = 40%, τ^2 = 0.0966, p = 0.20
comparison = Olanzapine_Risperidone
Volavka 2002 Olanzapine Risperidone 20 39 13 41 2.27 [0.91; 5.63] 0.8% 1.8%
Alvarez 2006 Olanzapine Risperidone 83 124 56 123 2.42 [1.45; 4.06] 2.4% 2.4%
Chen 2012 Olanzapine Risperidone 5 16 4 16 1.36 [0.29; 6.42] 0.4% 1.1%
Suzuki 2007 Olanzapine Risperidone 6 15 3 12 2.00 [0.38; 10.58] 0.3% 1.0%
Kinon 2009 Olanzapine Risperidone 94 186 94 192 1.07 [0.71; 1.59] 6.0% 2.6%
Common effect model 380 384 1.53 [1.15; 2.05] 9.9% --
Random effects model 1.68 [1.04; 2.70] -- 8.9%
Heterogeneity: I^2 = 43%, τ^2 = 0.1217, p = 0.14
comparison = Chlorpromazine_Levomepromazine
Lal 2006 Chlorpromazine Levomepromazine 6 19 11 19 0.34 [0.09; 1.27] 1.0% 1.3%
comparison = Fluphenazine_Haloperidol
Hall 1968 Fluphenazine Haloperidol 8 25 8 25 1.00 [0.30; 3.28] 0.7% 1.5%
Kinon 1993b Fluphenazine Haloperidol 3 34 1 13 1.16 [0.11; 12.29] 0.2% 0.6%
Common effect model 59 38 1.03 [0.36; 2.97] 0.9% --
Random effects model 1.03 [0.36; 2.98] -- 2.1%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.91
comparison = Chlorpromazine_Sulpiride
Toru 1972 Chlorpromazine Sulpiride 24 37 34 38 0.22 [0.06; 0.75] 1.5% 1.4%
comparison = Amisulpride_Olanzapine
Kahn 2018 Amisulpride Olanzapine 15 47 17 46 0.80 [0.34; 1.88] 1.5% 1.9%
comparison = Chlorpromazine_Quetiapine
AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine 9 130 10 130 0.89 [0.35; 2.27] 1.2% 1.8%
AstraZeneca 5077IL/0054 Chlorpromazine Quetiapine 22 119 25 117 0.83 [0.44; 1.58] 2.7% 2.2%
Common effect model 249 247 0.85 [0.50; 1.45] 3.9% --
Random effects model 0.85 [0.50; 1.45] -- 4.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.91
comparison = Haloperidol_Levomepromazine
Shalev 1993 Haloperidol Levomepromazine 9 18 16 21 0.31 [0.08; 1.22] 1.0% 1.3%
comparison = Haloperidol_Perphenazine
Shalev 1993 Haloperidol Perphenazine 9 18 15 21 0.40 [0.11; 1.50] 0.9% 1.3%
comparison = Levomepromazine_Perphenazine
Shalev 1993 Levomepromazine Perphenazine 16 21 15 21 1.28 [0.32; 5.09] 0.5% 1.3%
comparison = Olanzapine_Quetiapine
Suzuki 2007 Olanzapine Quetiapine 6 15 5 10 0.67 [0.13; 3.35] 0.5% 1.1%
comparison = Fluphenazine_LAI_Pipotiazine_LAI
Schlosberg 1978 Fluphenazine_LAI Pipotiazine_LAI 9 30 9 30 1.00 [0.33; 3.02] 0.8% 1.6%
comparison = Fluphenazine_LAI_Placebo
Schlosberg 1978 Fluphenazine_LAI Placebo 9 30 2 15 2.79 [0.52; 14.96] 0.2% 1.0%
comparison = Pipotiazine_LAI_Placebo
Schlosberg 1978 Pipotiazine_LAI Placebo 9 30 2 15 2.79 [0.52; 14.96] 0.2% 1.0%
comparison = Clopenthixol_LAI_Perphenazine_LAI
Ahlfors 1980 Clopenthixol_LAI Perphenazine_LAI 41 87 35 85 1.27 [0.70; 2.33] 2.5% 2.3%
Common effect model 3358 3590 0.95 [0.86; 1.05] 100.0% --
Random effects model 0.96 [0.78; 1.19] -- 100.0%
Heterogeneity: I^2 = 62%, τ^2 = 0.4082, p < 0.01
Test for subgroup differences (fixed effect): χ^2_{39} = 146.25, df = 39 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{39} = 132.96, df = 39 (p < 0.01)
0.01 0.1 1 10 100
Experimental Control

A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is OR.

8.4 Discontinuation due to any reason

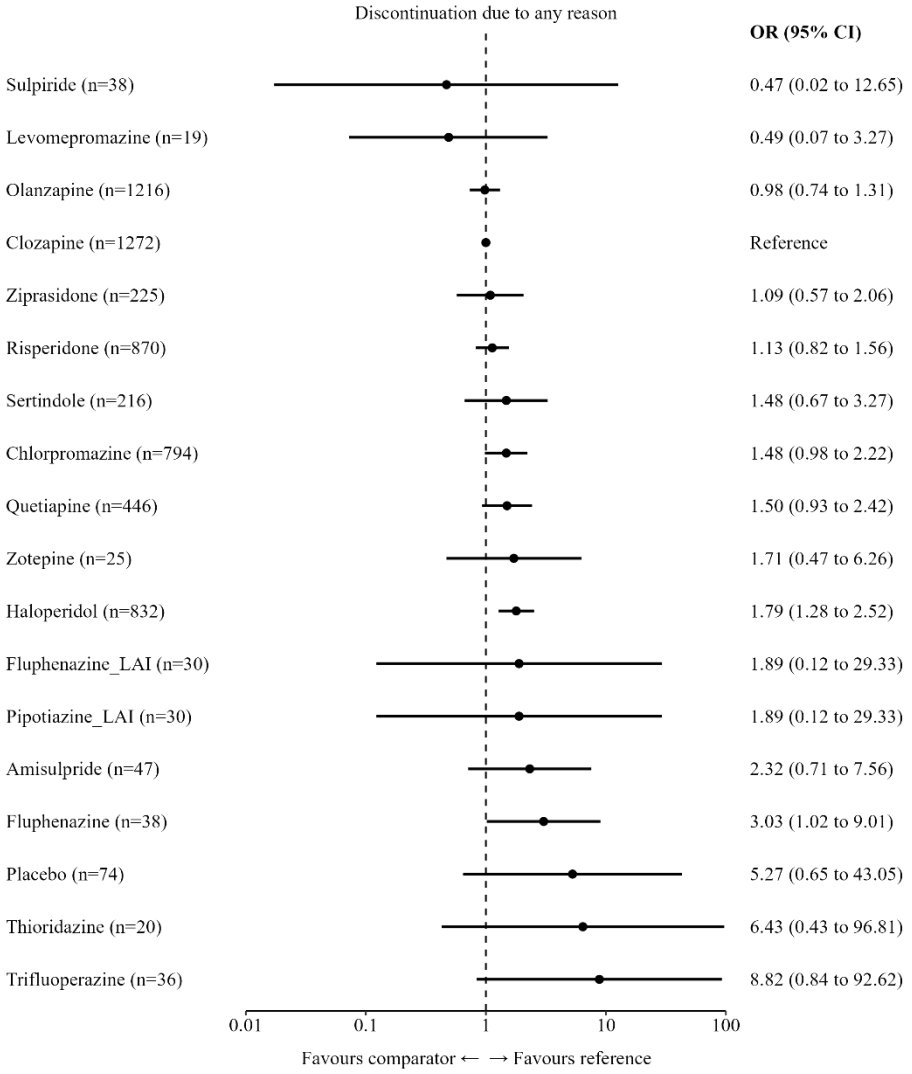
We transformed the original ORs to RRs and EERs vs. CER assuming the baseline discontinuation rate due to any reason with clozapine of 35% (namely CER). 35% was the average discontinuation rate due to any reason with clozapine across all clozapine-arms in the network meta-analysis, as estimated by a single-arm meta-analysis of proportions.

Network plot



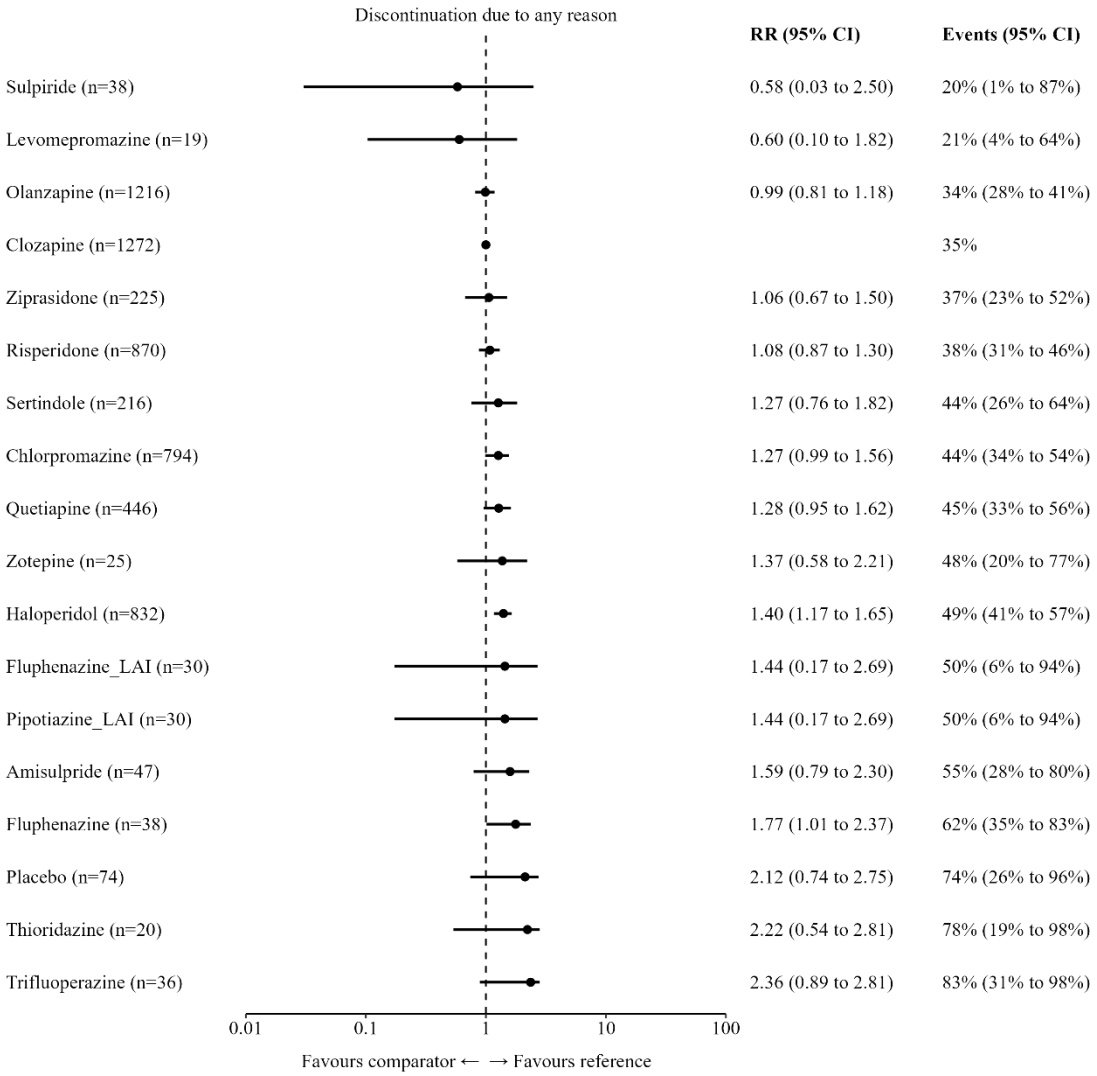
Lines link treatments with direct comparisons in trials; thickness of lines corresponds to the number of trials evaluating the comparison; size of the nodes corresponds to the number of participants assigned to the treatment.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as odds ratio (OR), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

Forest plot with RR and EER versus CER



For this forest plot, we transformed the original OR to RR and exposure events rates (EER, called "events" in the forest plot) using the formula indicated above. Therefore, we used an average discontinuation rate (due to any reason) with clozapine of 35% as the control event rate (CER).
Effect sizes are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table for the outcome: Discontinuation due to any reason (OR)

Sulpiride	NA	NA	NA	NA	NA	NA	0.32 (0.01 to 8.35)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.96 (0.02 to 41.48)	**Levomepromazine**	NA	NA	NA	NA	NA	0.33 (0.05 to 2.12)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.48 (0.02 to 12.96)	0.50 (0.07 to 3.36)	**Olanzapine**	0.90 (0.62 to 1.31)	NA	0.87 (0.57 to 1.33)	NA	0.89 (0.31 to 2.61)	0.79 (0.25 to 2.46)	NA	**0.51 (0.31 to 0.85)**	NA	NA	0.42 (0.13 to 1.33)	NA	NA	NA	NA
0.47 (0.02 to 12.65)	0.49 (0.07 to 3.27)	0.98 (0.74 to 1.31)	**Clozapine**	1.04 (0.44 to 2.41)	0.85 (0.57 to 1.28)	NA	0.76 (0.42 to 1.37)	**0.16 (0.03 to 0.86)**	0.58 (0.16 to 2.13)	**0.52 (0.33 to 0.83)**	NA	NA	NA	NA	NA	NA	NA
0.43 (0.02 to 12.09)	0.45 (0.06 to 3.21)	0.90 (0.46 to 1.79)	0.92 (0.49 to 1.75)	**Ziprasidone**	NA	NA	0.84 (0.35 to 2.01)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.41 (0.02 to 11.28)	0.43 (0.06 to 2.94)	0.87 (0.62 to 1.20)	0.88 (0.64 to 1.22)	0.96 (0.47 to 1.94)	**Risperidone**	0.77 (0.37 to 1.59)	1.69 (0.13 to 22.44)	0.49 (0.15 to 1.65)	NA	0.89 (0.42 to 1.91)	NA	NA	NA	0.20 (0.03 to 1.13)	NA	NA	NA
0.32 (0.01 to 9.38)	0.33 (0.04 to 2.58)	0.67 (0.30 to 1.48)	0.68 (0.31 to 1.50)	0.74 (0.27 to 2.03)	0.77 (0.37 to 1.59)	**Sertindole**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.32 (0.01 to 8.35)	0.33 (0.05 to 2.12)	0.66 (0.42 to 1.04)	0.68 (0.45 to 1.02)	0.74 (0.39 to 1.40)	0.77 (0.47 to 1.24)	1.00 (0.42 to 2.40)	**Chlorpromazine**	1.18 (0.69 to 2.01)	NA	2.96 (0.24 to 36.39)	NA	NA	NA	NA	0.32 (0.01 to 8.61)	0.32 (0.01 to 8.61)	0.32 (0.01 to 8.61)
0.31 (0.01 to 8.46)	0.32 (0.05 to 2.19)	0.65 (0.40 to 1.08)	0.67 (0.41 to 1.08)	0.72 (0.35 to 1.51)	0.75 (0.45 to 1.28)	0.98 (0.40 to 2.42)	0.98 (0.63 to 1.53)	**Quetiapine**	NA	1.20 (0.56 to 2.61)	NA	NA	NA	0.32 (0.06 to 1.78)	NA	NA	NA
0.27 (0.01 to 9.43)	0.28 (0.03 to 2.84)	0.57 (0.15 to 2.16)	0.58 (0.16 to 2.13)	0.63 (0.15 to 2.69)	0.66 (0.17 to 2.51)	0.86 (0.19 to 3.94)	0.86 (0.22 to 3.35)	0.88 (0.22 to 3.48)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA	NA
0.26 (0.01 to 7.11)	0.27 (0.04 to 1.85)	**0.55 (0.38 to 0.78)**	**0.56 (0.40 to 0.78)**	0.61 (0.30 to 1.23)	**0.63 (0.42 to 0.94)**	0.82 (0.36 to 1.89)	0.82 (0.51 to 1.32)	0.84 (0.51 to 1.36)	0.96 (0.25 to 3.65)	**Haloperidol**	NA	NA	NA	1.00 (0.23 to 4.40)	0.25 (0.02 to 3.96)	NA	NA
0.25 (0.00 to 17.61)	0.26 (0.01 to 7.04)	0.52 (0.03 to 8.07)	0.53 (0.03 to 8.18)	0.57 (0.03 to 9.43)	0.60 (0.04 to 9.36)	0.78 (0.05 to 13.41)	0.78 (0.05 to 12.06)	0.79 (0.05 to 12.46)	0.91 (0.04 to 18.76)	0.95 (0.06 to 14.57)	**Fluphenazine_LAI**	1.00 (0.29 to 3.40)	NA	NA	0.36 (0.06 to 2.09)	NA	NA
0.25 (0.00 to 17.61)	0.26 (0.01 to 7.04)	0.52 (0.03 to 8.07)	0.53 (0.03 to 8.18)	0.57 (0.03 to 9.43)	0.60 (0.04 to 9.36)	0.78 (0.05 to 13.41)	0.78 (0.05 to 12.06)	0.79 (0.05 to 12.46)	0.91 (0.04 to 18.76)	0.95 (0.06 to 14.57)	1.00 (0.29 to 3.40)	**Pipotiazine_LAI**	NA	NA	0.36 (0.06 to 2.09)	NA	NA
0.20 (0.01 to 6.65)	0.21 (0.02 to 1.95)	0.42 (0.13 to 1.33)	0.43 (0.13 to 1.40)	0.47 (0.12 to 1.78)	0.49 (0.15 to 1.61)	0.64 (0.16 to 2.57)	0.64 (0.19 to 2.18)	0.65 (0.19 to 2.26)	0.74 (0.13 to 4.26)	0.77 (0.23 to 2.56)	0.82 (0.04 to 15.96)	0.82 (0.04 to 15.96)	**Amisulpride**	NA	NA	NA	NA
0.15 (0.00 to 4.92)	0.16 (0.02 to 1.41)	**0.32 (0.11 to 0.97)**	**0.33 (0.11 to 0.98)**	0.36 (0.10 to 1.25)	0.37 (0.13 to 1.12)	0.49 (0.13 to 1.82)	0.49 (0.16 to 1.50)	0.50 (0.16 to 1.51)	0.57 (0.10 to 3.08)	0.59 (0.20 to 1.73)	0.63 (0.03 to 11.69)	0.63 (0.03 to 11.69)	0.77 (0.16 to 3.74)	**Fluphenazine**	NA	NA	NA
0.09 (0.00 to 4.32)	0.09 (0.01 to 1.52)	0.19 (0.02 to 1.53)	0.19 (0.02 to 1.55)	0.21 (0.02 to 1.81)	0.21 (0.03 to 1.78)	0.28 (0.03 to 2.62)	0.28 (0.03 to 2.28)	0.28 (0.03 to 2.37)	0.33 (0.03 to 3.83)	0.34 (0.04 to 2.75)	0.36 (0.06 to 2.09)	0.36 (0.06 to 2.09)	0.44 (0.04 to 4.83)	0.57 (0.06 to 5.95)	**Placebo**	1.00 (0.09 to 11.09)	0.57 (0.14 to 2.43)
0.07 (0.00 to 5.07)	0.08 (0.00 to 2.01)	0.15 (0.01 to 2.31)	0.16 (0.01 to 2.34)	0.17 (0.01 to 2.69)	0.18 (0.01 to 2.68)	0.23 (0.01 to 3.84)	0.23 (0.02 to 3.43)	0.23 (0.02 to 3.56)	0.27 (0.01 to 5.38)	0.28 (0.02 to 4.18)	0.29 (0.02 to 4.76)	0.29 (0.02 to 4.76)	0.36 (0.02 to 6.87)	0.47 (0.03 to 8.56)	0.82 (0.09 to 7.08)	**Thioridazine**	1.00 (0.09 to 11.09)
0.05 (0.00 to 2.97)	0.06 (0.00 to 1.10)	0.11 (0.01 to 1.17)	0.11 (0.01 to 1.19)	0.12 (0.01 to 1.38)	0.13 (0.01 to 1.36)	0.17 (0.01 to 1.98)	0.17 (0.02 to 1.75)	0.17 (0.02 to 1.82)	0.19 (0.01 to 2.85)	0.20 (0.02 to 2.12)	0.21 (0.02 to 2.06)	0.21 (0.02 to 2.06)	0.26 (0.02 to 3.61)	0.34 (0.03 to 4.47)	0.60 (0.14 to 2.48)	0.73 (0.08 to 6.55)	**Trifluoperazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is odd ratio (OR). Bold results indicate 95% CI excluding no effect. NA=not available.

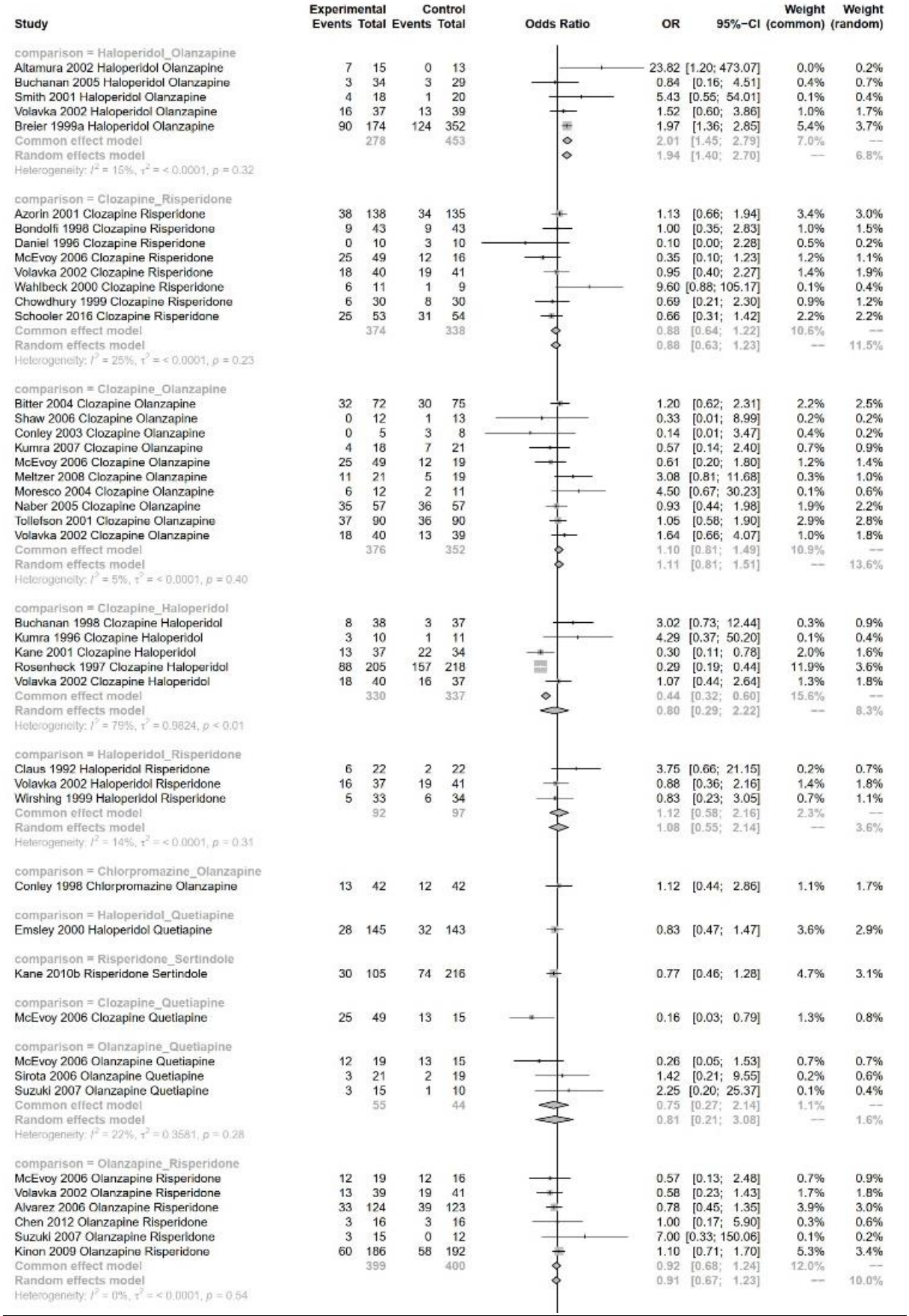
League table for the outcome: Discontinuation due to any reason (RR)

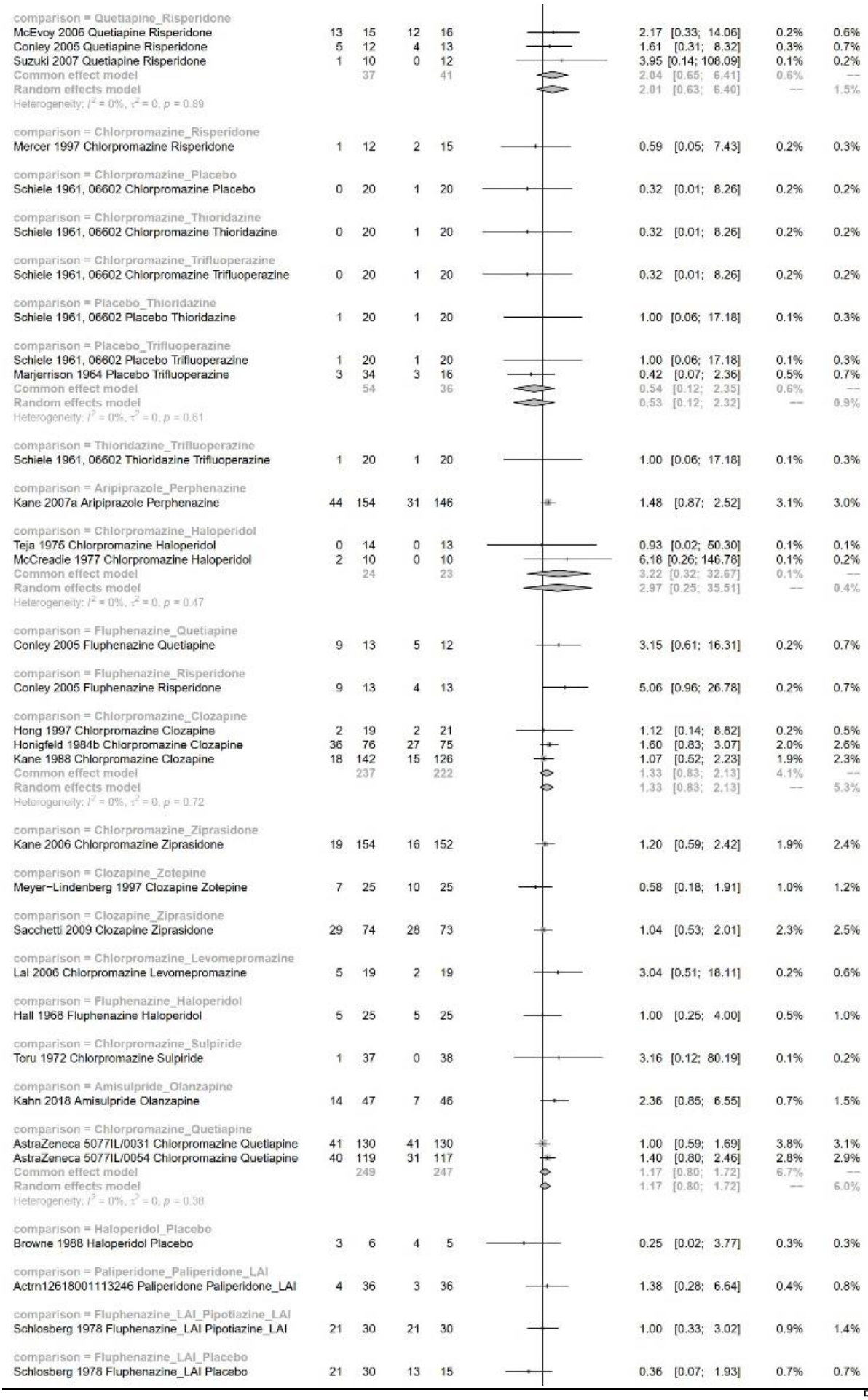
Sulpiride	NA	NA	NA	NA	NA	NA	0.43 (0.02 to 2.23)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.97 (0.02 to 5.43)	**Levomepromazine**	NA	NA	NA	NA	NA	0.44 (0.08 to 1.5)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.56 (0.03 to 2.94)	0.58 (0.1 to 2.01)	**Olanzapine**	0.93 (0.7 to 1.2)	NA	0.91 (0.66 to 1.21)	NA	0.93 (0.42 to 1.63)	0.86 (0.35 to 1.58)	NA	**0.64 (0.44 to 0.91)**	NA	NA	0.58 (0.23 to 1.15)	NA	NA	NA	NA
0.56 (0.03 to 2.9)	0.57 (0.1 to 1.97)	0.99 (0.8 to 1.2)	**Clozapine**	1.03 (0.53 to 1.68)	0.89 (0.66 to 1.18)	NA	0.83 (0.54 to 1.2)	**0.23 (0.05 to 0.91)**	0.7 (0.24 to 1.45)	**0.65 (0.46 to 0.89)**	NA	NA	NA	NA	NA	NA	NA
0.52 (0.03 to 2.75)	0.54 (0.08 to 1.91)	0.93 (0.55 to 1.44)	0.94 (0.58 to 1.42)	**Ziprasidone**	NA	NA	0.89 (0.46 to 1.46)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.5 (0.03 to 2.67)	0.52 (0.09 to 1.83)	0.91 (0.7 to 1.13)	0.91 (0.72 to 1.14)	0.97 (0.56 to 1.5)	**Risperidone**	0.84 (0.48 to 1.3)	1.34 (0.19 to 2.49)	0.61 (0.22 to 1.32)	NA	0.93 (0.56 to 1.38)	NA	NA	NA	0.36 (0.06 to 1.05)	NA	NA	NA
0.43 (0.02 to 2.27)	0.44 (0.06 to 1.62)	0.76 (0.41 to 1.26)	0.77 (0.42 to 1.26)	0.82 (0.37 to 1.47)	0.84 (0.48 to 1.3)	**Sertindole**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.43 (0.02 to 2.23)	0.44 (0.08 to 1.5)	0.76 (0.54 to 1.02)	0.77 (0.57 to 1.01)	0.82 (0.5 to 1.22)	0.84 (0.59 to 1.14)	1 (0.54 to 1.58)	**Chlorpromazine**	1.1 (0.78 to 1.45)	NA	1.62 (0.35 to 2.29)	NA	NA	NA	NA	0.6 (0.03 to 1.39)	0.63 (0.04 to 1.33)	0.69 (0.04 to 1.24)
0.42 (0.02 to 2.21)	0.43 (0.08 to 1.51)	0.75 (0.52 to 1.05)	0.77 (0.53 to 1.05)	0.81 (0.46 to 1.27)	0.83 (0.57 to 1.16)	0.99 (0.52 to 1.57)	0.99 (0.73 to 1.27)	**Quetiapine**	NA	1.11 (0.69 to 1.56)	NA	NA	NA	0.51 (0.12 to 1.24)	NA	NA	NA
0.39 (0.02 to 2.11)	0.4 (0.05 to 1.62)	0.69 (0.23 to 1.46)	0.7 (0.24 to 1.45)	0.74 (0.23 to 1.59)	0.77 (0.26 to 1.55)	0.91 (0.28 to 1.78)	0.91 (0.32 to 1.7)	0.93 (0.32 to 1.72)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA	NA
0.38 (0.02 to 1.99)	0.39 (0.07 to 1.36)	**0.68 (0.51 to 0.86)**	**0.69 (0.54 to 0.86)**	0.73 (0.43 to 1.12)	**0.75 (0.56 to 0.96)**	0.89 (0.49 to 1.38)	0.89 (0.64 to 1.16)	0.9 (0.64 to 1.18)	0.98 (0.37 to 1.73)	**Haloperidol**	NA	NA	NA	1 (0.4 to 1.53)	0.51 (0.06 to 1.31)	NA	NA
0.37 (0 to 2.15)	0.38 (0.02 to 1.95)	0.66 (0.05 to 1.99)	0.67 (0.05 to 1.99)	0.7 (0.05 to 2.03)	0.73 (0.07 to 2.03)	0.86 (0.08 to 2.1)	0.86 (0.08 to 2.08)	0.87 (0.08 to 2.09)	0.95 (0.07 to 2.16)	0.97 (0.1 to 2.12)	**Fluphenazine_LAI**	1 (0.42 to 1.67)	NA	NA	0.64 (0.17 to 1.2)	NA	NA
0.37 (0 to 2.15)	0.38 (0.02 to 1.95)	0.66 (0.05 to 1.99)	0.67 (0.05 to 1.99)	0.7 (0.05 to 2.03)	0.73 (0.07 to 2.03)	0.86 (0.08 to 2.1)	0.86 (0.08 to 2.08)	0.87 (0.08 to 2.09)	0.95 (0.07 to 2.16)	0.97 (0.1 to 2.12)	1 (0.42 to 1.67)	**Pipotiazine_LAI**	NA	NA	0.64 (0.17 to 1.2)	NA	NA
0.33 (0.02 to 1.78)	0.34 (0.04 to 1.33)	0.58 (0.23 to 1.15)	0.59 (0.23 to 1.17)	0.63 (0.21 to 1.29)	0.65 (0.26 to 1.24)	0.78 (0.27 to 1.46)	0.78 (0.31 to 1.39)	0.78 (0.31 to 1.4)	0.85 (0.23 to 1.65)	0.87 (0.37 to 1.46)	0.9 (0.07 to 1.93)	0.9 (0.07 to 1.93)	**Amisulpride**	NA	NA	NA	NA
0.28 (0 to 1.56)	0.3 (0.04 to 1.15)	**0.51 (0.22 to 0.99)**	**0.52 (0.22 to 0.99)**	0.56 (0.2 to 1.1)	0.57 (0.25 to 1.05)	0.68 (0.25 to 1.25)	0.68 (0.3 to 1.18)	0.69 (0.3 to 1.18)	0.75 (0.2 to 1.43)	0.76 (0.36 to 1.23)	0.79 (0.06 to 1.69)	0.79 (0.06 to 1.69)	0.88 (0.3 to 1.49)	**Fluphenazine**	NA	NA	NA
0.24 (0 to 1.32)	0.24 (0.03 to 1.12)	0.42 (0.06 to 1.12)	0.42 (0.06 to 1.13)	0.45 (0.06 to 1.17)	0.45 (0.09 to 1.16)	0.55 (0.09 to 1.25)	0.55 (0.09 to 1.22)	0.55 (0.09 to 1.23)	0.61 (0.09 to 1.31)	0.62 (0.12 to 1.25)	0.64 (0.17 to 1.2)	0.64 (0.17 to 1.2)	0.71 (0.12 to 1.34)	0.81 (0.17 to 1.36)	**Placebo**	1 (0.26 to 1.34)	0.86 (0.43 to 1.15)
0.21 (0 to 1.29)	0.24 (0 to 1.16)	0.39 (0.04 to 1.19)	0.41 (0.04 to 1.19)	0.42 (0.04 to 1.21)	0.44 (0.04 to 1.21)	0.52 (0.04 to 1.26)	0.52 (0.07 to 1.25)	0.52 (0.07 to 1.25)	0.57 (0.04 to 1.29)	0.58 (0.07 to 1.27)	0.59 (0.07 to 1.28)	0.59 (0.07 to 1.28)	0.67 (0.07 to 1.31)	0.76 (0.1 to 1.33)	0.94 (0.26 to 1.31)	**Thioridazine**	1 (0.31 to 1.24)
0.2 (0 to 1.17)	0.23 (0 to 1.02)	0.36 (0.04 to 1.03)	0.36 (0.04 to 1.04)	0.39 (0.04 to 1.06)	0.41 (0.04 to 1.06)	0.49 (0.04 to 1.12)	0.49 (0.09 to 1.1)	0.49 (0.09 to 1.11)	0.52 (0.04 to 1.16)	0.54 (0.09 to 1.13)	0.55 (0.09 to 1.13)	0.55 (0.09 to 1.13)	0.62 (0.09 to 1.19)	0.7 (0.13 to 1.2)	0.87 (0.43 to 1.15)	0.93 (0.29 to 1.22)	**Trifluoperazine**

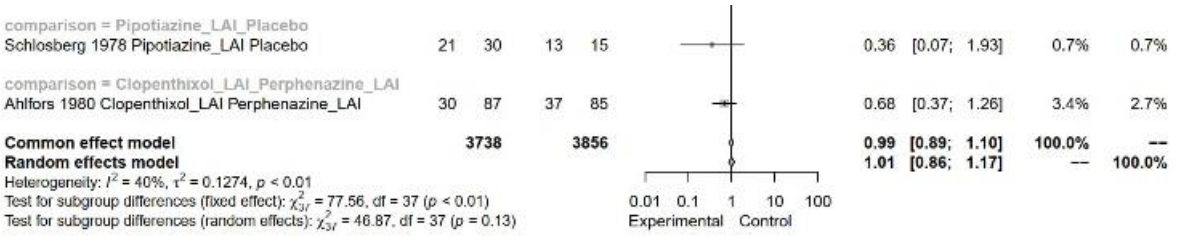
The original results given in OR (and their 95% CI) are transformed to RR (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column) using the formula described above. For this transformation, we assumed a discontinuation rate (due to any reason) with clozapine of 35% as the control event rate (CER) for all comparisons of active antipsychotic versus clozapine.

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses




comparison = Quetiapine_Risperidone
McEvoy 2006 Quetiapine Risperidone 13 15 12 16 2.17 [0.33; 14.06] 0.2% 0.6%
Conley 2005 Quetiapine Risperidone 5 12 4 13 1.61 [0.31; 8.32] 0.3% 0.7%
Suzuki 2007 Quetiapine Risperidone 1 10 0 12 3.95 [0.14; 108.09] 0.1% 0.2%
Common effect model 37 41 2.04 [0.65; 6.41] 0.6% —
Random effects model 2.01 [0.63; 6.40] — 1.5%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.89
comparison = Chlorpromazine_Risperidone
Mercer 1997 Chlorpromazine Risperidone 1 12 2 15 0.59 [0.05; 7.43] 0.2% 0.3%
comparison = Chlorpromazine_Placebo
Schiele 1961, 06602 Chlorpromazine Placebo 0 20 1 20 0.32 [0.01; 8.26] 0.2% 0.2%
comparison = Chlorpromazine_Thioridazine
Schiele 1961, 06602 Chlorpromazine Thioridazine 0 20 1 20 0.32 [0.01; 8.26] 0.2% 0.2%
comparison = Chlorpromazine_Trifluoperazine
Schiele 1961, 06602 Chlorpromazine Trifluoperazine 0 20 1 20 0.32 [0.01; 8.26] 0.2% 0.2%
comparison = Placebo_Thioridazine
Schiele 1961, 06602 Placebo Thioridazine 1 20 1 20 1.00 [0.06; 17.18] 0.1% 0.3%
comparison = Placebo_Trifluoperazine
Schiele 1961, 06602 Placebo Trifluoperazine 1 20 1 20 1.00 [0.06; 17.18] 0.1% 0.3%
Marjerrison 1964 Placebo Trifluoperazine 3 34 3 16 0.42 [0.07; 2.36] 0.5% 0.7%
Common effect model 54 36 0.54 [0.12; 2.35] 0.6% —
Random effects model 0.53 [0.12; 2.32] — 0.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.61
comparison = Thioridazine_Trifluoperazine
Schiele 1961, 06602 Thioridazine Trifluoperazine 1 20 1 20 1.00 [0.06; 17.18] 0.1% 0.3%
comparison = Aripiprazole_Perphenazine
Kane 2007a Aripiprazole Perphenazine 44 154 31 146 1.48 [0.87; 2.52] 3.1% 3.0%
comparison = Chlorpromazine_Haloperidol
Teja 1975 Chlorpromazine Haloperidol 0 14 0 13 0.93 [0.02; 50.30] 0.1% 0.1%
McCreadie 1977 Chlorpromazine Haloperidol 2 10 0 10 6.18 [0.26; 146.78] 0.1% 0.2%
Common effect model 24 23 3.22 [0.32; 32.67] 0.1% —
Random effects model 2.97 [0.25; 35.51] — 0.4%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.47
comparison = Fluphenazine_Quetiapine
Conley 2005 Fluphenazine Quetiapine 9 13 5 12 3.15 [0.61; 16.31] 0.2% 0.7%
comparison = Fluphenazine_Risperidone
Conley 2005 Fluphenazine Risperidone 9 13 4 13 5.06 [0.96; 26.78] 0.2% 0.7%
comparison = Chlorpromazine_Clozapine
Hong 1997 Chlorpromazine Clozapine 2 19 2 21 1.12 [0.14; 8.82] 0.2% 0.5%
Honigfeld 1984b Chlorpromazine Clozapine 36 76 27 75 1.60 [0.83; 3.07] 2.0% 2.6%
Kane 1988 Chlorpromazine Clozapine 18 142 15 126 1.07 [0.52; 2.23] 1.9% 2.3%
Common effect model 237 222 1.33 [0.83; 2.13] 4.1% —
Random effects model 1.33 [0.83; 2.13] — 5.3%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.72
comparison = Chlorpromazine_Ziprasidone
Kane 2006 Chlorpromazine Ziprasidone 19 154 16 152 1.20 [0.59; 2.42] 1.9% 2.4%
comparison = Clozapine_Zotepine
Meyer−Lindenberg 1997 Clozapine Zotepine 7 25 10 25 0.58 [0.18; 1.91] 1.0% 1.2%
comparison = Clozapine_Ziprasidone
Sacchetti 2009 Clozapine Ziprasidone 29 74 28 73 1.04 [0.53; 2.01] 2.3% 2.5%
comparison = Chlorpromazine_Levomepromazine
Lal 2006 Chlorpromazine Levomepromazine 5 19 2 19 3.04 [0.51; 18.11] 0.2% 0.6%
comparison = Fluphenazine_Haloperidol
Hall 1968 Fluphenazine Haloperidol 5 25 5 25 1.00 [0.25; 4.00] 0.5% 1.0%
comparison = Chlorpromazine_Sulpiride
Toru 1972 Chlorpromazine Sulpiride 1 37 0 38 3.16 [0.12; 80.19] 0.1% 0.2%
comparison = Amisulpride_Olanzapine
Kahn 2018 Amisulpride Olanzapine 14 47 7 46 2.36 [0.85; 6.55] 0.7% 1.5%
comparison = Chlorpromazine_Quetiapine
AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine 41 130 41 130 1.00 [0.59; 1.69] 3.8% 3.1%
AstraZeneca 5077IL/0054 Chlorpromazine Quetiapine 40 119 31 117 1.40 [0.80; 2.46] 2.8% 2.9%
Common effect model 249 247 1.17 [0.80; 1.72] 6.7% —
Random effects model 1.17 [0.80; 1.72] — 6.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.38
comparison = Haloperidol_Placebo
Browne 1988 Haloperidol Placebo 3 6 4 5 0.25 [0.02; 3.77] 0.3% 0.3%
comparison = Paliperidone_Paliperidone_LAI
Actrn12618001113246 Paliperidone Paliperidone_LAI 4 36 3 36 1.38 [0.28; 6.64] 0.4% 0.8%
comparison = Fluphenazine_LAI_Pipotiazine_LAI
Schlosberg 1978 Fluphenazine_LAI Pipotiazine_LAI 21 30 21 30 1.00 [0.33; 3.02] 0.9% 1.4%
comparison = Fluphenazine_LAI_Placebo
Schlosberg 1978 Fluphenazine_LAI Placebo 21 30 13 15 0.36 [0.07; 1.93] 0.7% 0.7%

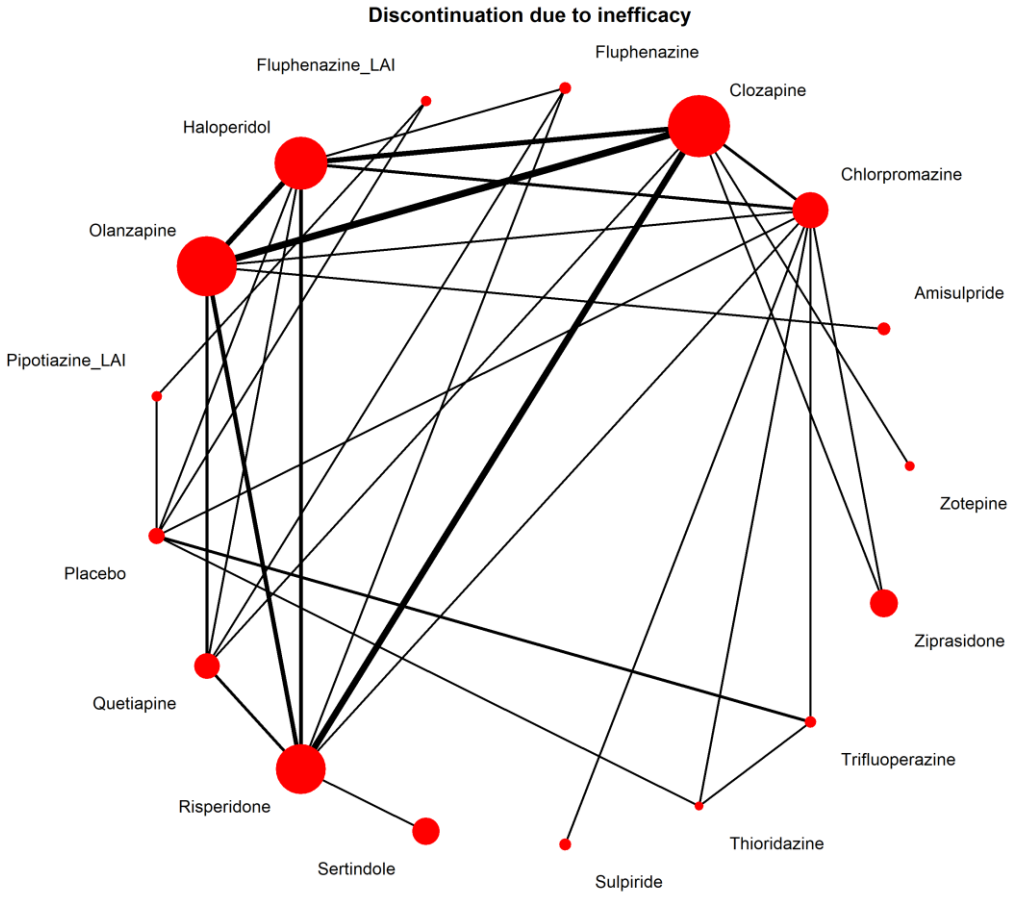


A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is OR.

8.5 Discontinuation due to inefficacy

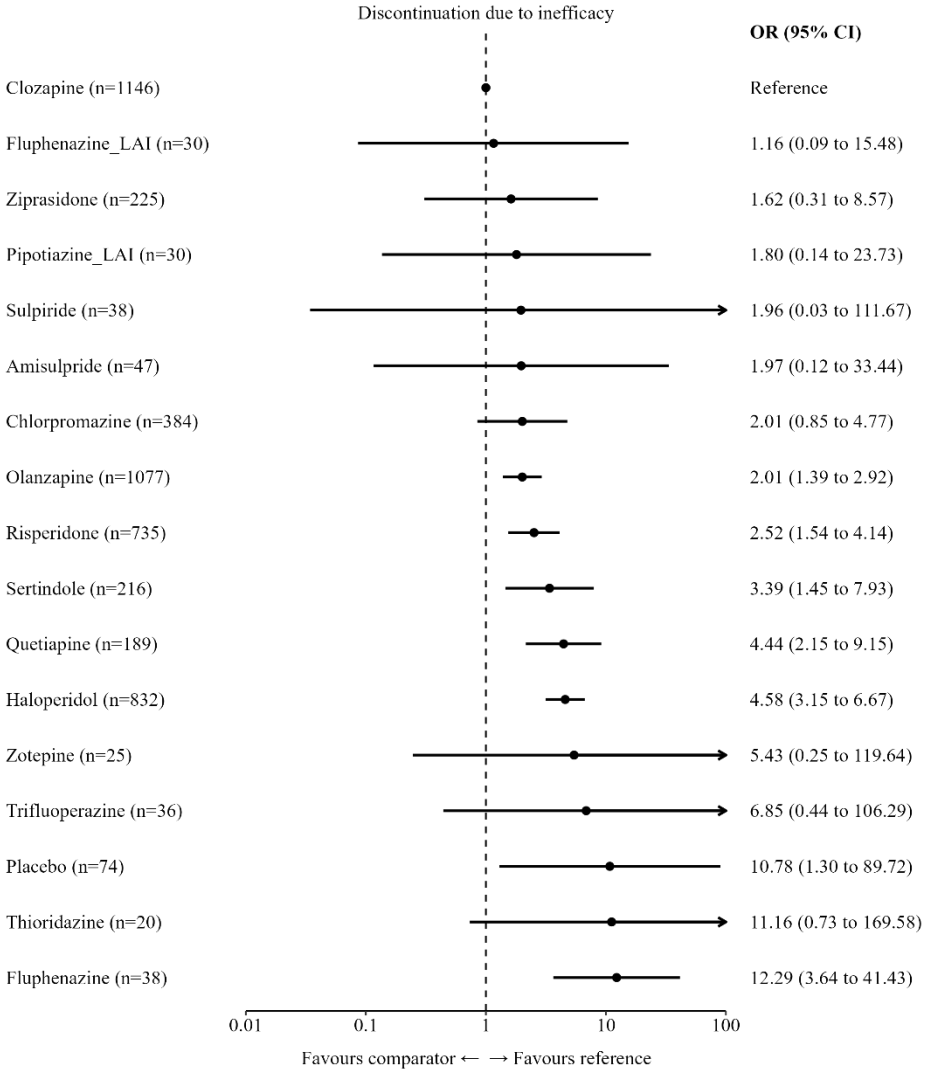
We transformed the original ORs to RRs and EERs vs. CER assuming the baseline discontinuation rate due to inefficacy with clozapine of 6% (namely CER). 6% was the average discontinuation rate due to efficacy with clozapine across all clozapine -arms in the network meta-analysis, as estimated by a single-arm meta-analysis of proportions.

Network plot



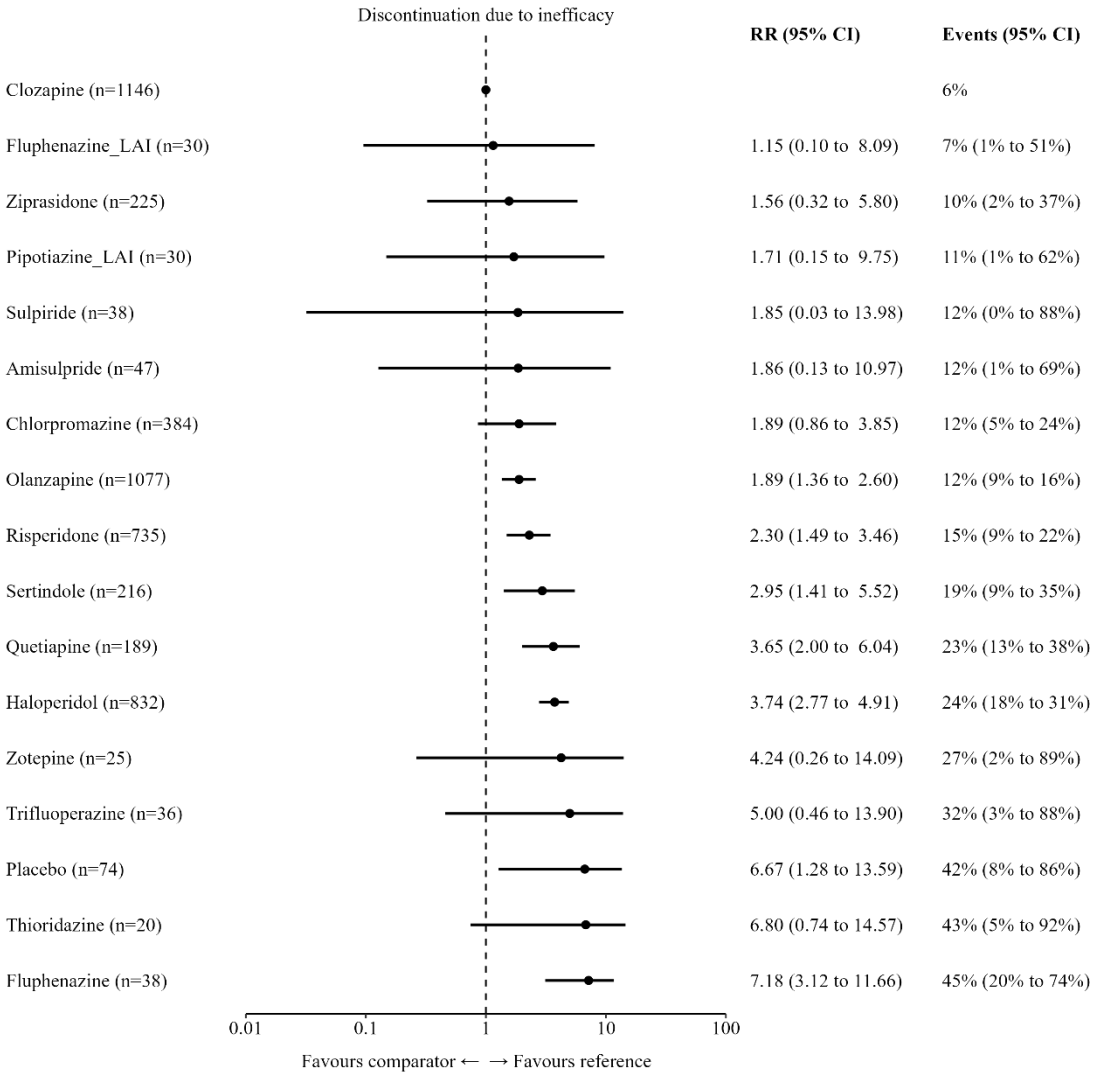
Lines link treatments with direct comparisons in trials; thickness of lines corresponds to the number of trials evaluating the comparison; size of the nodes corresponds to the number of participants assigned to the treatment.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as odds ratio (OR), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

Forest plot with RR and EER versus CER



For this forest plot, we transformed the original OR to RR and exposure events rates (EER, called "events" in the forest plot) using the formula indicated above. Therefore, we used an average discontinuation rate (due to inefficacy) with clozapine of 6% as the control event rate (CER).
Effect sizes are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table for the outcome: Discontinuation due to inefficacy (OR)

Clozapine	NA	0.65 (0.10 to 4.04)	NA	NA	NA	0.40 (0.12 to 1.29)	0.77 (0.47 to 1.25)	**0.31 (0.17 to 0.57)**	NA	**0.17 (0.04 to 0.69)**	**0.16 (0.10 to 0.27)**	0.18 (0.01 to 4.06)	NA	NA	NA	NA
0.87 (0.06 to 11.59)	**Fluphenazine_LAI**	NA	0.64 (0.22 to 1.90)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**0.11 (0.02 to 0.48)**	NA	NA
0.62 (0.12 to 3.26)	0.71 (0.03 to 15.26)	**Ziprasidone**	NA	NA	NA	1.01 (0.02 to 51.61)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.56 (0.04 to 7.34)	0.64 (0.22 to 1.90)	0.90 (0.04 to 19.07)	**Pipotiazine_LAI**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**0.17 (0.04 to 0.73)**	NA	NA
0.51 (0.01 to 29.12)	0.59 (0.01 to 67.10)	0.83 (0.01 to 63.66)	0.92 (0.01 to 103.54)	**Sulpiride**	NA	0.97 (0.02 to 50.59)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.51 (0.03 to 8.64)	0.59 (0.01 to 26.88)	0.82 (0.03 to 21.97)	0.91 (0.02 to 41.40)	1.00 (0.01 to 137.34)	**Amisulpride**	NA	0.98 (0.06 to 16.22)	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.50 (0.21 to 1.18)	0.57 (0.04 to 7.80)	0.81 (0.13 to 4.90)	0.89 (0.07 to 11.96)	0.97 (0.02 to 50.59)	0.98 (0.05 to 18.62)	**Chlorpromazine**	0.37 (0.07 to 2.05)	1.24 (0.02 to 67.33)	NA	NA	0.96 (0.06 to 16.38)	NA	1.00 (0.02 to 53.08)	0.32 (0.01 to 8.30)	0.32 (0.01 to 8.30)	NA
0.50 (0.34 to 0.72)	0.57 (0.04 to 7.70)	0.81 (0.15 to 4.42)	0.89 (0.07 to 11.80)	0.97 (0.02 to 55.81)	0.98 (0.06 to 16.22)	1.00 (0.41 to 2.43)	**Olanzapine**	1.19 (0.51 to 2.76)	NA	0.73 (0.20 to 2.61)	**0.53 (0.35 to 0.78)**	NA	NA	NA	NA	NA
0.40 (0.24 to 0.65)	0.46 (0.03 to 6.32)	0.64 (0.11 to 3.64)	0.71 (0.05 to 9.68)	0.78 (0.01 to 45.24)	0.78 (0.04 to 13.57)	0.80 (0.30 to 2.09)	0.80 (0.47 to 1.35)	**Risperidone**	0.74 (0.37 to 1.48)	0.90 (0.29 to 2.83)	**0.33 (0.12 to 0.90)**	NA	NA	NA	NA	0.19 (0.03 to 1.04)
0.29 (0.13 to 0.69)	0.34 (0.02 to 5.14)	0.48 (0.07 to 3.09)	0.53 (0.04 to 7.88)	0.58 (0.01 to 35.69)	0.58 (0.03 to 10.97)	0.59 (0.18 to 1.94)	0.59 (0.25 to 1.41)	0.74 (0.37 to 1.48)	**Sertindole**	NA	NA	NA	NA	NA	NA	NA
0.23 (0.11 to 0.46)	0.26 (0.02 to 3.75)	0.37 (0.06 to 2.24)	0.41 (0.03 to 5.75)	0.44 (0.01 to 26.61)	0.44 (0.02 to 8.04)	0.45 (0.15 to 1.35)	**0.45 (0.22 to 0.93)**	0.57 (0.26 to 1.23)	0.76 (0.27 to 2.15)	**Quetiapine**	1.43 (0.55 to 3.73)	NA	NA	NA	NA	0.21 (0.04 to 1.17)
0.22 (0.15 to 0.32)	0.25 (0.02 to 3.34)	0.35 (0.06 to 1.94)	0.39 (0.03 to 5.12)	0.43 (0.01 to 24.55)	0.43 (0.03 to 7.27)	0.44 (0.18 to 1.08)	**0.44 (0.31 to 0.61)**	**0.55 (0.33 to 0.93)**	0.74 (0.31 to 1.76)	0.97 (0.49 to 1.92)	**Haloperidol**	NA	NA	0.25 (0.02 to 3.79)	NA	0.64 (0.10 to 4.23)
0.18 (0.01 to 4.06)	0.21 (0.00 to 12.07)	0.30 (0.01 to 10.02)	0.33 (0.01 to 18.60)	0.36 (0.00 to 58.66)	0.36 (0.01 to 24.05)	0.37 (0.01 to 9.20)	0.37 (0.02 to 8.36)	0.47 (0.02 to 10.67)	0.62 (0.03 to 15.45)	0.82 (0.03 to 19.60)	0.84 (0.04 to 19.04)	**Zotepine**	NA	NA	NA	NA
0.15 (0.01 to 2.26)	0.17 (0.01 to 1.99)	0.24 (0.01 to 5.72)	0.26 (0.02 to 3.05)	0.29 (0.00 to 34.95)	0.29 (0.01 to 14.54)	0.29 (0.02 to 4.54)	0.29 (0.02 to 4.55)	0.37 (0.02 to 5.87)	0.49 (0.03 to 8.59)	0.65 (0.04 to 10.76)	0.67 (0.04 to 10.27)	0.79 (0.01 to 49.37)	**Trifluoperazine**	0.68 (0.09 to 4.94)	0.32 (0.01 to 8.30)	NA
0.09 (0.01 to 0.77)	**0.11 (0.02 to 0.48)**	0.15 (0.01 to 2.18)	**0.17 (0.04 to 0.73)**	0.18 (0.00 to 16.18)	0.18 (0.01 to 6.15)	0.19 (0.02 to 1.58)	0.19 (0.02 to 1.55)	0.23 (0.03 to 2.02)	0.31 (0.03 to 3.02)	0.41 (0.05 to 3.74)	0.42 (0.05 to 3.49)	0.50 (0.01 to 21.38)	0.64 (0.09 to 4.53)	**Placebo**	1.00 (0.09 to 10.55)	NA
0.09 (0.01 to 1.36)	0.10 (0.01 to 1.47)	0.15 (0.01 to 3.45)	0.16 (0.01 to 2.26)	0.18 (0.00 to 21.00)	0.18 (0.00 to 8.82)	0.18 (0.01 to 2.68)	0.18 (0.01 to 2.75)	0.23 (0.01 to 3.54)	0.30 (0.02 to 5.18)	0.40 (0.02 to 6.49)	0.41 (0.03 to 6.20)	0.49 (0.01 to 29.94)	0.61 (0.04 to 8.46)	0.97 (0.11 to 8.65)	**Thioridazine**	NA
0.08 (0.02 to 0.27)	0.09 (0.01 to 1.61)	0.13 (0.02 to 1.03)	0.15 (0.01 to 2.47)	0.16 (0.00 to 10.77)	0.16 (0.01 to 3.41)	**0.16 (0.04 to 0.71)**	**0.16 (0.05 to 0.55)**	**0.21 (0.06 to 0.69)**	0.28 (0.07 to 1.11)	0.36 (0.10 to 1.25)	0.37 (0.11 to 1.23)	0.44 (0.02 to 12.26)	0.56 (0.03 to 10.93)	0.88 (0.08 to 9.79)	0.91 (0.05 to 17.50)	**Fluphenazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is odd ratio (OR). Bold results indicate 95% CI excluding no effect. NA=not available.

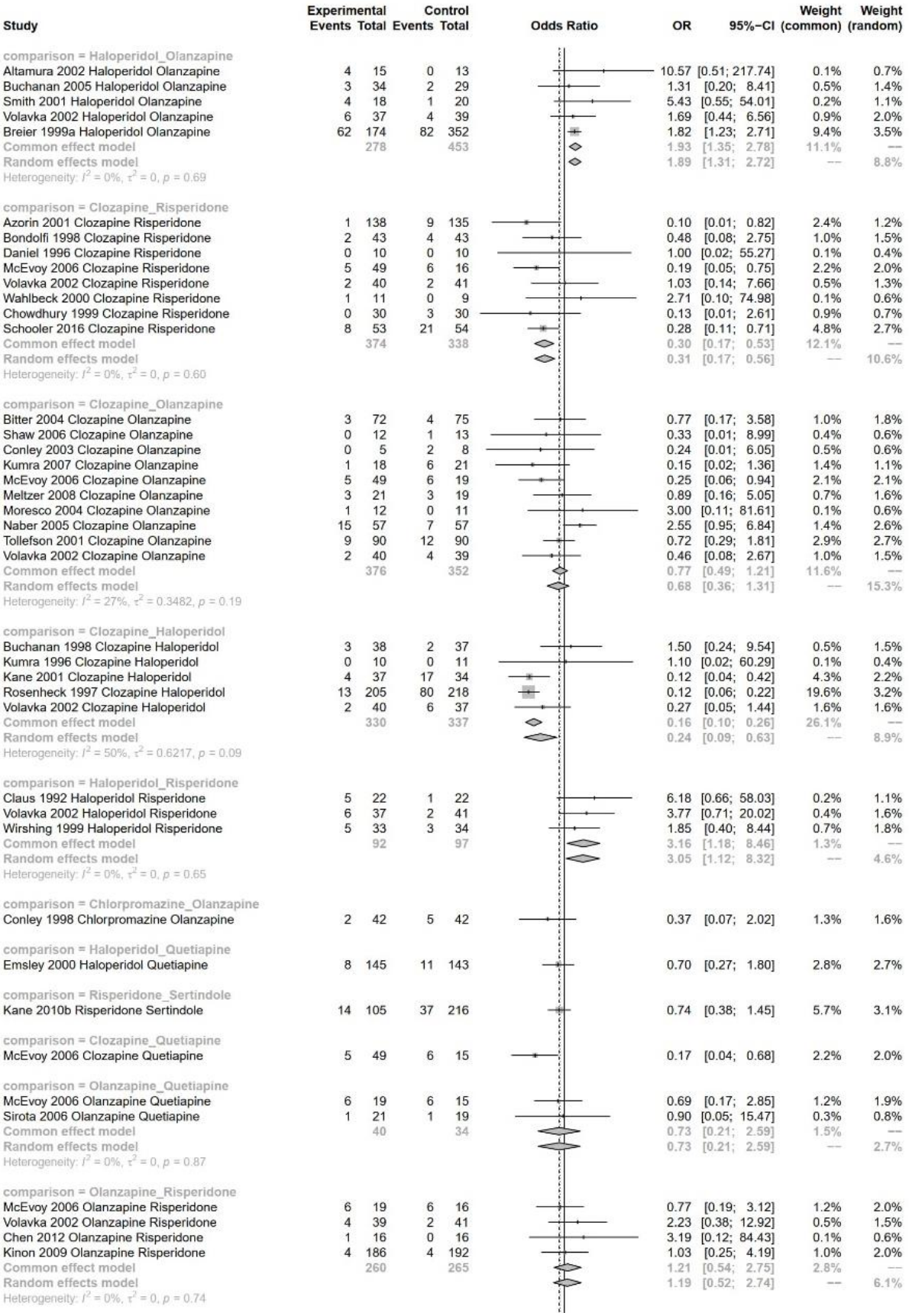
League table for the outcome: Discontinuation due to inefficacy (RR)

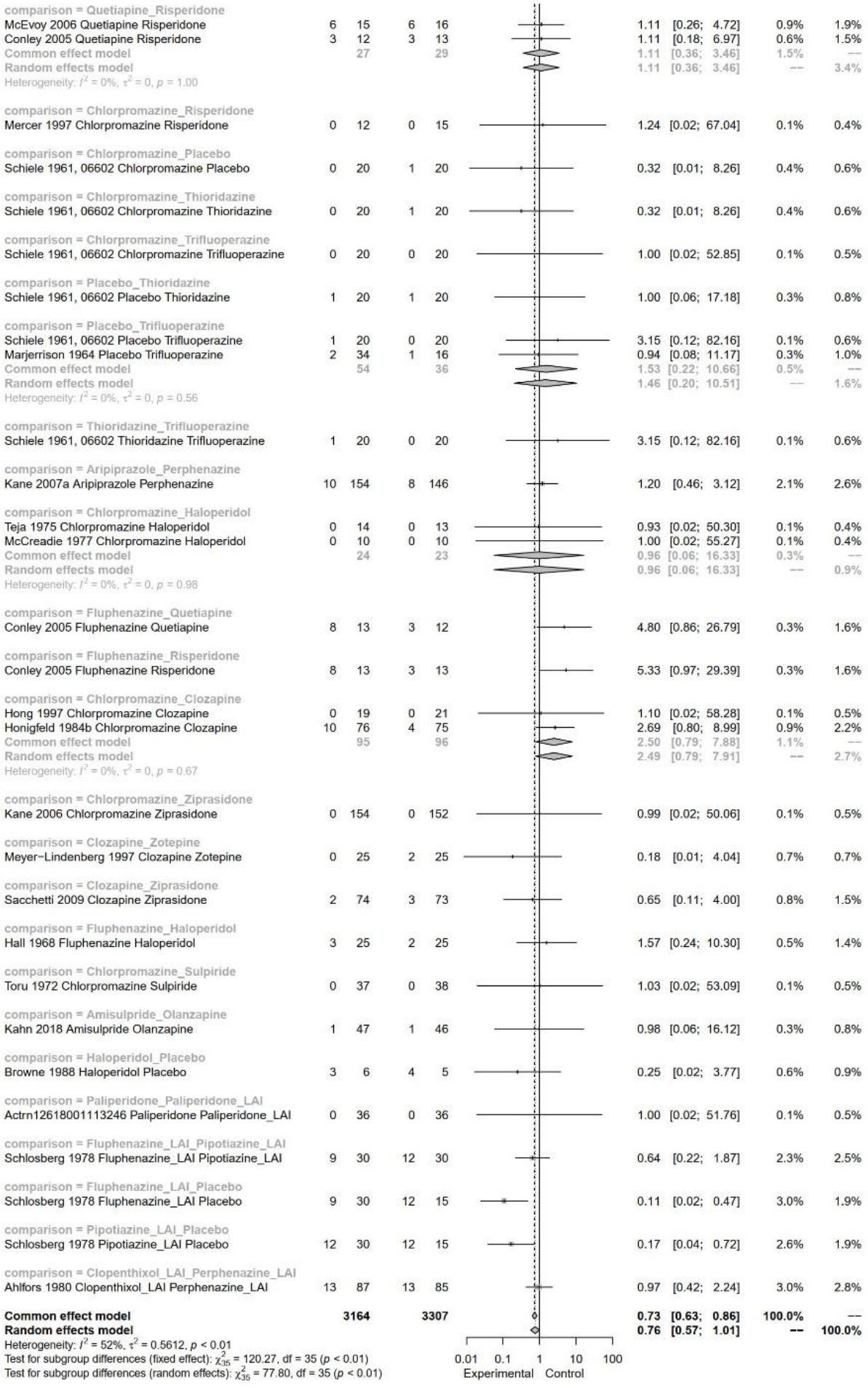
Clozapine	NA	0.67 (0.11 to 3.1)	NA	NA	NA	0.43 (0.13 to 1.25)	0.79 (0.5 to 1.21)	**0.35 (0.19 to 0.61)**	NA	**0.21 (0.05 to 0.74)**	**0.2 (0.13 to 0.33)**	0.23 (0.01 to 2.2)	NA	NA	NA	NA
0.88 (0.06 to 6.51)	**Fluphenazine_LAI**	NA	0.67 (0.24 to 1.73)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**0.18 (0.03 to 0.62)**	NA	NA
0.64 (0.13 to 2.66)	0.73 (0.03 to 6.28)	**Ziprasidone**	NA	NA	NA	1.01 (0.02 to 7.15)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.59 (0.04 to 4.32)	0.67 (0.24 to 1.73)	0.91 (0.04 to 6.36)	**Pipotiazine_LAI**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	**0.26 (0.07 to 0.83)**	NA	NA
0.54 (0.01 to 6.64)	0.62 (0.01 to 7.49)	0.85 (0.01 to 7.45)	0.93 (0.01 to 7.75)	**Sulpiride**	NA	0.97 (0.02 to 7.13)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.54 (0.03 to 4.5)	0.62 (0.01 to 6.53)	0.84 (0.03 to 6.23)	0.92 (0.02 to 7.06)	1 (0.01 to 7.88)	**Amisulpride**	NA	0.98 (0.07 to 5.65)	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.53 (0.23 to 1.15)	0.6 (0.05 to 4.25)	0.83 (0.15 to 3.31)	0.9 (0.08 to 5.1)	0.97 (0.02 to 7.13)	0.98 (0.06 to 5.88)	**Chlorpromazine**	0.4 (0.08 to 1.82)	1.2 (0.02 to 6.18)	NA	NA	0.97 (0.08 to 3.47)	NA	1 (0.03 to 2.99)	0.45 (0.02 to 2)	0.46 (0.02 to 1.98)	NA
0.53 (0.37 to 0.75)	0.6 (0.05 to 4.22)	0.83 (0.17 to 3.11)	0.9 (0.08 to 5.07)	0.97 (0.02 to 7.21)	0.98 (0.07 to 5.65)	1 (0.44 to 2.07)	**Olanzapine**	1.16 (0.55 to 2.19)	NA	0.78 (0.25 to 1.89)	**0.6 (0.42 to 0.82)**	NA	NA	NA	NA	NA
0.44 (0.27 to 0.69)	0.5 (0.04 to 3.52)	0.68 (0.13 to 2.61)	0.74 (0.06 to 4.22)	0.81 (0.01 to 5.96)	0.81 (0.05 to 4.72)	0.82 (0.33 to 1.8)	0.82 (0.51 to 1.28)	**Risperidone**	0.78 (0.42 to 1.36)	0.92 (0.35 to 1.98)	**0.39 (0.15 to 0.92)**	NA	NA	NA	NA	0.3 (0.05 to 1.02)
0.34 (0.16 to 0.73)	0.39 (0.02 to 2.87)	0.53 (0.09 to 2.21)	0.58 (0.05 to 3.41)	0.63 (0.01 to 4.69)	0.63 (0.04 to 3.78)	0.64 (0.21 to 1.65)	0.64 (0.29 to 1.31)	0.78 (0.42 to 1.36)	**Sertindole**	NA	NA	NA	NA	NA	NA	NA
0.28 (0.14 to 0.53)	0.32 (0.03 to 2.27)	0.43 (0.08 to 1.73)	0.48 (0.04 to 2.71)	0.51 (0.01 to 3.78)	0.51 (0.03 to 3.02)	0.52 (0.19 to 1.25)	**0.52 (0.27 to 0.95)**	0.63 (0.32 to 1.17)	0.81 (0.33 to 1.69)	**Quetiapine**	1.3 (0.62 to 2.25)	NA	NA	NA	NA	0.33 (0.07 to 1.08)
0.27 (0.19 to 0.38)	0.31 (0.03 to 2.13)	0.42 (0.08 to 1.58)	0.46 (0.04 to 2.57)	0.5 (0.01 to 3.67)	0.5 (0.04 to 2.89)	0.51 (0.22 to 1.06)	**0.51 (0.37 to 0.67)**	**0.62 (0.39 to 0.95)**	0.79 (0.37 to 1.49)	0.98 (0.56 to 1.57)	**Haloperidol**	NA	NA	0.37 (0.03 to 1.72)	NA	0.77 (0.17 to 1.7)
0.23 (0.01 to 2.2)	0.27 (0 to 2.98)	0.37 (0.01 to 2.88)	0.4 (0.01 to 3.19)	0.44 (0 to 3.48)	0.44 (0.01 to 3.28)	0.45 (0.01 to 2.83)	0.45 (0.03 to 2.76)	0.55 (0.03 to 2.92)	0.69 (0.04 to 3.11)	0.86 (0.04 to 3.21)	0.88 (0.05 to 3.19)	**Zotepine**	NA	NA	NA	NA
0.21 (0.01 to 1.61)	0.23 (0.01 to 1.51)	0.32 (0.01 to 2.27)	0.34 (0.03 to 1.84)	0.38 (0 to 2.93)	0.38 (0.01 to 2.71)	0.38 (0.03 to 2.12)	0.38 (0.03 to 2.12)	0.46 (0.03 to 2.28)	0.59 (0.04 to 2.49)	0.73 (0.06 to 2.6)	0.75 (0.06 to 2.58)	0.85 (0.01 to 2.98)	**Trifluoperazine**	0.79 (0.15 to 1.83)	0.46 (0.02 to 1.98)	NA
0.15 (0.02 to 0.85)	**0.18 (0.03 to 0.62)**	0.24 (0.02 to 1.44)	**0.26 (0.07 to 0.83)**	0.28 (0 to 2.14)	0.28 (0.02 to 1.91)	0.29 (0.03 to 1.26)	0.29 (0.03 to 1.25)	0.34 (0.05 to 1.4)	0.44 (0.05 to 1.61)	0.55 (0.08 to 1.71)	0.56 (0.08 to 1.68)	0.64 (0.02 to 2.18)	0.76 (0.15 to 1.8)	**Placebo**	1 (0.15 to 2.04)	NA
0.15 (0.02 to 1.18)	0.16 (0.02 to 1.22)	0.24 (0.02 to 1.67)	0.25 (0.02 to 1.46)	0.28 (0 to 2.16)	0.28 (0 to 2)	0.28 (0.02 to 1.55)	0.28 (0.02 to 1.56)	0.35 (0.02 to 1.68)	0.43 (0.03 to 1.83)	0.54 (0.03 to 1.91)	0.55 (0.05 to 1.89)	0.63 (0.02 to 2.19)	0.74 (0.07 to 1.99)	0.98 (0.18 to 1.99)	**Thioridazine**	NA
0.14 (0.04 to 0.41)	0.16 (0.02 to 1.26)	0.22 (0.04 to 1.02)	0.25 (0.02 to 1.47)	0.26 (0 to 1.95)	0.26 (0.02 to 1.61)	**0.26 (0.07 to 0.82)**	**0.26 (0.09 to 0.69)**	**0.33 (0.11 to 0.81)**	0.42 (0.12 to 1.06)	0.51 (0.17 to 1.12)	0.52 (0.19 to 1.11)	0.59 (0.04 to 1.97)	0.7 (0.05 to 1.95)	0.93 (0.14 to 1.93)	0.95 (0.09 to 2.03)	**Fluphenazine**

The original results given in OR (and their 95% CI) are transformed to RR (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column) using the formula described above. For this transformation, we assumed a discontinuation rate (due to inefficacy) with clozapine of 6% as the control event rate (CER) for all comparisons of active antipsychotic versus clozapine.

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses



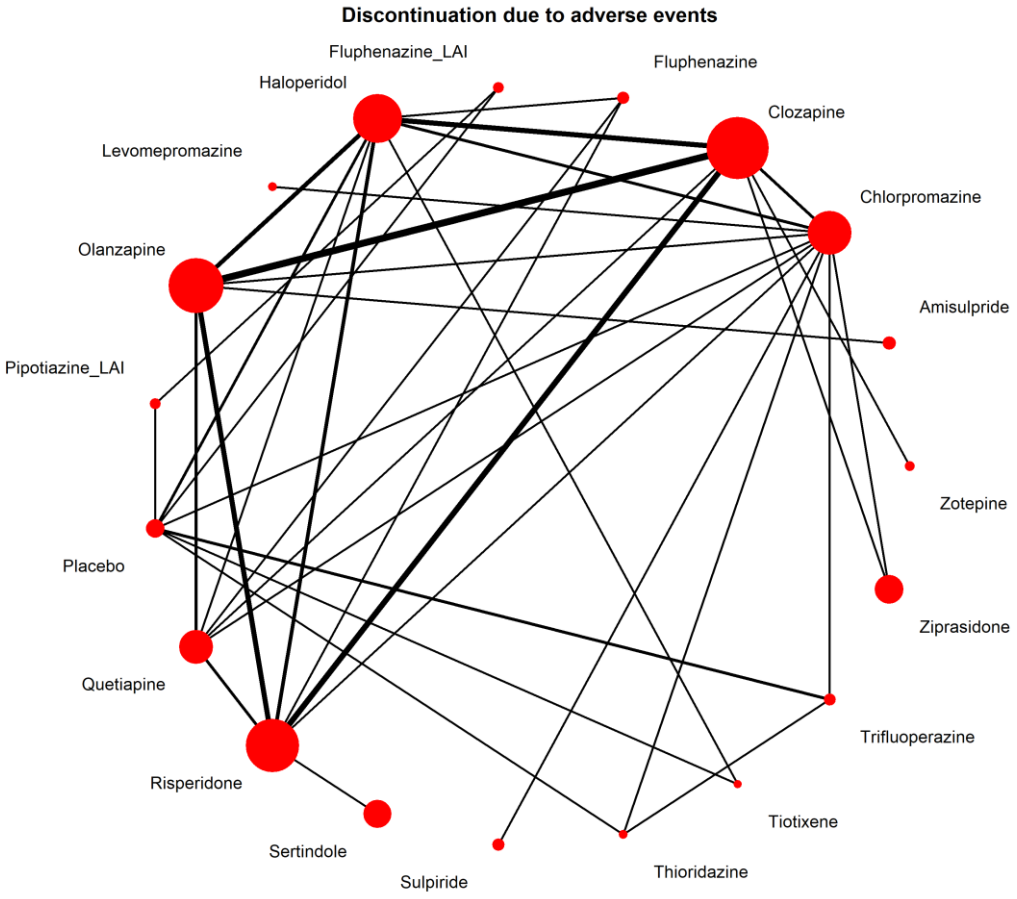

comparison = Quetiapine_Risperidone
McEvoy 2006 Quetiapine Risperidone 6 15 6 16 1.11 [0.26; 4.72] 0.9% 1.9%
Conley 2005 Quetiapine Risperidone 3 12 3 13 1.11 [0.18; 6.97] 0.6% 1.5%
Common effect model 27 29 1.11 [0.36; 3.46] 1.5% --
Random effects model 1.11 [0.36; 3.46] -- 3.4%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 1.00
comparison = Chlorpromazine_Risperidone
Mercer 1997 Chlorpromazine Risperidone 0 12 0 15 1.24 [0.02; 67.04] 0.1% 0.4%
comparison = Chlorpromazine_Placebo
Schiele 1961, 06602 Chlorpromazine Placebo 0 20 1 20 0.32 [0.01; 8.26] 0.4% 0.6%
comparison = Chlorpromazine_Thioridazine
Schiele 1961, 06602 Chlorpromazine Thioridazine 0 20 1 20 0.32 [0.01; 8.26] 0.4% 0.6%
comparison = Chlorpromazine_Trifluoperazine
Schiele 1961, 06602 Chlorpromazine Trifluoperazine 0 20 0 20 1.00 [0.02; 52.85] 0.1% 0.5%
comparison = Placebo_Thioridazine
Schiele 1961, 06602 Placebo Thioridazine 1 20 1 20 1.00 [0.06; 17.18] 0.3% 0.8%
comparison = Placebo_Trifluoperazine
Schiele 1961, 06602 Placebo Trifluoperazine 1 20 0 20 3.15 [0.12; 82.16] 0.1% 0.6%
Marjerrison 1964 Placebo Trifluoperazine 2 34 1 16 0.94 [0.08; 11.17] 0.3% 1.0%
Common effect model 54 36 1.53 [0.22; 10.66] 0.5% --
Random effects model 1.46 [0.20; 10.51] -- 1.6%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.56
comparison = Thioridazine_Trifluoperazine
Schiele 1961, 06602 Thioridazine Trifluoperazine 1 20 0 20 3.15 [0.12; 82.16] 0.1% 0.6%
comparison = Aripiprazole_Perphenazine
Kane 2007a Aripiprazole Perphenazine 10 154 8 146 1.20 [0.46; 3.12] 2.1% 2.6%
comparison = Chlorpromazine_Haloperidol
Teja 1975 Chlorpromazine Haloperidol 0 14 0 13 0.93 [0.02; 50.30] 0.1% 0.4%
McCreadie 1977 Chlorpromazine Haloperidol 0 10 0 10 1.00 [0.02; 55.27] 0.1% 0.4%
Common effect model 24 23 0.96 [0.06; 16.33] 0.3% --
Random effects model 0.96 [0.06; 16.33] -- 0.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.98
comparison = Fluphenazine_Quetiapine
Conley 2005 Fluphenazine Quetiapine 8 13 3 12 4.80 [0.86; 26.79] 0.3% 1.6%
comparison = Fluphenazine_Risperidone
Conley 2005 Fluphenazine Risperidone 8 13 3 13 5.33 [0.97; 29.39] 0.3% 1.6%
comparison = Chlorpromazine_Clozapine
Hong 1997 Chlorpromazine Clozapine 0 19 0 21 1.10 [0.02; 58.28] 0.1% 0.5%
Honigfeld 1984b Chlorpromazine Clozapine 10 76 4 75 2.69 [0.80; 8.99] 0.9% 2.2%
Common effect model 95 96 2.50 [0.79; 7.88] 1.1% --
Random effects model 2.49 [0.79; 7.91] -- 2.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.67
comparison = Chlorpromazine_Ziprasidone
Kane 2006 Chlorpromazine Ziprasidone 0 154 0 152 0.99 [0.02; 50.06] 0.1% 0.5%
comparison = Clozapine_Zotepine
Meyer−Lindenberg 1997 Clozapine Zotepine 0 25 2 25 0.18 [0.01; 4.04] 0.7% 0.7%
comparison = Clozapine_Ziprasidone
Sacchetti 2009 Clozapine Ziprasidone 2 74 3 73 0.65 [0.11; 4.00] 0.8% 1.5%
comparison = Fluphenazine_Haloperidol
Hall 1968 Fluphenazine Haloperidol 3 25 2 25 1.57 [0.24; 10.30] 0.5% 1.4%
comparison = Chlorpromazine_Sulpiride
Toru 1972 Chlorpromazine Sulpiride 0 37 0 38 1.03 [0.02; 53.09] 0.1% 0.5%
comparison = Amisulpride_Olanzapine
Kahn 2018 Amisulpride Olanzapine 1 47 1 46 0.98 [0.06; 16.12] 0.3% 0.8%
comparison = Haloperidol_Placebo
Browne 1988 Haloperidol Placebo 3 6 4 5 0.25 [0.02; 3.77] 0.6% 0.9%
comparison = Paliperidone_Paliperidone_LAI
Actrn12618001113246 Paliperidone Paliperidone_LAI 0 36 0 36 1.00 [0.02; 51.76] 0.1% 0.5%
comparison = Fluphenazine_LAI_Pipotiazine_LAI
Schlosberg 1978 Fluphenazine_LAI Pipotiazine_LAI 9 30 12 30 0.64 [0.22; 1.87] 2.3% 2.5%
comparison = Fluphenazine_LAI_Placebo
Schlosberg 1978 Fluphenazine_LAI Placebo 9 30 12 15 0.11 [0.02; 0.47] 3.0% 1.9%
comparison = Pipotiazine_LAI_Placebo
Schlosberg 1978 Pipotiazine_LAI Placebo 12 30 12 15 0.17 [0.04; 0.72] 2.6% 1.9%
comparison = Clopenthixol_LAI_Perphenazine_LAI
Ahlfors 1980 Clopenthixol_LAI Perphenazine_LAI 13 87 13 85 0.97 [0.42; 2.24] 3.0% 2.8%
Common effect model 3164 3307 0.73 [0.63; 0.86] 100.0% --
Random effects model 0.76 [0.57; 1.01] -- 100.0%
Heterogeneity: I^2 = 52%, τ^2 = 0.5612, p < 0.01
Test for subgroup differences (fixed effect): χ^2_{35} = 120.27, df = 35 (p < 0.01)
Test for subgroup differences (random effects): χ^2_{35} = 77.80, df = 35 (p < 0.01)
0.01 0.1 1 10 100
Experimental Control

A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is OR.

8.6 Discontinuation due to adverse events

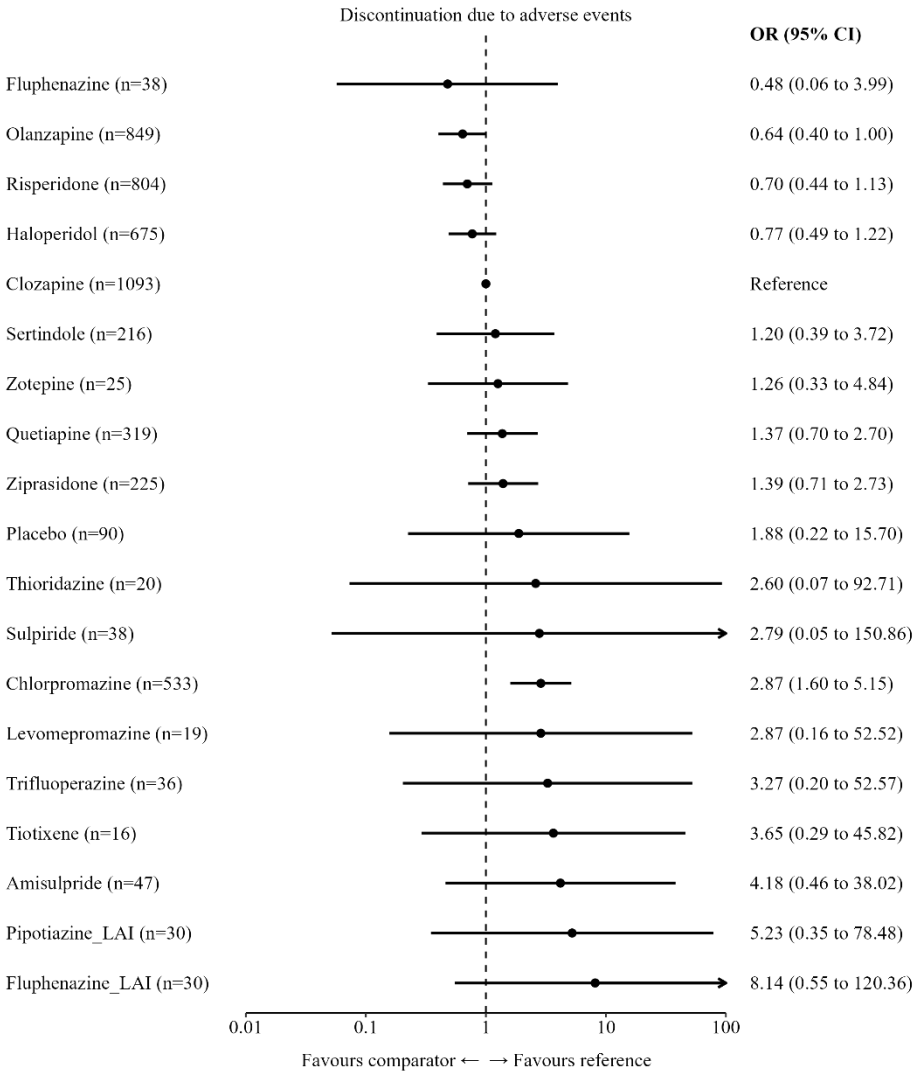
We transformed the original ORs to RRs and EERs vs. CER assuming the baseline discontinuation rate due to adverse events with clozapine of 12% (namely CER). 12% was the average discontinuation rate due to adverse events with clozapine across all clozapine -arms in the network meta-analysis, as estimated by a single-arm meta-analysis of proportions.

Network plot



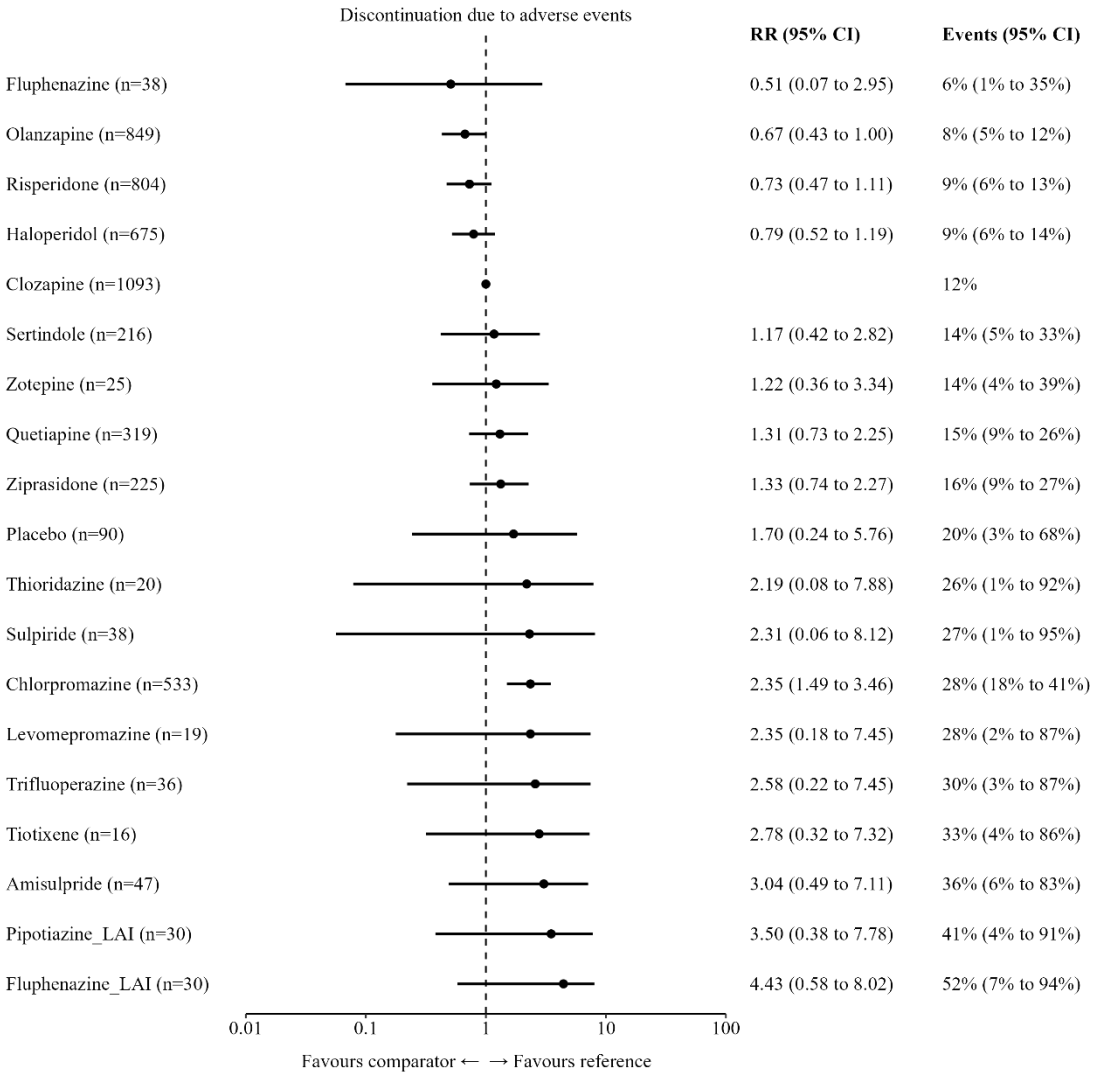
Lines link treatments with direct comparisons in trials; thickness of lines corresponds to the number of trials evaluating the comparison; size of the nodes corresponds to the number of participants assigned to the treatment.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as odds ratio (OR), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

Forest plot with RR and EER versus CER



For this forest plot, we transformed the original OR to RR and exposure events rates (EER, called "events" in the forest plot) using the formula indicated above. Therefore, we used an average discontinuation rate (due to adverse events) with clozapine of 12% as the control event rate (CER).
Effect sizes are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table for the outcome: Discontinuation due to adverse events (OR)

Fluphenazine	NA	1.00 (0.02 to 54.16)	1.00 (0.06 to 16.93)	NA	NA	NA	0.16 (0.01 to 3.60)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.75 (0.09 to 6.49)	**Olanzapine**	1.04 (0.52 to 2.10)	0.72 (0.11 to 4.67)	**0.57 (0.32 to 0.99)**	NA	NA	0.55 (0.10 to 3.12)	NA	NA	NA	NA	0.15 (0.02 to 1.27)	NA	NA	NA	0.15 (0.02 to 1.32)	NA	NA
0.68 (0.08 to 5.85)	0.90 (0.53 to 1.53)	**Risperidone**	2.46 (0.41 to 14.74)	0.70 (0.39 to 1.26)	0.59 (0.21 to 1.63)	NA	0.13 (0.01 to 1.15)	NA	NA	NA	NA	2.59 (0.10 to 69.34)	NA	NA	NA	NA	NA	NA
0.62 (0.08 to 5.06)	0.82 (0.45 to 1.52)	0.91 (0.49 to 1.71)	**Haloperidol**	0.84 (0.50 to 1.42)	NA	NA	0.39 (0.13 to 1.14)	NA	0.45 (0.03 to 5.73)	NA	NA	0.51 (0.04 to 6.50)	NA	NA	0.17 (0.01 to 3.73)	NA	NA	NA
0.48 (0.06 to 3.99)	0.64 (0.40 to 1.00)	0.70 (0.44 to 1.13)	0.77 (0.49 to 1.22)	**Clozapine**	NA	0.79 (0.21 to 3.03)	0.44 (0.10 to 1.94)	0.91 (0.41 to 2.00)	NA	NA	NA	**0.35 (0.14 to 0.85)**	NA	NA	NA	NA	NA	NA
0.40 (0.04 to 4.32)	0.53 (0.17 to 1.67)	0.59 (0.21 to 1.63)	0.64 (0.19 to 2.14)	0.83 (0.27 to 2.57)	**Sertindole**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.38 (0.03 to 4.66)	0.50 (0.12 to 2.08)	0.56 (0.13 to 2.31)	0.61 (0.15 to 2.53)	0.79 (0.21 to 3.03)	0.95 (0.16 to 5.51)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.35 (0.04 to 2.91)	0.46 (0.21 to 1.00)	0.51 (0.23 to 1.12)	0.56 (0.28 to 1.13)	0.73 (0.37 to 1.43)	0.88 (0.24 to 3.18)	0.92 (0.20 to 4.13)	**Quetiapine**	NA	NA	NA	NA	**0.30 (0.12 to 0.72)**	NA	NA	NA	NA	NA	NA
0.34 (0.04 to 3.13)	0.46 (0.21 to 1.01)	0.51 (0.22 to 1.14)	0.55 (0.25 to 1.22)	0.72 (0.37 to 1.40)	0.86 (0.23 to 3.19)	0.91 (0.20 to 4.07)	0.99 (0.41 to 2.40)	**Ziprasidone**	NA	NA	NA	0.75 (0.25 to 2.22)	NA	NA	NA	NA	NA	NA
0.25 (0.01 to 4.90)	0.34 (0.04 to 2.94)	0.37 (0.04 to 3.27)	0.41 (0.05 to 3.36)	0.53 (0.06 to 4.45)	0.64 (0.06 to 7.03)	0.67 (0.05 to 8.30)	0.73 (0.08 to 6.44)	0.74 (0.08 to 6.73)	**Placebo**	1.00 (0.02 to 52.85)	NA	1.00 (0.02 to 52.85)	NA	0.59 (0.06 to 5.97)	0.56 (0.07 to 4.80)	NA	0.36 (0.07 to 1.93)	0.23 (0.04 to 1.21)
0.18 (0.00 to 11.39)	0.24 (0.01 to 8.90)	0.27 (0.01 to 9.89)	0.30 (0.01 to 10.56)	0.38 (0.01 to 13.70)	0.46 (0.01 to 19.49)	0.49 (0.01 to 22.08)	0.53 (0.01 to 19.30)	0.54 (0.01 to 19.88)	0.72 (0.02 to 22.27)	**Thioridazine**	NA	1.00 (0.02 to 52.85)	NA	1.00 (0.02 to 52.85)	NA	NA	NA	NA
0.17 (0.00 to 15.35)	0.23 (0.00 to 12.52)	0.25 (0.00 to 13.91)	0.28 (0.01 to 15.15)	0.36 (0.01 to 19.33)	0.43 (0.01 to 27.04)	0.45 (0.01 to 30.42)	0.49 (0.01 to 26.96)	0.50 (0.01 to 27.65)	0.67 (0.01 to 59.71)	0.93 (0.00 to 189.06)	**Sulpiride**	0.97 (0.02 to 50.37)	NA	NA	NA	NA	NA	NA
0.17 (0.02 to 1.44)	**0.22 (0.11 to 0.45)**	**0.25 (0.12 to 0.51)**	**0.27 (0.14 to 0.53)**	**0.35 (0.19 to 0.63)**	0.42 (0.12 to 1.47)	0.44 (0.10 to 1.91)	**0.48 (0.24 to 0.95)**	0.49 (0.23 to 1.02)	0.65 (0.08 to 5.54)	0.91 (0.03 to 31.85)	0.97 (0.02 to 50.37)	**Chlorpromazine**	1.00 (0.06 to 17.25)	1.00 (0.02 to 52.85)	NA	NA	NA	NA
0.17 (0.00 to 5.94)	0.22 (0.01 to 4.16)	0.25 (0.01 to 4.63)	0.27 (0.01 to 5.03)	0.35 (0.02 to 6.38)	0.42 (0.02 to 9.42)	0.44 (0.02 to 10.83)	0.48 (0.03 to 8.95)	0.49 (0.03 to 9.22)	0.65 (0.02 to 23.02)	0.91 (0.01 to 86.50)	0.97 (0.01 to 126.43)	1.00 (0.06 to 17.25)	**Levomepromazine**	NA	NA	NA	NA	NA
0.15 (0.00 to 4.65)	0.19 (0.01 to 3.22)	0.22 (0.01 to 3.58)	0.24 (0.01 to 3.76)	0.31 (0.02 to 4.92)	0.37 (0.02 to 7.32)	0.39 (0.02 to 8.45)	0.42 (0.03 to 7.01)	0.43 (0.03 to 7.26)	0.57 (0.06 to 5.34)	0.80 (0.02 to 28.48)	0.85 (0.01 to 106.19)	0.88 (0.05 to 14.04)	0.88 (0.02 to 46.70)	**Trifluoperazine**	NA	NA	NA	NA
0.13 (0.01 to 3.41)	0.17 (0.01 to 2.26)	0.19 (0.01 to 2.51)	0.21 (0.02 to 2.59)	0.27 (0.02 to 3.44)	0.33 (0.02 to 5.22)	0.35 (0.02 to 6.07)	0.38 (0.03 to 4.95)	0.38 (0.03 to 5.15)	0.51 (0.07 to 3.97)	0.71 (0.01 to 34.47)	0.77 (0.01 to 84.07)	0.79 (0.06 to 10.08)	0.79 (0.02 to 35.97)	0.90 (0.05 to 17.11)	**Tiotixene**	NA	NA	NA
0.11 (0.01 to 2.41)	0.15 (0.02 to 1.32)	0.17 (0.02 to 1.55)	0.18 (0.02 to 1.74)	0.24 (0.03 to 2.17)	0.29 (0.02 to 3.32)	0.30 (0.02 to 3.99)	0.33 (0.03 to 3.25)	0.33 (0.03 to 3.33)	0.45 (0.02 to 9.52)	0.62 (0.01 to 41.19)	0.67 (0.01 to 63.32)	0.69 (0.07 to 6.64)	0.69 (0.02 to 26.16)	0.78 (0.02 to 26.94)	0.87 (0.03 to 24.86)	**Amisulpride**	NA	NA
0.09 (0.00 to 2.74)	0.12 (0.01 to 1.88)	0.13 (0.01 to 2.09)	0.15 (0.01 to 2.17)	0.19 (0.01 to 2.87)	0.23 (0.01 to 4.29)	0.24 (0.01 to 4.96)	0.26 (0.02 to 4.11)	0.27 (0.02 to 4.26)	0.36 (0.07 to 1.93)	0.50 (0.01 to 22.66)	0.53 (0.00 to 64.34)	0.55 (0.04 to 8.31)	0.55 (0.01 to 28.11)	0.63 (0.04 to 10.21)	0.70 (0.05 to 9.84)	0.80 (0.02 to 26.14)	**Pipotiazine_LAI**	0.64 (0.22 to 1.87)
0.06 (0.00 to 1.74)	0.08 (0.01 to 1.19)	0.09 (0.01 to 1.32)	0.09 (0.01 to 1.38)	0.12 (0.01 to 1.82)	0.15 (0.01 to 2.72)	0.16 (0.01 to 3.15)	0.17 (0.01 to 2.60)	0.17 (0.01 to 2.70)	0.23 (0.04 to 1.21)	0.32 (0.01 to 14.42)	0.34 (0.00 to 41.04)	0.35 (0.02 to 5.27)	0.35 (0.01 to 17.90)	0.40 (0.02 to 6.47)	0.45 (0.03 to 6.23)	0.51 (0.02 to 16.62)	0.64 (0.22 to 1.87)	**Fluphenazine_LAI**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is odd ratio (OR). Bold results indicate 95% CI excluding no effect. NA=not available.

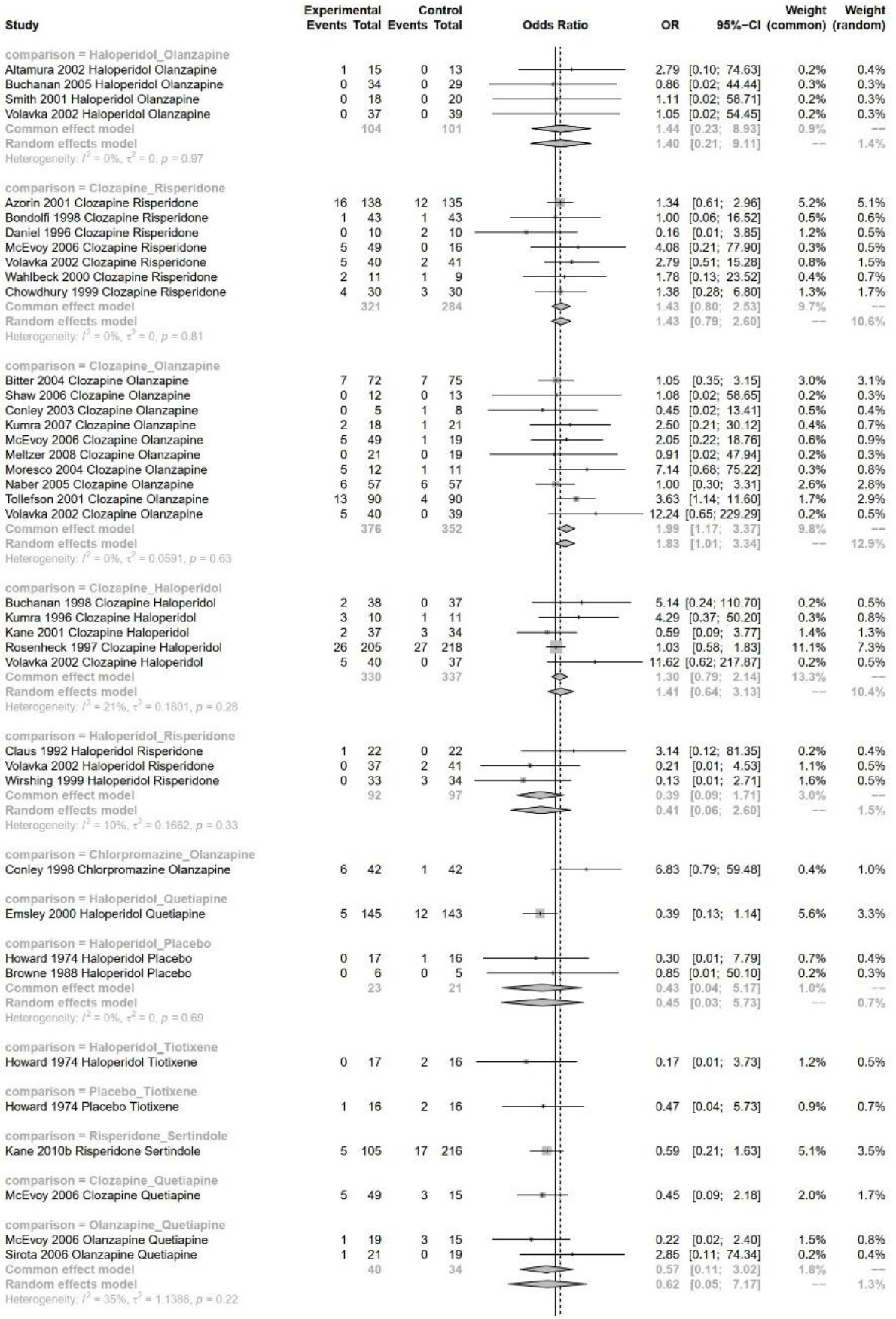
League table for the outcome: Discontinuation due to adverse events (RR)

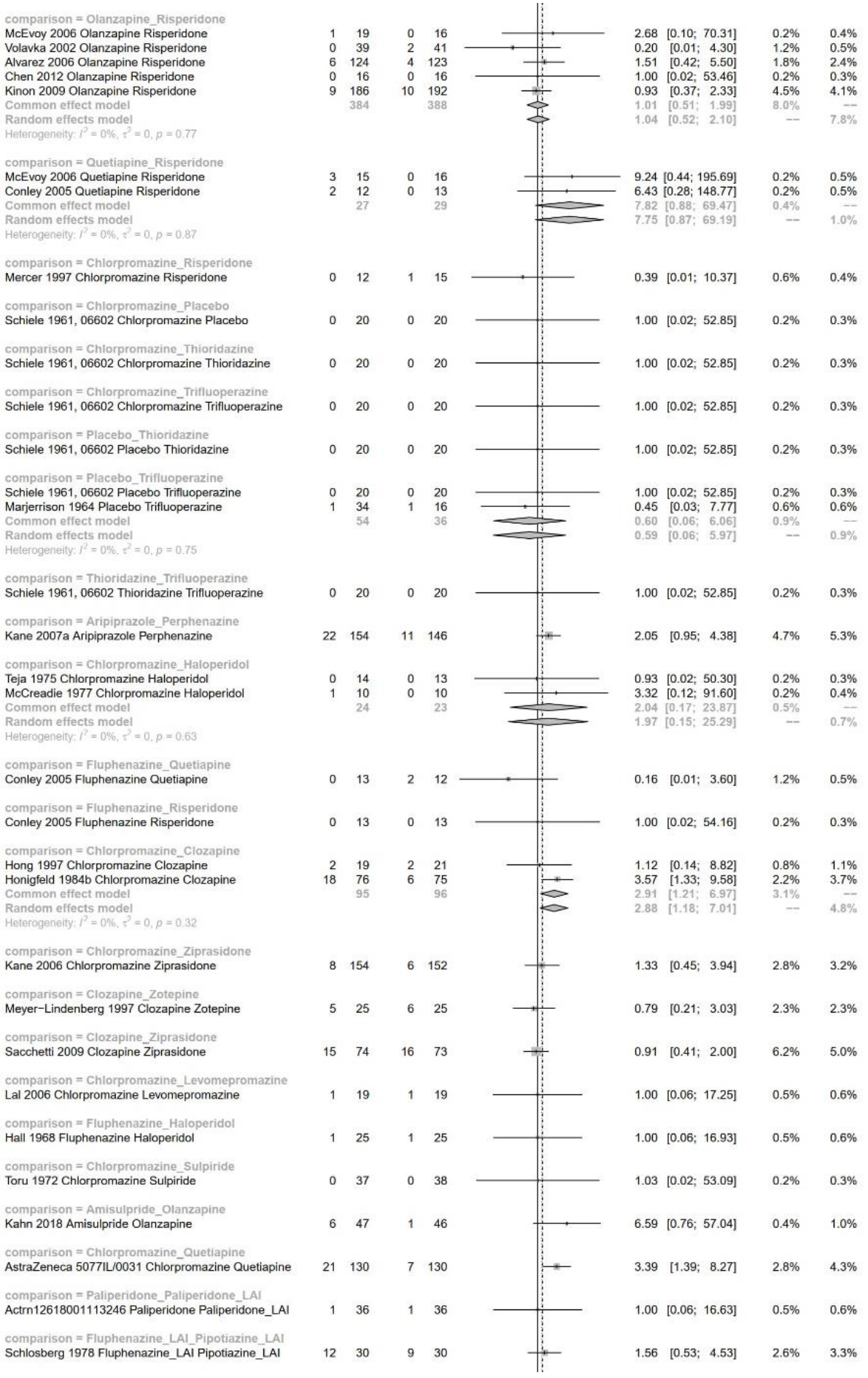
Fluphenazine	NA	1 (0.02 to 22.16)	1 (0.06 to 11.48)	NA	NA	NA	0.17 (0.01 to 3.17)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.75 (0.09 to 5.72)	**Olanzapine**	1.04 (0.53 to 2.04)	0.73 (0.11 to 4.21)	**0.58 (0.33 to 0.99)**	NA	NA	0.56 (0.1 to 2.81)	NA	NA	NA	NA	0.16 (0.02 to 1.24)	NA	NA	NA	0.17 (0.02 to 1.26)	NA	NA
0.69 (0.08 to 5.17)	0.9 (0.54 to 1.51)	**Risperidone**	2.36 (0.42 to 10.46)	0.71 (0.4 to 1.25)	0.6 (0.22 to 1.58)	NA	0.14 (0.01 to 1.14)	NA	NA	NA	NA	2.23 (0.11 to 8.69)	NA	NA	NA	NA	NA	NA
0.63 (0.08 to 4.51)	0.82 (0.46 to 1.5)	0.91 (0.5 to 1.67)	**Haloperidol**	0.85 (0.51 to 1.4)	NA	NA	0.4 (0.14 to 1.13)	NA	0.47 (0.03 to 4.31)	NA	NA	0.54 (0.04 to 4.16)	NA	NA	0.19 (0.01 to 2.77)	NA	NA	NA
0.49 (0.06 to 3.58)	0.65 (0.41 to 1)	0.71 (0.45 to 1.12)	0.78 (0.5 to 1.21)	**Clozapine**	NA	0.8 (0.22 to 2.76)	0.45 (0.1 to 1.85)	0.91 (0.42 to 1.9)	NA	NA	NA	**0.37 (0.15 to 0.86)**	NA	NA	NA	NA	NA	NA
0.41 (0.04 to 3.75)	0.54 (0.18 to 1.62)	0.6 (0.22 to 1.58)	0.65 (0.2 to 2.03)	0.84 (0.28 to 2.4)	**Sertindole**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.39 (0.03 to 3.96)	0.51 (0.13 to 1.98)	0.57 (0.14 to 2.17)	0.62 (0.16 to 2.36)	0.8 (0.22 to 2.76)	0.95 (0.17 to 4.53)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.36 (0.04 to 2.65)	0.47 (0.22 to 1)	0.52 (0.24 to 1.11)	0.57 (0.29 to 1.12)	0.74 (0.38 to 1.4)	0.89 (0.25 to 2.86)	0.92 (0.21 to 3.55)	**Quetiapine**	NA	NA	NA	NA	**0.32 (0.13 to 0.74)**	NA	NA	NA	NA	NA	NA
0.35 (0.04 to 2.81)	0.47 (0.22 to 1.01)	0.52 (0.23 to 1.13)	0.56 (0.26 to 1.21)	0.73 (0.38 to 1.37)	0.87 (0.24 to 2.86)	0.91 (0.21 to 3.5)	0.99 (0.42 to 2.23)	**Ziprasidone**	NA	NA	NA	0.77 (0.27 to 1.97)	NA	NA	NA	NA	NA	NA
0.26 (0.01 to 3.85)	0.36 (0.04 to 2.59)	0.39 (0.04 to 2.82)	0.43 (0.05 to 2.89)	0.55 (0.06 to 3.59)	0.66 (0.06 to 4.95)	0.69 (0.05 to 5.5)	0.74 (0.09 to 4.67)	0.75 (0.09 to 4.81)	**Placebo**	1 (0.02 to 9.09)	NA	1 (0.02 to 8.4)	NA	0.62 (0.07 to 3.82)	0.59 (0.08 to 3.23)	NA	0.4 (0.08 to 1.67)	0.29 (0.05 to 1.15)
0.19 (0 to 5.8)	0.26 (0.01 to 5.14)	0.29 (0.01 to 5.42)	0.32 (0.01 to 5.6)	0.4 (0.01 to 6.29)	0.48 (0.01 to 7.18)	0.51 (0.01 to 7.47)	0.55 (0.01 to 7.15)	0.56 (0.01 to 7.22)	0.74 (0.02 to 7.49)	**Thioridazine**	NA	1 (0.02 to 8.4)	NA	1 (0.02 to 7.68)	NA	NA	NA	NA
0.19 (0 to 6.35)	0.25 (0 to 5.86)	0.27 (0 to 6.11)	0.3 (0.01 to 6.32)	0.38 (0.01 to 6.88)	0.46 (0.01 to 7.57)	0.48 (0.01 to 7.79)	0.52 (0.01 to 7.56)	0.53 (0.01 to 7.61)	0.69 (0.01 to 8.78)	0.94 (0 to 9.66)	**Sulpiride**	0.97 (0.02 to 8.34)	NA	NA	NA	NA	NA	NA
0.19 (0.02 to 1.38)	**0.24 (0.12 to 0.48)**	**0.27 (0.13 to 0.54)**	**0.29 (0.15 to 0.56)**	**0.37 (0.21 to 0.65)**	0.45 (0.13 to 1.4)	0.47 (0.11 to 1.75)	**0.51 (0.26 to 0.95)**	0.52 (0.25 to 1.02)	0.67 (0.09 to 3.79)	0.92 (0.03 to 7.68)	0.97 (0.02 to 8.34)	**Chlorpromazine**	1 (0.07 to 6.49)	1 (0.02 to 7.68)	NA	NA	NA	NA
0.19 (0 to 3.95)	0.24 (0.01 to 3.15)	0.27 (0.01 to 3.38)	0.29 (0.01 to 3.56)	0.37 (0.02 to 4.12)	0.45 (0.02 to 5.07)	0.47 (0.02 to 5.41)	0.51 (0.03 to 4.94)	0.52 (0.03 to 5.01)	0.67 (0.02 to 7.09)	0.92 (0.01 to 8.89)	0.97 (0.01 to 9.16)	1 (0.07 to 6.49)	**Levomepromazine**	NA	NA	NA	NA	NA
0.17 (0 to 3.29)	0.21 (0.01 to 2.57)	0.24 (0.01 to 2.77)	0.26 (0.01 to 2.86)	0.34 (0.02 to 3.41)	0.4 (0.02 to 4.26)	0.42 (0.02 to 4.58)	0.45 (0.03 to 4.17)	0.46 (0.03 to 4.25)	0.6 (0.07 to 3.58)	0.82 (0.02 to 6.92)	0.86 (0.01 to 8.22)	0.89 (0.06 to 5.66)	0.89 (0.02 to 7.55)	**Trifluoperazine**	NA	NA	NA	NA
0.15 (0.01 to 2.61)	0.19 (0.01 to 1.95)	0.21 (0.01 to 2.1)	0.23 (0.02 to 2.15)	0.3 (0.02 to 2.62)	0.36 (0.02 to 3.39)	0.38 (0.02 to 3.69)	0.41 (0.03 to 3.29)	0.41 (0.03 to 3.37)	0.54 (0.08 to 2.88)	0.74 (0.01 to 6.54)	0.79 (0.01 to 7.25)	0.81 (0.07 to 4.67)	0.81 (0.02 to 6.59)	0.91 (0.06 to 5.6)	**Tiotixene**	NA	NA	NA
0.13 (0.01 to 2)	0.17 (0.02 to 1.26)	0.19 (0.02 to 1.44)	0.2 (0.02 to 1.57)	0.27 (0.03 to 1.85)	0.32 (0.02 to 2.48)	0.33 (0.02 to 2.78)	0.37 (0.03 to 2.45)	0.37 (0.03 to 2.49)	0.49 (0.02 to 4.25)	0.66 (0.01 to 6.01)	0.7 (0.01 to 6.28)	0.72 (0.08 to 3.65)	0.72 (0.02 to 5.61)	0.81 (0.02 to 5.64)	0.89 (0.03 to 5.55)	**Amisulpride**	NA	NA
0.11 (0 to 2.11)	0.14 (0.01 to 1.64)	0.15 (0.01 to 1.76)	0.18 (0.01 to 1.81)	0.22 (0.01 to 2.18)	0.26 (0.01 to 2.75)	0.28 (0.01 to 2.97)	0.3 (0.02 to 2.69)	0.31 (0.02 to 2.74)	0.4 (0.08 to 1.67)	0.55 (0.01 to 4.84)	0.58 (0 to 5.47)	0.6 (0.05 to 3.71)	0.6 (0.01 to 5.02)	0.67 (0.05 to 3.98)	0.74 (0.06 to 3.93)	0.83 (0.02 to 4.96)	**Pipotiazine_LAI**	0.7 (0.27 to 1.53)
0.08 (0 to 1.46)	0.1 (0.01 to 1.14)	0.12 (0.01 to 1.22)	0.12 (0.01 to 1.26)	0.15 (0.01 to 1.51)	0.19 (0.01 to 1.89)	0.2 (0.01 to 2.04)	0.22 (0.01 to 1.85)	0.22 (0.01 to 1.89)	0.29 (0.05 to 1.15)	0.39 (0.01 to 3.27)	0.41 (0 to 3.67)	0.42 (0.03 to 2.53)	0.42 (0.01 to 3.38)	0.47 (0.03 to 2.71)	0.52 (0.04 to 2.67)	0.58 (0.03 to 3.34)	0.7 (0.27 to 1.53)	**Fluphenazine_LAI**

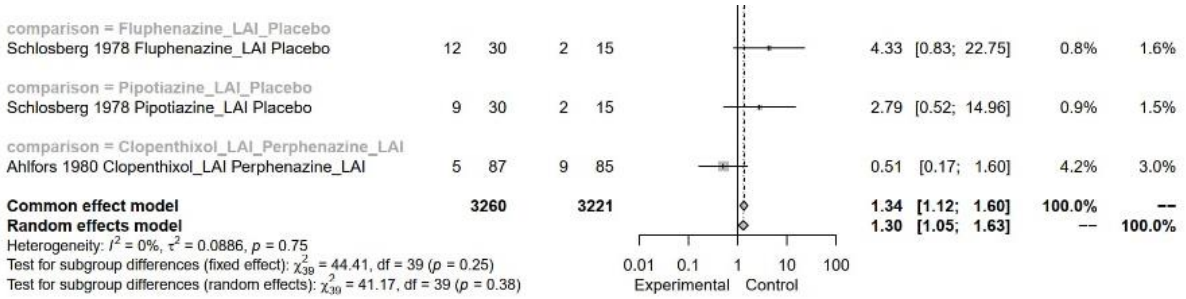
The original results given in OR (and their 95% CI) are transformed to RR (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column) using the formula described above. For this transformation, we assumed a discontinuation rate (due to adverse events) with clozapine of 12% as the control event rate (CER) for all comparisons of active antipsychotic versus clozapine.

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses




comparison = Olanzapine_Risperidone
McEvoy 2006 Olanzapine Risperidone 1 19 0 16 2.68 [0.10; 70.31] 0.2% 0.4%
Volavka 2002 Olanzapine Risperidone 0 39 2 41 0.20 [0.01; 4.30] 1.2% 0.5%
Alvarez 2006 Olanzapine Risperidone 6 124 4 123 1.51 [0.42; 5.50] 1.8% 2.4%
Chen 2012 Olanzapine Risperidone 0 16 0 16 1.00 [0.02; 53.46] 0.2% 0.3%
Kinon 2009 Olanzapine Risperidone 9 186 10 192 0.93 [0.37; 2.33] 4.5% 4.1%
Common effect model 384 388 1.01 [0.51; 1.99] 8.0% --
Random effects model 1.04 [0.52; 2.10] -- 7.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.77
comparison = Quetiapine_Risperidone
McEvoy 2006 Quetiapine Risperidone 3 15 0 16 9.24 [0.44; 195.69] 0.2% 0.5%
Conley 2005 Quetiapine Risperidone 2 12 0 13 6.43 [0.28; 148.77] 0.2% 0.5%
Common effect model 27 29 7.82 [0.88; 69.47] 0.4% --
Random effects model 7.75 [0.87; 69.19] -- 1.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.87
comparison = Chlorpromazine_Risperidone
Mercer 1997 Chlorpromazine Risperidone 0 12 1 15 0.39 [0.01; 10.37] 0.6% 0.4%
comparison = Chlorpromazine_Placebo
Schiele 1961, 06602 Chlorpromazine Placebo 0 20 0 20 1.00 [0.02; 52.85] 0.2% 0.3%
comparison = Chlorpromazine_Thioridazine
Schiele 1961, 06602 Chlorpromazine Thioridazine 0 20 0 20 1.00 [0.02; 52.85] 0.2% 0.3%
comparison = Chlorpromazine_Trifluoperazine
Schiele 1961, 06602 Chlorpromazine Trifluoperazine 0 20 0 20 1.00 [0.02; 52.85] 0.2% 0.3%
comparison = Placebo_Thioridazine
Schiele 1961, 06602 Placebo Thioridazine 0 20 0 20 1.00 [0.02; 52.85] 0.2% 0.3%
comparison = Placebo_Trifluoperazine
Schiele 1961, 06602 Placebo Trifluoperazine 0 20 0 20 1.00 [0.02; 52.85] 0.2% 0.3%
Marjerrison 1964 Placebo Trifluoperazine 1 34 1 16 0.45 [0.03; 7.77] 0.6% 0.6%
Common effect model 54 36 0.60 [0.06; 6.06] 0.9% --
Random effects model 0.59 [0.06; 5.97] -- 0.9%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.75
comparison = Thioridazine_Trifluoperazine
Schiele 1961, 06602 Thioridazine Trifluoperazine 0 20 0 20 1.00 [0.02; 52.85] 0.2% 0.3%
comparison = Aripiprazole_Perphenazine
Kane 2007a Aripiprazole Perphenazine 22 154 11 146 2.05 [0.95; 4.38] 4.7% 5.3%
comparison = Chlorpromazine_Haloperidol
Teja 1975 Chlorpromazine Haloperidol 0 14 0 13 0.93 [0.02; 50.30] 0.2% 0.3%
McCreadie 1977 Chlorpromazine Haloperidol 1 10 0 10 3.32 [0.12; 91.60] 0.2% 0.4%
Common effect model 24 23 2.04 [0.17; 23.87] 0.5% --
Random effects model 1.97 [0.15; 25.29] -- 0.7%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.63
comparison = Fluphenazine_Quetiapine
Conley 2005 Fluphenazine Quetiapine 0 13 2 12 0.16 [0.01; 3.60] 1.2% 0.5%
comparison = Fluphenazine_Risperidone
Conley 2005 Fluphenazine Risperidone 0 13 0 13 1.00 [0.02; 54.16] 0.2% 0.3%
comparison = Chlorpromazine_Clozapine
Hong 1997 Chlorpromazine Clozapine 2 19 2 21 1.12 [0.14; 8.82] 0.8% 1.1%
Honigfeld 1984b Chlorpromazine Clozapine 18 76 6 75 3.57 [1.33; 9.58] 2.2% 3.7%
Common effect model 95 96 2.91 [1.21; 6.97] 3.1% --
Random effects model 2.88 [1.18; 7.01] -- 4.8%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.32
comparison = Chlorpromazine_Ziprasidone
Kane 2006 Chlorpromazine Ziprasidone 8 154 6 152 1.33 [0.45; 3.94] 2.8% 3.2%
comparison = Clozapine_Zotepine
Meyer−Lindenberg 1997 Clozapine Zotepine 5 25 6 25 0.79 [0.21; 3.03] 2.3% 2.3%
comparison = Clozapine_Ziprasidone
Sacchetti 2009 Clozapine Ziprasidone 15 74 16 73 0.91 [0.41; 2.00] 6.2% 5.0%
comparison = Chlorpromazine_Levomepromazine
Lal 2006 Chlorpromazine Levomepromazine 1 19 1 19 1.00 [0.06; 17.25] 0.5% 0.6%
comparison = Fluphenazine_Haloperidol
Hall 1968 Fluphenazine Haloperidol 1 25 1 25 1.00 [0.06; 16.93] 0.5% 0.6%
comparison = Chlorpromazine_Sulpiride
Toru 1972 Chlorpromazine Sulpiride 0 37 0 38 1.03 [0.02; 53.09] 0.2% 0.3%
comparison = Amisulpride_Olanzapine
Kahn 2018 Amisulpride Olanzapine 6 47 1 46 6.59 [0.76; 57.04] 0.4% 1.0%
comparison = Chlorpromazine_Quetiapine
AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine 21 130 7 130 3.39 [1.39; 8.27] 2.8% 4.3%
comparison = Paliperidone_Paliperidone_LAI
Actrn12618001113246 Paliperidone Paliperidone_LAI 1 36 1 36 1.00 [0.06; 16.63] 0.5% 0.6%
comparison = Fluphenazine_LAI_Pipotiazine_LAI
Schlosberg 1978 Fluphenazine_LAI Pipotiazine_LAI 12 30 9 30 1.56 [0.53; 4.53] 2.6% 3.3%

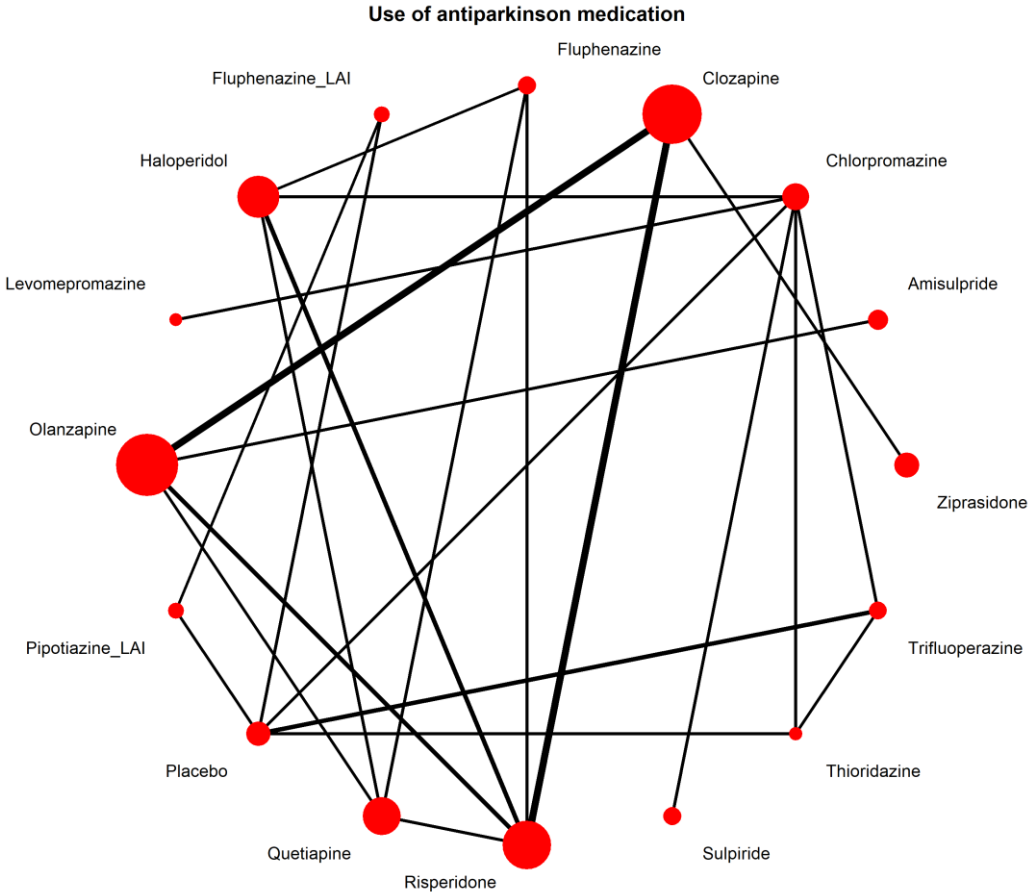


A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is OR.

8.7 Use of antiparkinsonian medication

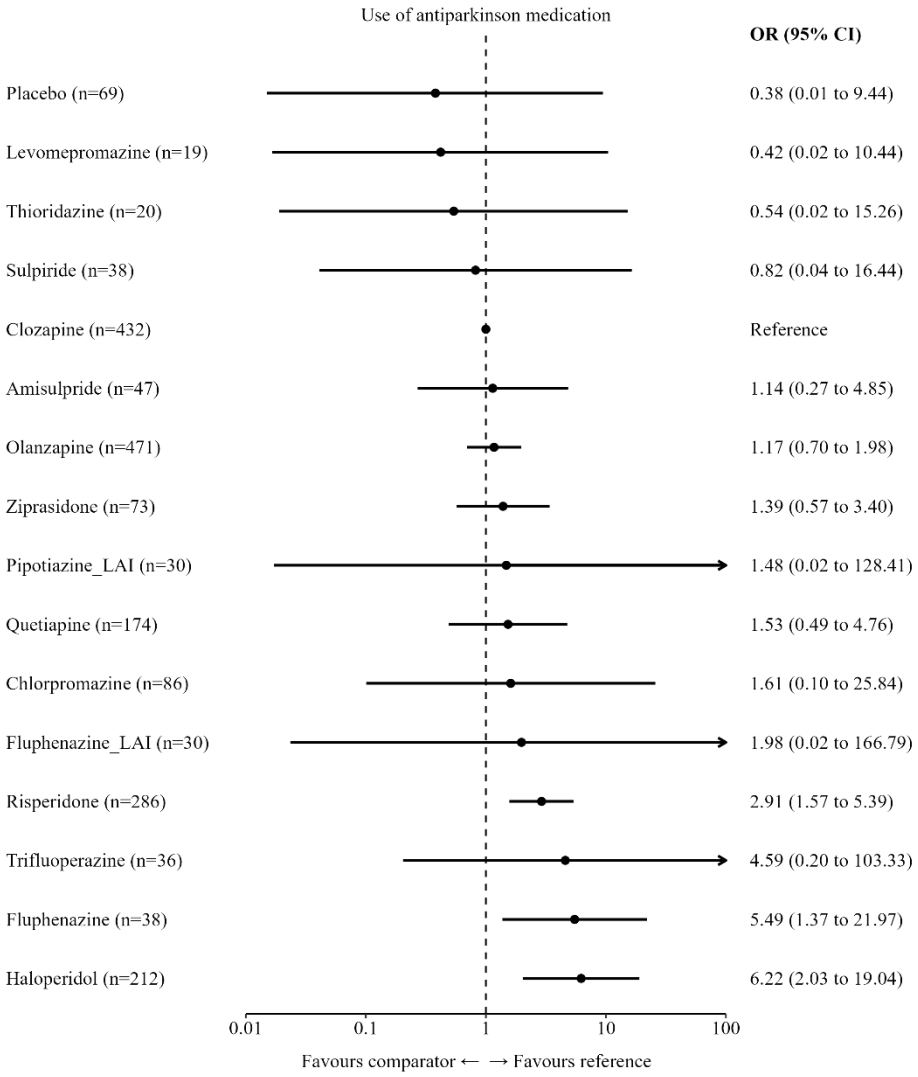
We transformed the original ORs to RRs and EERs vs. CER assuming the baseline risk of using antiparkinsonian medication with clozapine of 24% (namely CER). 24% was the average risk of using antiparkinsonian medication with clozapine across all clozapine-arms in the network meta-analysis, as estimated by a single-arm meta-analysis of proportions.

Network plot



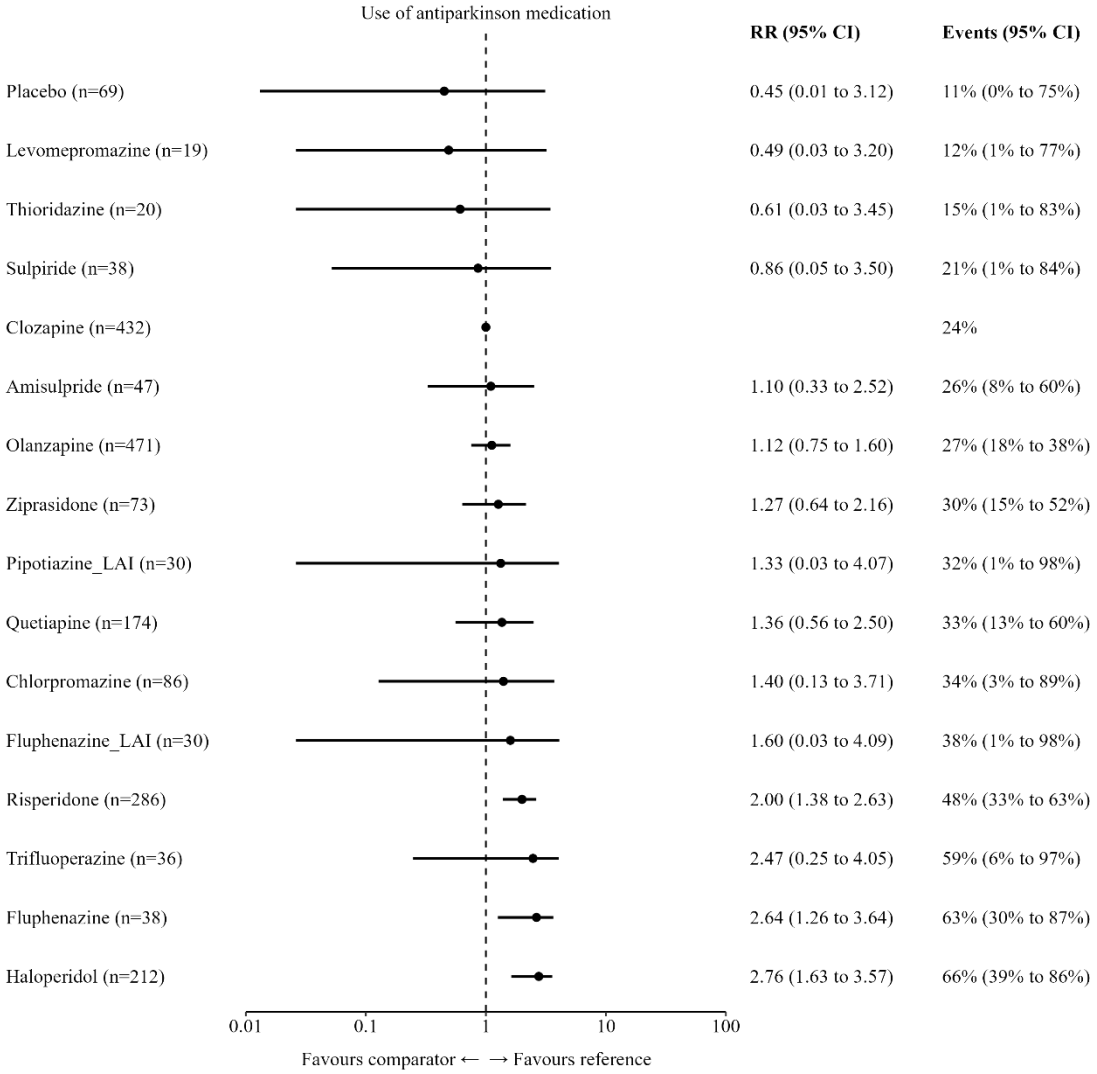
Lines link treatments with direct comparisons in trials; thickness of lines corresponds to the number of trials evaluating the comparison; size of the nodes corresponds to the number of participants assigned to the treatment.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as odds ratio (OR), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

Forest plot with RR and EER versus CER



For this forest plot, we transformed the original OR to RR and exposure events rates (EER, called "events" in the forest plot) using the formula indicated above. Therefore, we used an average rate of using antiparkinsonian medication with clozapine of 24% as the control event rate (CER).
Effect sizes are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table for the outcome: Use of antiparkinsonian medication (OR)

Placebo	NA	1.00 (0.12 to 8.56)	NA	NA	NA	NA	NA	0.25 (0.01 to 5.54)	NA	0.33 (0.05 to 2.17)	0.19 (0.01 to 3.99)	NA	**0.08 (0.02 to 0.30)**	NA	NA
0.90 (0.09 to 9.21)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	NA	0.26 (0.05 to 1.33)	NA	NA	NA	NA	NA
0.70 (0.10 to 4.92)	0.77 (0.06 to 9.32)	**Thioridazine**	NA	NA	NA	NA	NA	NA	NA	0.33 (0.05 to 2.17)	NA	NA	**0.14 (0.02 to 0.82)**	NA	NA
0.46 (0.06 to 3.37)	0.51 (0.07 to 3.72)	0.65 (0.07 to 5.84)	**Sulpiride**	NA	NA	NA	NA	NA	NA	0.51 (0.16 to 1.58)	NA	NA	NA	NA	NA
0.38 (0.01 to 9.44)	0.42 (0.02 to 10.44)	0.54 (0.02 to 15.26)	0.82 (0.04 to 16.44)	**Clozapine**	NA	1.02 (0.57 to 1.81)	0.72 (0.29 to 1.75)	NA	NA	NA	NA	**0.24 (0.11 to 0.55)**	NA	NA	NA
0.33 (0.01 to 10.64)	0.36 (0.01 to 11.76)	0.47 (0.01 to 17.05)	0.72 (0.03 to 18.86)	0.87 (0.21 to 3.71)	**Amisulpride**	0.98 (0.25 to 3.75)	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.32 (0.01 to 7.91)	0.35 (0.01 to 8.75)	0.46 (0.02 to 12.80)	0.70 (0.04 to 13.76)	0.85 (0.51 to 1.44)	0.98 (0.25 to 3.75)	**Olanzapine**	NA	NA	1.12 (0.25 to 5.07)	NA	NA	**0.46 (0.24 to 0.92)**	NA	NA	NA
0.27 (0.01 to 7.66)	0.30 (0.01 to 8.47)	0.39 (0.01 to 12.33)	0.59 (0.03 to 13.45)	0.72 (0.29 to 1.75)	0.82 (0.15 to 4.49)	0.84 (0.30 to 2.37)	**Ziprasidone**	NA	NA	NA	NA	NA	NA	NA	NA
0.25 (0.01 to 5.54)	0.28 (0.01 to 13.32)	0.36 (0.01 to 13.95)	0.55 (0.01 to 21.82)	0.67 (0.01 to 58.37)	0.77 (0.01 to 80.54)	0.79 (0.01 to 67.63)	0.94 (0.01 to 88.77)	**Pipotiazine_LAI**	NA	NA	0.75 (0.15 to 3.73)	NA	NA	NA	NA
0.25 (0.01 to 5.97)	0.27 (0.01 to 6.60)	0.35 (0.01 to 9.67)	0.54 (0.03 to 10.37)	0.65 (0.21 to 2.04)	0.75 (0.13 to 4.17)	0.77 (0.26 to 2.23)	0.91 (0.21 to 3.87)	0.97 (0.01 to 82.01)	**Quetiapine**	NA	NA	1.83 (0.23 to 14.65)	NA	0.75 (0.12 to 4.79)	**0.16 (0.04 to 0.64)**
0.23 (0.05 to 1.20)	0.26 (0.05 to 1.33)	0.33 (0.05 to 2.17)	0.51 (0.16 to 1.58)	0.62 (0.04 to 9.92)	0.71 (0.03 to 15.20)	0.73 (0.05 to 11.41)	0.86 (0.05 to 15.89)	0.92 (0.03 to 30.26)	0.95 (0.06 to 14.58)	**Chlorpromazine**	NA	NA	0.41 (0.09 to 1.76)	NA	0.26 (0.02 to 3.28)
0.19 (0.01 to 3.99)	0.21 (0.00 to 9.68)	0.27 (0.01 to 10.11)	0.42 (0.01 to 15.83)	0.51 (0.01 to 42.59)	0.58 (0.01 to 58.83)	0.59 (0.01 to 49.34)	0.70 (0.01 to 64.80)	0.75 (0.15 to 3.73)	0.77 (0.01 to 63.51)	0.82 (0.03 to 25.94)	**Fluphenazine_LAI**	NA	NA	NA	NA
0.13 (0.01 to 3.10)	0.14 (0.01 to 3.43)	0.19 (0.01 to 5.03)	0.28 (0.01 to 5.39)	**0.34 (0.19 to 0.64)**	0.39 (0.09 to 1.69)	**0.40 (0.23 to 0.71)**	0.48 (0.16 to 1.42)	0.51 (0.01 to 42.77)	0.53 (0.18 to 1.50)	0.56 (0.04 to 8.43)	0.68 (0.01 to 55.54)	**Risperidone**	NA	0.41 (0.06 to 3.02)	0.50 (0.15 to 1.75)
0.08 (0.02 to 0.30)	**0.09 (0.01 to 0.79)**	**0.12 (0.02 to 0.69)**	0.18 (0.03 to 1.10)	0.22 (0.01 to 4.91)	0.25 (0.01 to 7.30)	0.26 (0.01 to 5.66)	0.30 (0.01 to 7.74)	0.32 (0.01 to 9.13)	0.33 (0.02 to 7.24)	0.35 (0.09 to 1.45)	0.43 (0.02 to 11.76)	0.63 (0.03 to 13.60)	**Trifluoperazine**	NA	NA
0.07 (0.00 to 1.72)	0.08 (0.00 to 1.90)	0.10 (0.00 to 2.78)	0.15 (0.01 to 2.99)	**0.18 (0.05 to 0.73)**	0.21 (0.03 to 1.40)	**0.21 (0.06 to 0.82)**	0.25 (0.05 to 1.32)	0.27 (0.00 to 23.38)	**0.28 (0.08 to 0.99)**	0.29 (0.02 to 4.70)	0.36 (0.00 to 30.37)	0.53 (0.15 to 1.90)	0.84 (0.04 to 18.82)	**Fluphenazine**	1.23 (0.30 to 4.97)
0.06 (0.00 to 1.24)	0.07 (0.00 to 1.37)	0.09 (0.00 to 2.02)	0.13 (0.01 to 2.13)	**0.16 (0.05 to 0.49)**	0.18 (0.03 to 1.03)	**0.19 (0.06 to 0.55)**	**0.22 (0.05 to 0.94)**	0.24 (0.00 to 17.89)	**0.25 (0.09 to 0.68)**	0.26 (0.02 to 3.28)	0.32 (0.00 to 23.22)	0.47 (0.18 to 1.24)	0.74 (0.04 to 13.49)	0.88 (0.29 to 2.70)	**Haloperidol**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is odd ratio (OR). Bold results indicate 95% CI excluding no effect. NA=not available.

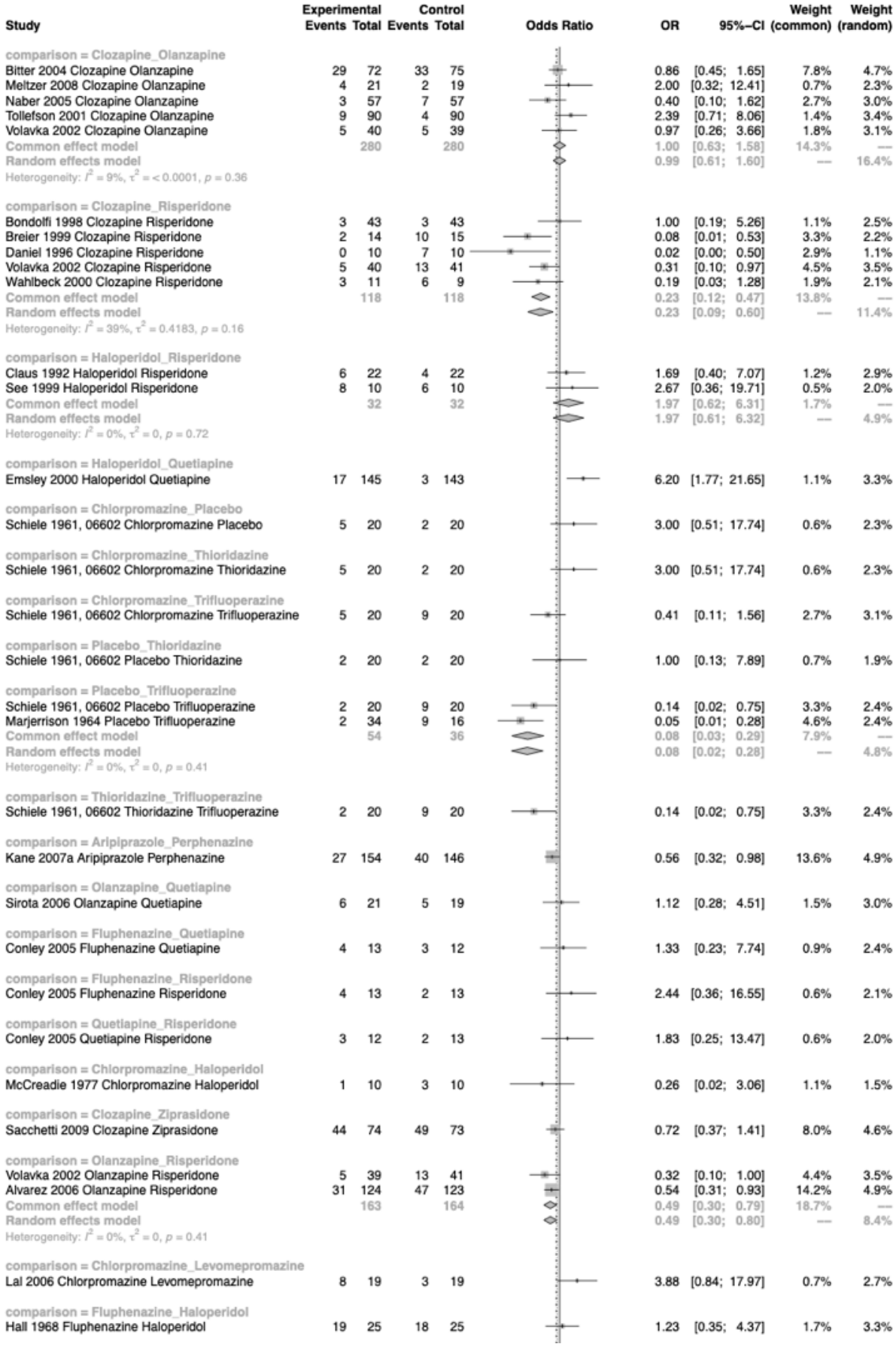
League table for the outcome: Use of antiparkinsonian medication (RR)

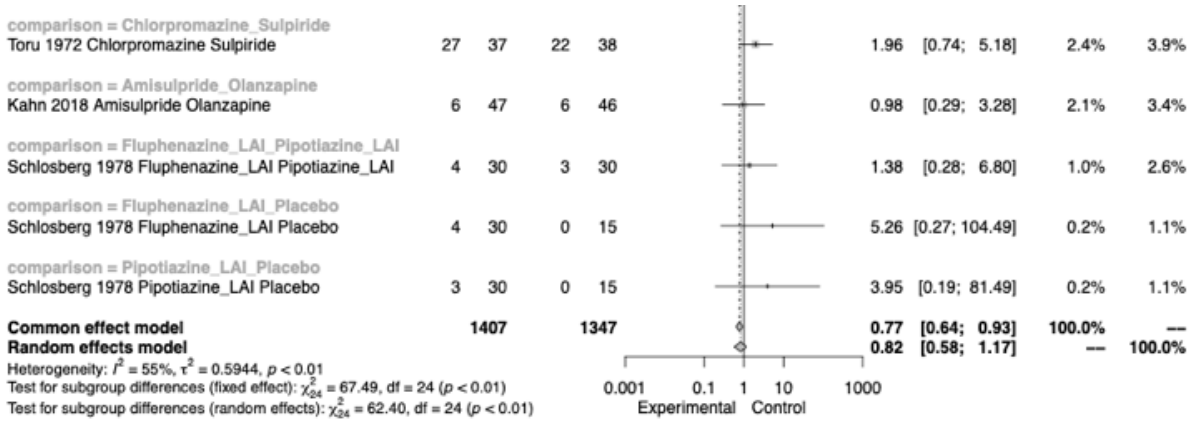
Placebo	NA	1 (0.13 to 6.29)	NA	NA	NA	NA	NA	0.27 (0.01 to 3.61)	NA	0.36 (0.06 to 1.89)	0.22 (0.01 to 2.75)	NA	**0.11 (0.03 to 0.38)**	NA	NA
0.9 (0.09 to 7.04)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	NA	0.29 (0.06 to 1.28)	NA	NA	NA	NA	NA
0.71 (0.1 to 4.15)	0.78 (0.06 to 6.67)	**Thioridazine**	NA	NA	NA	NA	NA	NA	NA	0.36 (0.06 to 1.89)	NA	NA	**0.19 (0.03 to 0.87)**	NA	NA
0.48 (0.06 to 2.91)	0.53 (0.07 to 3.14)	0.67 (0.07 to 4.4)	**Sulpiride**	NA	NA	NA	NA	NA	NA	0.54 (0.18 to 1.47)	NA	NA	NA	NA	NA
0.4 (0.01 to 5.59)	0.44 (0.02 to 5.89)	0.56 (0.02 to 7.05)	0.83 (0.04 to 7.27)	**Clozapine**	NA	1.02 (0.59 to 1.68)	0.74 (0.31 to 1.62)	NA	NA	NA	NA	**0.28 (0.13 to 0.61)**	NA	NA	NA
0.35 (0.01 to 5.67)	0.38 (0.01 to 5.94)	0.49 (0.01 to 6.93)	0.74 (0.03 to 7.18)	0.88 (0.23 to 2.98)	**Amisulpride**	0.98 (0.27 to 2.97)	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.34 (0.01 to 4.76)	0.37 (0.01 to 5.03)	0.49 (0.02 to 6.02)	0.72 (0.04 to 6.2)	0.86 (0.54 to 1.38)	0.98 (0.27 to 2.97)	**Olanzapine**	NA	NA	1.1 (0.28 to 3.39)	NA	NA	**0.52 (0.28 to 0.94)**	NA	NA	NA
0.29 (0.01 to 4.44)	0.32 (0.01 to 4.67)	0.42 (0.01 to 5.52)	0.62 (0.03 to 5.71)	0.74 (0.31 to 1.62)	0.84 (0.17 to 3.25)	0.85 (0.32 to 2.06)	**Ziprasidone**	NA	NA	NA	NA	NA	NA	NA	NA
0.27 (0.01 to 3.61)	0.31 (0.01 to 5.43)	0.39 (0.01 to 5.52)	0.58 (0.01 to 6.32)	0.7 (0.01 to 7.52)	0.79 (0.01 to 7.77)	0.81 (0.01 to 7.64)	0.95 (0.01 to 7.83)	**Pipotiazine_LAI**	NA	NA	0.78 (0.17 to 2.64)	NA	NA	NA	NA
0.28 (0.01 to 3.72)	0.3 (0.01 to 3.92)	0.38 (0.01 to 4.7)	0.57 (0.03 to 4.84)	0.68 (0.23 to 1.81)	0.77 (0.15 to 3.01)	0.79 (0.29 to 1.94)	0.92 (0.23 to 2.87)	0.97 (0.01 to 7.53)	**Quetiapine**	NA	NA	1.56 (0.27 to 3.83)	NA	0.82 (0.17 to 2.13)	**0.23 (0.06 to 0.73)**
0.25 (0.06 to 1.17)	0.29 (0.06 to 1.28)	0.36 (0.06 to 1.89)	0.54 (0.18 to 1.47)	0.65 (0.05 to 4.66)	0.74 (0.03 to 5.44)	0.76 (0.06 to 4.93)	0.88 (0.06 to 5.51)	0.93 (0.03 to 6.44)	0.96 (0.07 to 5.37)	**Chlorpromazine**	NA	NA	0.5 (0.12 to 1.44)	NA	0.35 (0.03 to 1.81)
0.22 (0.01 to 2.75)	0.24 (0 to 4.19)	0.3 (0.01 to 4.25)	0.46 (0.01 to 4.88)	0.55 (0.01 to 5.85)	0.62 (0.01 to 6.04)	0.63 (0.01 to 5.94)	0.73 (0.01 to 6.09)	0.78 (0.17 to 2.64)	0.8 (0.01 to 6.08)	0.84 (0.04 to 5.44)	**Fluphenazine_LAI**	NA	NA	NA	NA
0.16 (0.01 to 2.16)	0.17 (0.01 to 2.28)	0.23 (0.01 to 2.74)	0.33 (0.01 to 2.82)	**0.39 (0.23 to 0.69)**	0.45 (0.11 to 1.48)	**0.46 (0.27 to 0.76)**	0.54 (0.19 to 1.31)	0.57 (0.01 to 4.43)	0.59 (0.22 to 1.36)	0.62 (0.05 to 3.32)	0.73 (0.01 to 4.51)	**Risperidone**	NA	0.51 (0.09 to 1.82)	0.61 (0.22 to 1.38)
0.11 (0.03 to 0.38)	**0.12 (0.01 to 0.84)**	**0.16 (0.03 to 0.76)**	0.24 (0.04 to 1.07)	0.28 (0.01 to 2.29)	0.32 (0.01 to 2.57)	0.33 (0.01 to 2.4)	0.38 (0.01 to 2.61)	0.4 (0.01 to 2.71)	0.41 (0.03 to 2.57)	0.43 (0.12 to 1.28)	0.52 (0.03 to 2.84)	0.71 (0.04 to 2.91)	**Trifluoperazine**	NA	NA
0.1 (0 to 1.39)	0.11 (0 to 1.47)	0.14 (0 to 1.75)	0.21 (0.01 to 1.81)	**0.25 (0.07 to 0.8)**	0.28 (0.04 to 1.24)	**0.28 (0.09 to 0.87)**	0.33 (0.07 to 1.19)	0.36 (0 to 2.8)	**0.37 (0.11 to 0.99)**	0.38 (0.03 to 2.12)	0.46 (0 to 2.85)	0.63 (0.21 to 1.47)	0.89 (0.06 to 2.74)	**Fluphenazine**	1.14 (0.4 to 2.05)
0.09 (0 to 1.14)	0.1 (0 to 1.21)	0.13 (0 to 1.48)	0.19 (0.02 to 1.52)	**0.23 (0.08 to 0.6)**	0.25 (0.05 to 1.02)	**0.27 (0.09 to 0.66)**	**0.31 (0.08 to 0.96)**	0.33 (0 to 2.54)	**0.34 (0.13 to 0.77)**	0.35 (0.03 to 1.81)	0.42 (0 to 2.6)	0.58 (0.25 to 1.14)	0.82 (0.06 to 2.47)	0.92 (0.39 to 1.68)	**Haloperidol**

The original results given in OR (and their 95% CI) are transformed to RR (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column) using the formula described above. For this transformation, we assumed a rate of using antiparkinsonian medication with clozapine of 24% as the control event rate (CER) for all comparisons of active antipsychotic versus clozapine.

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses

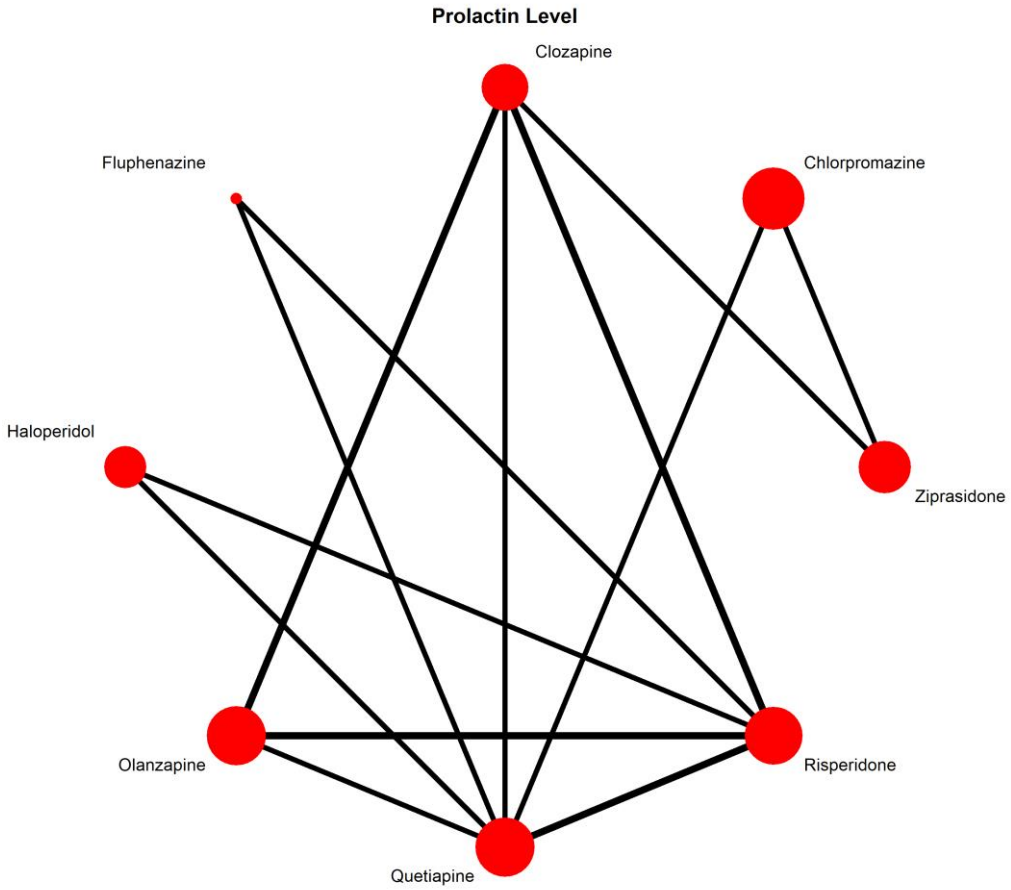




A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is OR.

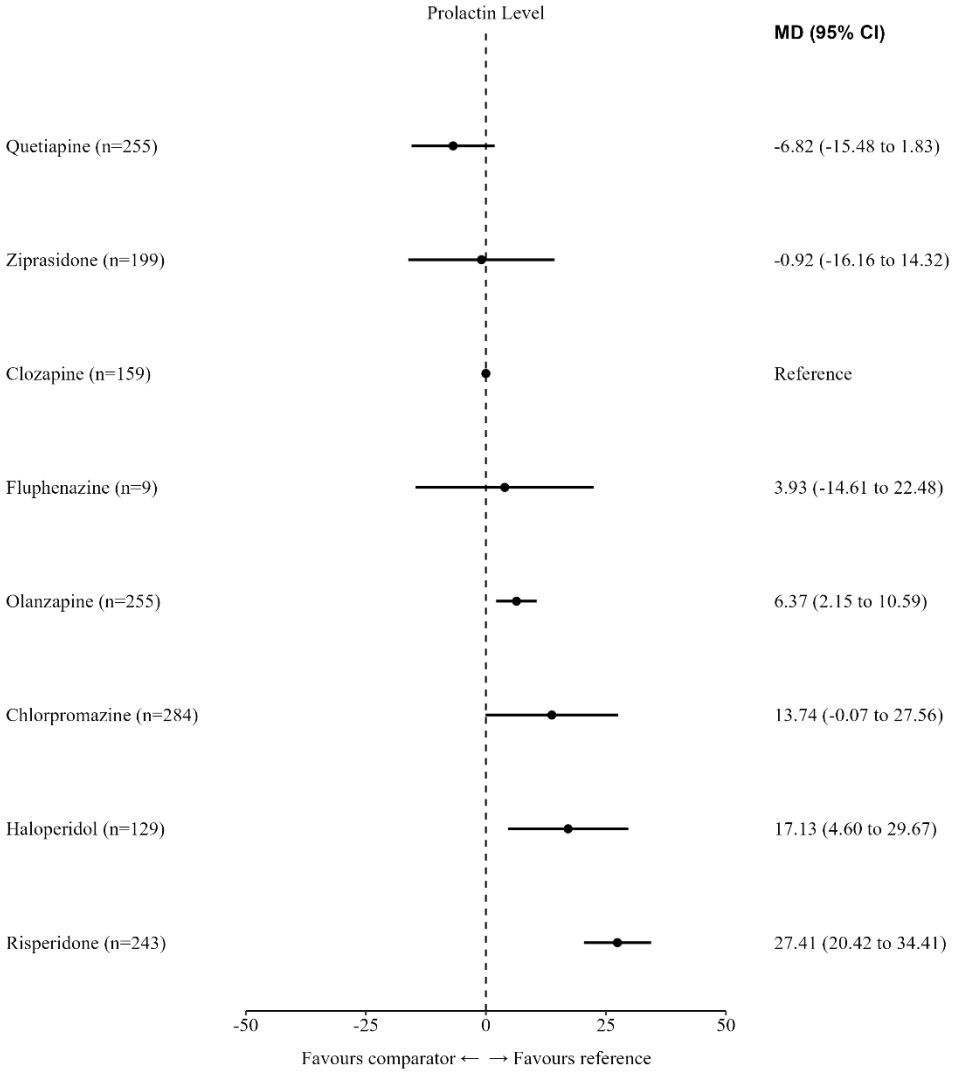
8.8 Prolactin levels

Network plot



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.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



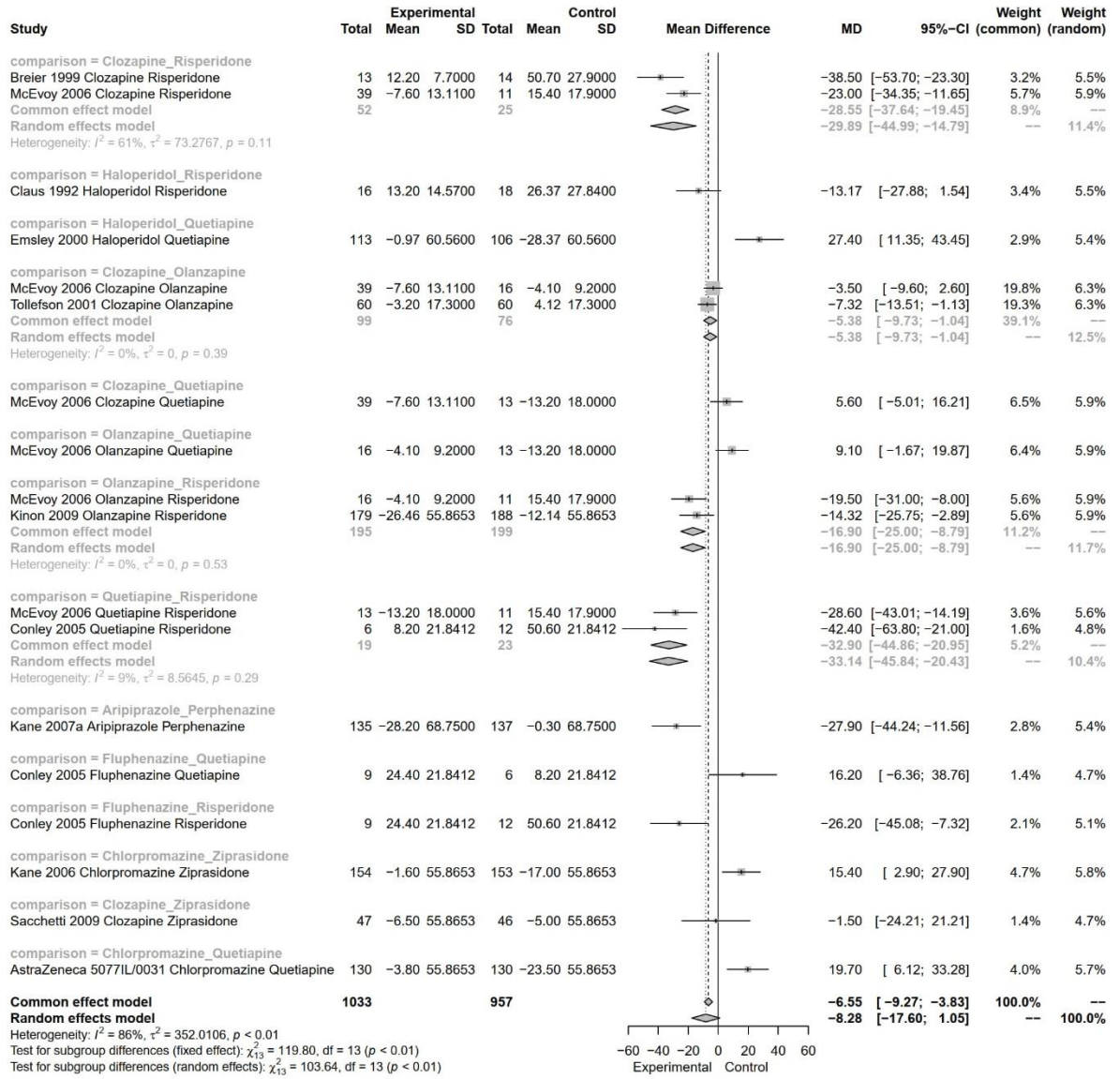
Effect sizes, measured as mean difference (MD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table for the outcome: Prolactin levels

Quetiapine	NA	-5.60 (-16.21 to 5.01)	-16.20 (-38.76 to 6.36)	-9.10 (-19.87 to 1.67)	**-19.70 (-33.28 to -6.12)**	**-27.40 (-43.45 to -11.35)**	**-32.90 (-44.86 to -20.95)**
-5.90 (-20.63 to 8.83)	**Ziprasidone**	1.50 (-21.21 to 24.21)	NA	NA	**-15.40 (-27.90 to -2.90)**	NA	NA
-6.82 (-15.48 to 1.83)	-0.92 (-16.16 to 14.32)	**Clozapine**	NA	**-5.38 (-9.73 to -1.04)**	NA	NA	**-28.55 (-37.64 to -19.45)**
-10.76 (-29.29 to 7.78)	-4.86 (-27.90 to 18.19)	-3.93 (-22.48 to 14.61)	**Fluphenazine**	NA	NA	NA	**-26.20 (-45.08 to -7.32)**
-13.19 (-21.95 to -4.43)	-7.29 (-22.80 to 8.22)	**-6.37 (-10.59 to -2.15)**	-2.43 (-20.96 to 16.10)	**Olanzapine**	NA	NA	**-16.90 (-25.00 to -8.79)**
-20.57 (-32.74 to -8.39)	**-14.67 (-26.08 to -3.26)**	-13.74 (-27.56 to 0.07)	-9.81 (-31.62 to 12.00)	-7.38 (-21.38 to 6.62)	**Chlorpromazine**	NA	NA
-23.96 (-35.92 to -12.00)	-18.06 (-36.38 to 0.27)	**-17.13 (-29.67 to -4.60)**	-13.20 (-33.80 to 7.40)	-10.77 (-23.30 to 1.76)	-3.39 (-20.07 to 13.28)	**Haloperidol**	-13.17 (-27.88 to 1.54)
-34.24 (-43.51 to -24.96)	**-28.34 (-44.41 to -12.26)**	**-27.41 (-34.41 to -20.42)**	**-23.48 (-41.23 to -5.73)**	**-21.05 (-27.93 to -14.16)**	-13.67 (-28.16 to 0.82)	-10.28 (-21.92 to 1.36)	**Risperidone**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is mean difference (MD). Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses

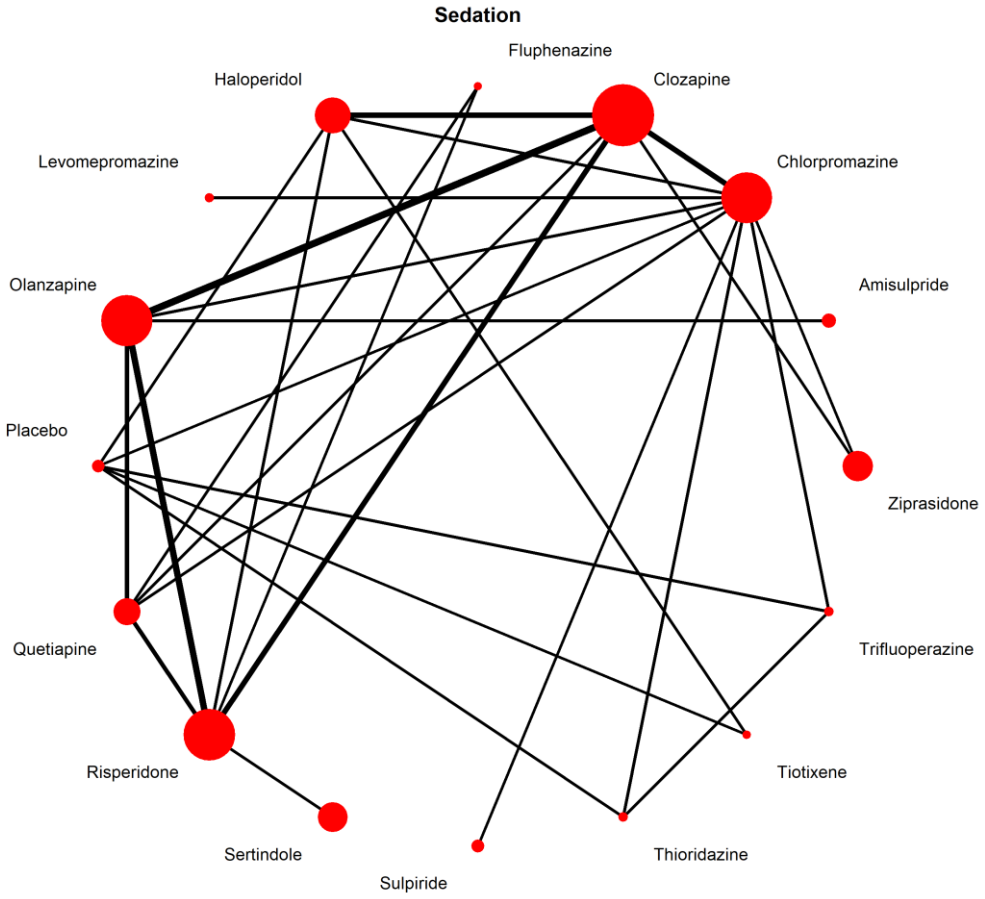


A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is mean difference (MD).

8.9 Sedation

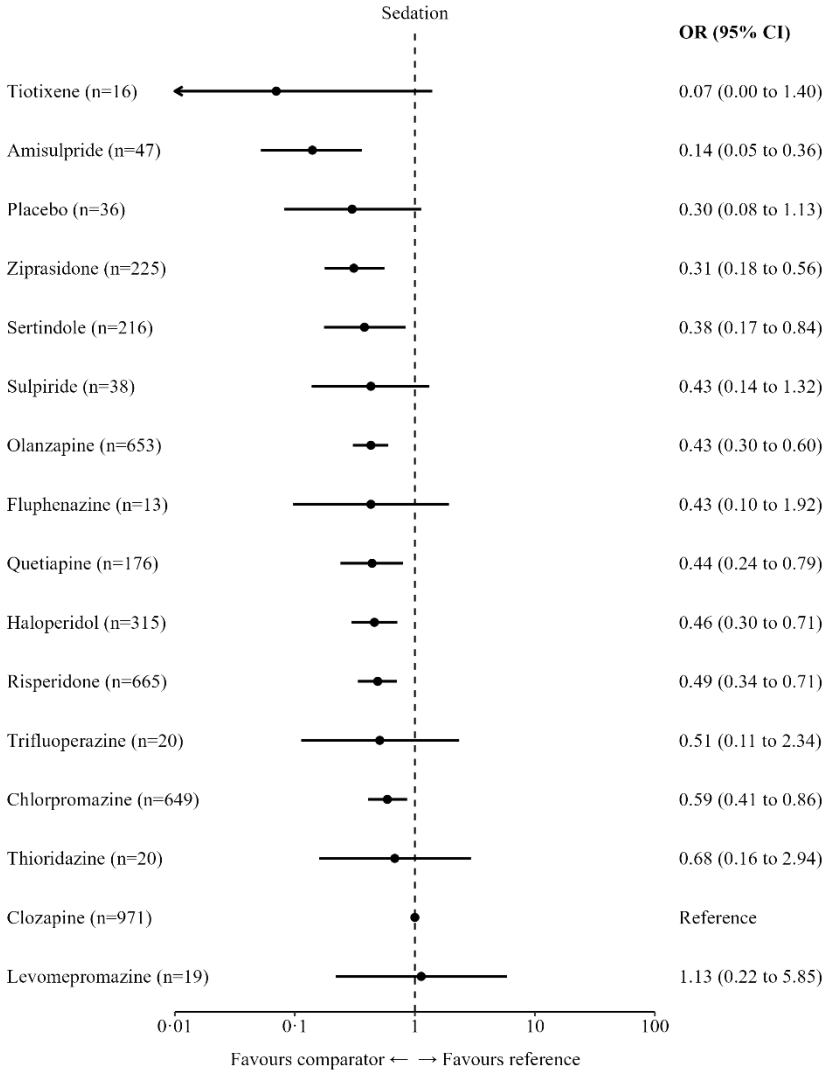
We transformed the original ORs to RRs and EERs vs. CER assuming the baseline risk of sedation with clozapine of 47% (namely CER). 47% was the average risk of sedation with clozapine across all clozapine-arms in the network meta-analysis, as estimated by a single-arm meta-analysis of proportions.

Network plot



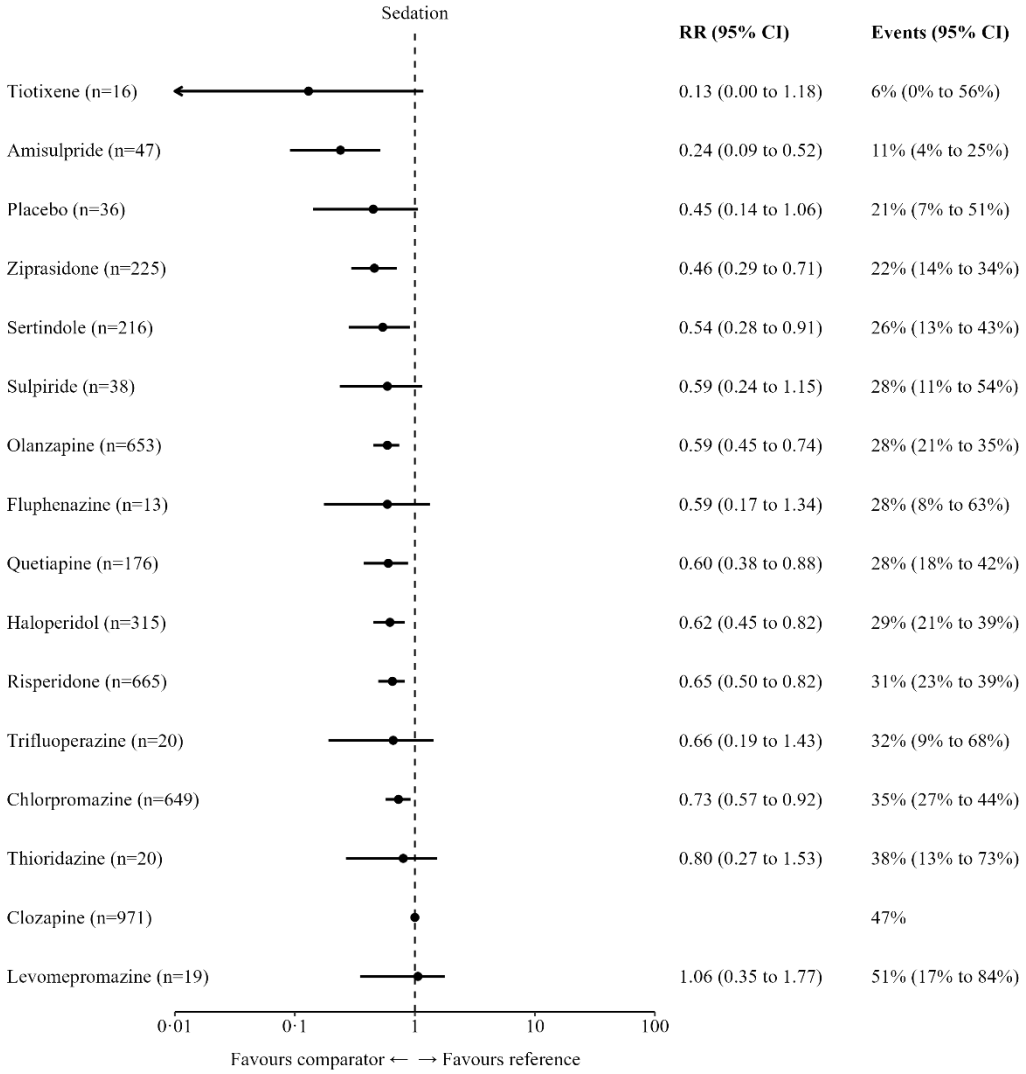
Lines link treatments with direct comparisons in trials; thickness of lines corresponds to the number of trials evaluating the comparison; size of the nodes corresponds to the number of participants assigned to the treatment.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as odds ratio (OR), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

Forest plot with RR and EER versus CER



For this forest plot, we transformed the original OR to RR and exposure events rates (EER, called "events" in the forest plot) using the formula indicated above. Therefore, we used an average sedation rate with clozapine of 47% as the control event rate (CER).
Effect sizes are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis

League table for the outcome: Sedation (OR)

Tiotixene	NA	0.31 (0.01 to 8.28)	NA	NA	NA	NA	NA	NA	0.13 (0.01 to 2.64)	NA	NA	NA	NA	NA	NA
0.49 (0.02 to 11.78)	**Amisulpride**	NA	NA	NA	NA	**0.32 (0.13 to 0.80)**	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.22 (0.01 to 4.99)	0.45 (0.09 to 2.30)	**Placebo**	NA	NA	NA	NA	NA	NA	0.40 (0.05 to 3.09)	NA	0.71 (0.14 to 3.66)	0.71 (0.14 to 3.66)	0.53 (0.11 to 2.60)	NA	NA
0.22 (0.01 to 4.64)	0.44 (0.14 to 1.32)	0.96 (0.24 to 3.84)	**Ziprasidone**	NA	NA	NA	NA	NA	NA	NA	NA	0.59 (0.35 to 1.01)	NA	**0.19 (0.06 to 0.61)**	NA
0.18 (0.01 to 4.01)	0.36 (0.11 to 1.21)	0.79 (0.17 to 3.62)	0.82 (0.32 to 2.14)	**Sertindole**	NA	NA	NA	NA	NA	0.79 (0.39 to 1.56)	NA	NA	NA	NA	NA
0.16 (0.01 to 3.96)	0.32 (0.07 to 1.40)	0.71 (0.13 to 3.81)	0.74 (0.23 to 2.38)	0.90 (0.23 to 3.51)	**Sulpiride**	NA	NA	NA	NA	NA	NA	0.72 (0.25 to 2.09)	NA	NA	NA
0.16 (0.01 to 3.32)	**0.32 (0.13 to 0.80)**	0.71 (0.18 to 2.72)	0.74 (0.39 to 1.39)	0.90 (0.40 to 2.00)	1.00 (0.31 to 3.18)	**Olanzapine**	NA	0.92 (0.24 to 3.58)	NA	1.02 (0.58 to 1.81)	NA	0.51 (0.21 to 1.21)	NA	**0.44 (0.29 to 0.67)**	NA
0.16 (0.01 to 4.56)	0.32 (0.05 to 1.85)	0.70 (0.10 to 5.05)	0.73 (0.15 to 3.52)	0.89 (0.17 to 4.53)	0.99 (0.16 to 6.27)	0.99 (0.22 to 4.48)	**Fluphenazine**	1.33 (0.23 to 7.74)	NA	0.71 (0.14 to 3.61)	NA	NA	NA	NA	NA
0.16 (0.01 to 3.36)	**0.31 (0.10 to 0.96)**	0.69 (0.17 to 2.81)	0.72 (0.35 to 1.49)	0.88 (0.34 to 2.28)	0.98 (0.29 to 3.24)	0.98 (0.51 to 1.86)	0.99 (0.22 to 4.44)	**Quetiapine**	NA	0.94 (0.30 to 2.99)	NA	0.72 (0.37 to 1.38)	NA	0.61 (0.18 to 2.06)	NA
0.15 (0.01 to 2.98)	**0.30 (0.10 to 0.86)**	0.66 (0.18 to 2.48)	0.68 (0.34 to 1.39)	0.83 (0.35 to 2.01)	0.93 (0.28 to 3.09)	0.93 (0.54 to 1.60)	0.94 (0.20 to 4.42)	0.95 (0.46 to 1.97)	**Haloperidol**	0.82 (0.23 to 2.85)	NA	**9.33 (1.19 to 72.99)**	NA	**0.40 (0.24 to 0.65)**	NA
0.14 (0.01 to 2.91)	**0.28 (0.10 to 0.77)**	0.62 (0.16 to 2.41)	0.65 (0.33 to 1.26)	0.79 (0.39 to 1.56)	0.88 (0.27 to 2.84)	0.88 (0.58 to 1.33)	0.89 (0.20 to 3.88)	0.90 (0.46 to 1.74)	0.94 (0.55 to 1.63)	**Risperidone**	NA	NA	NA	**0.50 (0.31 to 0.80)**	NA
0.13 (0.00 to 3.56)	0.27 (0.04 to 1.60)	0.59 (0.13 to 2.77)	0.61 (0.13 to 2.91)	0.75 (0.14 to 4.07)	0.83 (0.13 to 5.16)	0.83 (0.18 to 3.88)	0.84 (0.10 to 6.91)	0.85 (0.18 to 4.12)	0.89 (0.19 to 4.21)	0.95 (0.20 to 4.48)	**Trifluoperazine**	1.00 (0.21 to 4.71)	0.75 (0.17 to 3.33)	NA	NA
0.11 (0.01 to 2.38)	**0.23 (0.08 to 0.64)**	0.51 (0.14 to 1.88)	**0.53 (0.33 to 0.87)**	0.65 (0.28 to 1.51)	0.72 (0.25 to 2.09)	0.72 (0.46 to 1.14)	0.73 (0.16 to 3.29)	0.74 (0.42 to 1.28)	0.77 (0.44 to 1.35)	0.82 (0.50 to 1.36)	0.87 (0.20 to 3.82)	**Chlorpromazine**	0.75 (0.17 to 3.33)	0.67 (0.42 to 1.09)	0.52 (0.11 to 2.60)
0.10 (0.00 to 2.60)	0.20 (0.04 to 1.14)	0.44 (0.10 to 1.96)	0.46 (0.10 to 2.06)	0.56 (0.11 to 2.89)	0.62 (0.11 to 3.69)	0.62 (0.14 to 2.74)	0.63 (0.08 to 4.97)	0.64 (0.14 to 2.92)	0.67 (0.15 to 2.98)	0.71 (0.16 to 3.17)	0.75 (0.17 to 3.33)	0.87 (0.21 to 3.59)	**Thioridazine**	NA	NA
0.07 (0.00 to 1.40)	**0.14 (0.05 to 0.36)**	0.30 (0.08 to 1.13)	**0.31 (0.18 to 0.56)**	**0.38 (0.17 to 0.84)**	0.43 (0.14 to 1.32)	**0.43 (0.30 to 0.60)**	0.43 (0.10 to 1.92)	**0.44 (0.24 to 0.79)**	**0.46 (0.30 to 0.71)**	**0.49 (0.34 to 0.71)**	0.51 (0.11 to 2.34)	**0.59 (0.41 to 0.86)**	0.68 (0.16 to 2.94)	**Clozapine**	NA
0.06 (0.00 to 1.86)	**0.12 (0.02 to 0.81)**	0.27 (0.03 to 2.11)	0.28 (0.05 to 1.49)	0.34 (0.06 to 2.08)	0.38 (0.06 to 2.59)	0.38 (0.07 to 2.00)	0.38 (0.04 to 3.45)	0.39 (0.07 to 2.10)	0.41 (0.07 to 2.22)	0.43 (0.08 to 2.31)	0.45 (0.05 to 4.04)	0.52 (0.11 to 2.60)	0.61 (0.07 to 5.17)	0.89 (0.17 to 4.59)	**Levomepromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is odd ratio (OR). Bold results indicate 95% CI excluding no effect. NA=not available.

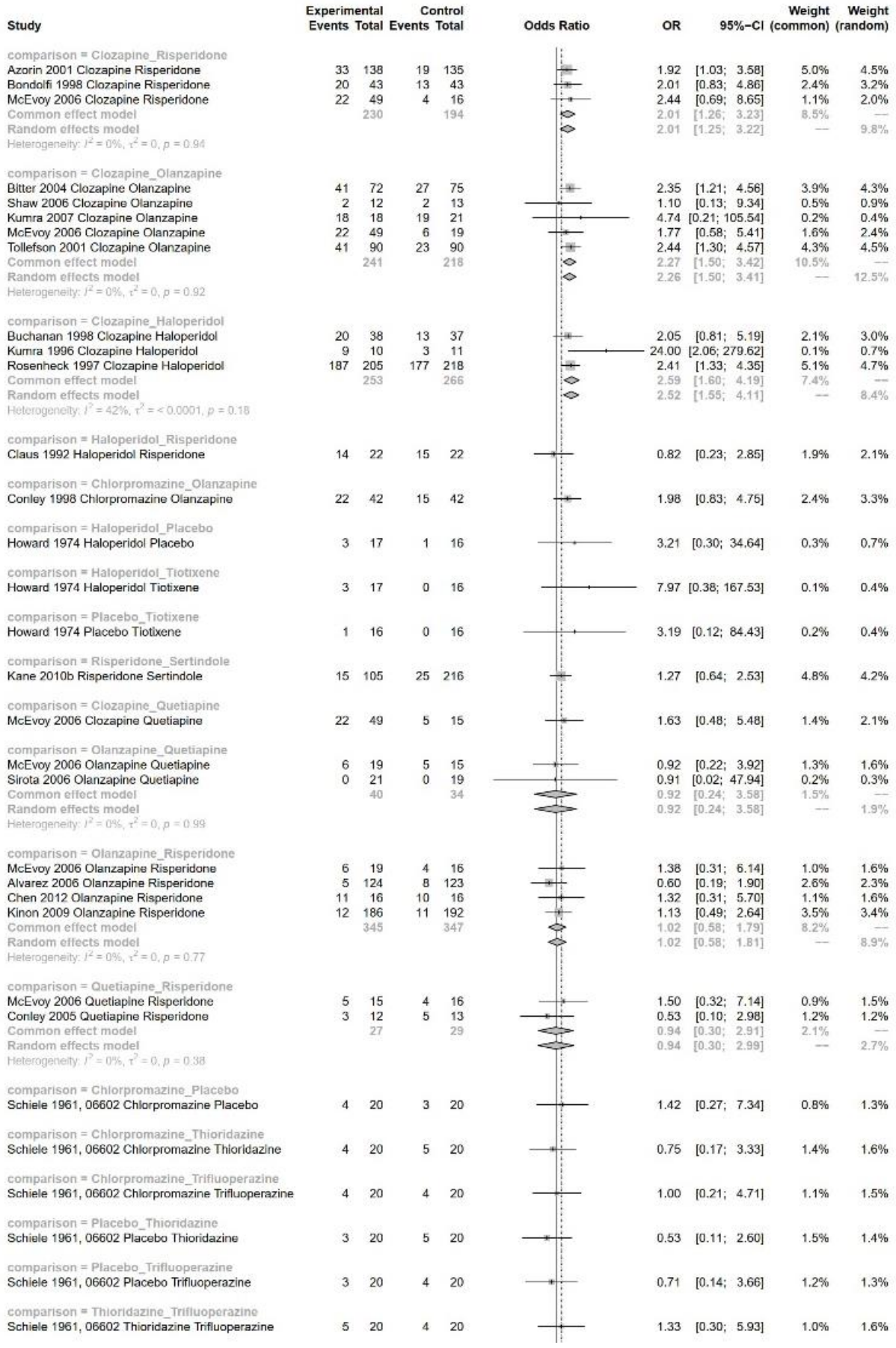
League table for the outcome: Sedation (RR)

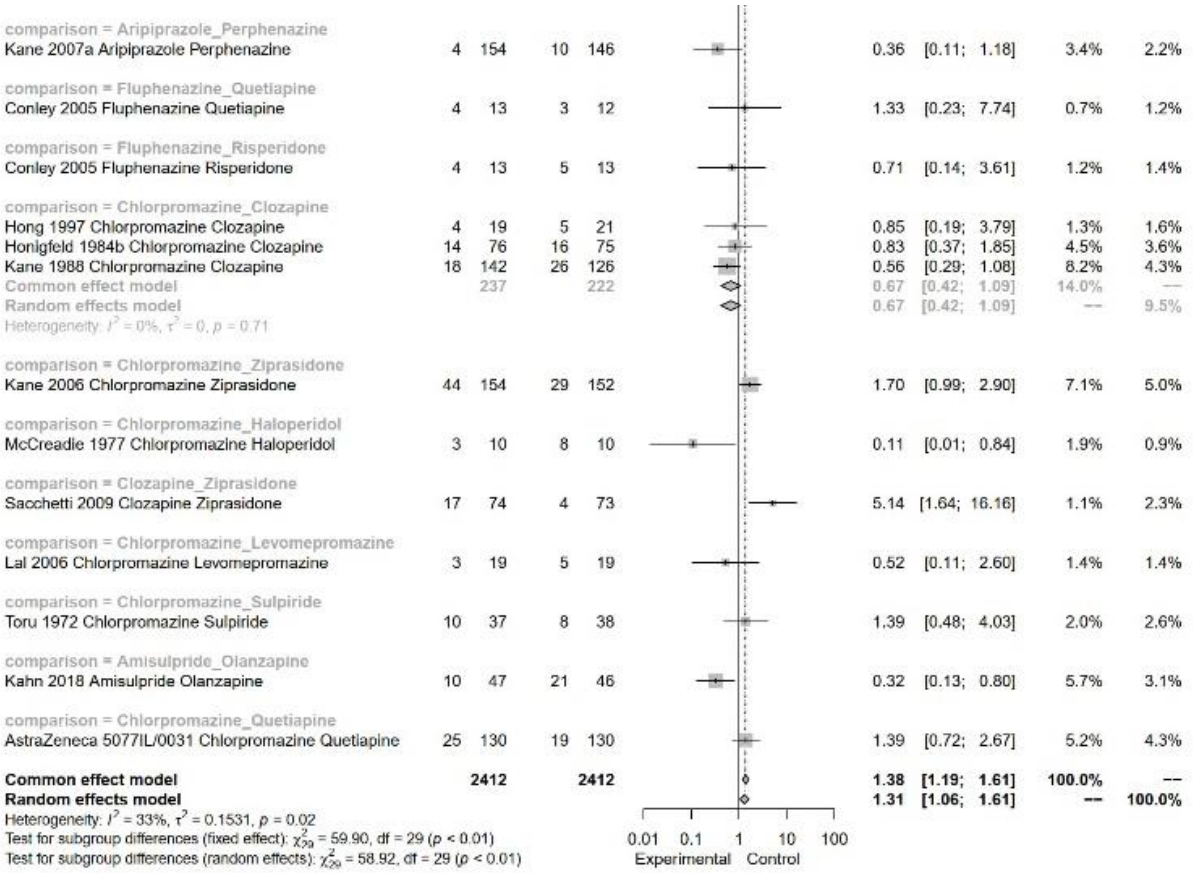
Tiotixene	NA	0.53 (0.02 to 1.55)	NA	NA	NA	NA	NA	NA	0.33 (0.03 to 1.24)	NA	NA	NA	NA	NA	NA
0.62 (0.03 to 2.21)	**Amisulpride**	NA	NA	NA	NA	**0.59 (0.32 to 0.93)**	NA	NA	NA	NA	NA	NA	NA	NA	NA
0.41 (0.02 to 1.47)	0.67 (0.2 to 1.29)	**Placebo**	NA	NA	NA	NA	NA	NA	0.68 (0.15 to 1.26)	NA	0.9 (0.36 to 1.26)	0.91 (0.39 to 1.23)	0.83 (0.35 to 1.16)	NA	NA
0.42 (0.02 to 1.45)	0.67 (0.29 to 1.11)	0.98 (0.44 to 1.41)	**Ziprasidone**	NA	NA	NA	NA	NA	NA	NA	NA	0.85 (0.68 to 1)	NA	**0.58 (0.27 to 0.9)**	NA
0.39 (0.03 to 1.35)	0.62 (0.26 to 1.06)	0.92 (0.37 to 1.34)	0.93 (0.57 to 1.23)	**Sertindole**	NA	NA	NA	NA	NA	0.93 (0.68 to 1.12)	NA	NA	NA	NA	NA
0.37 (0.03 to 1.32)	0.59 (0.19 to 1.1)	0.88 (0.32 to 1.31)	0.9 (0.48 to 1.23)	0.97 (0.48 to 1.3)	**Sulpiride**	NA	NA	NA	NA	NA	NA	0.91 (0.57 to 1.15)	NA	NA	NA
0.37 (0.03 to 1.29)	**0.59 (0.32 to 0.93)**	0.88 (0.4 to 1.26)	0.9 (0.66 to 1.1)	0.97 (0.67 to 1.19)	1 (0.58 to 1.29)	**Olanzapine**	NA	0.97 (0.5 to 1.3)	NA	1.01 (0.82 to 1.15)	NA	0.8 (0.51 to 1.05)	NA	**0.82 (0.71 to 0.92)**	NA
0.37 (0.03 to 1.33)	0.59 (0.14 to 1.17)	0.88 (0.26 to 1.35)	0.89 (0.35 to 1.3)	0.96 (0.39 to 1.33)	1 (0.37 to 1.37)	1 (0.47 to 1.33)	**Fluphenazine**	1.09 (0.48 to 1.38)	NA	0.89 (0.36 to 1.27)	NA	NA	NA	NA	NA
0.37 (0.03 to 1.29)	**0.58 (0.26 to 0.99)**	0.87 (0.39 to 1.26)	0.89 (0.63 to 1.12)	0.96 (0.62 to 1.22)	0.99 (0.56 to 1.28)	0.99 (0.77 to 1.17)	1 (0.47 to 1.33)	**Quetiapine**	NA	0.98 (0.59 to 1.24)	NA	0.91 (0.7 to 1.08)	NA	0.9 (0.56 to 1.1)	NA
0.36 (0.03 to 1.26)	**0.58 (0.27 to 0.95)**	0.86 (0.42 to 1.23)	0.87 (0.63 to 1.09)	0.94 (0.64 to 1.18)	0.98 (0.56 to 1.26)	0.98 (0.79 to 1.13)	0.98 (0.45 to 1.31)	0.98 (0.73 to 1.18)	**Haloperidol**	0.94 (0.5 to 1.24)	NA	**1.3 (1.04 to 1.34)**	NA	**0.8 (0.65 to 0.92)**	NA
0.36 (0.03 to 1.24)	**0.57 (0.27 to 0.92)**	0.85 (0.39 to 1.21)	0.86 (0.63 to 1.06)	0.93 (0.68 to 1.12)	0.96 (0.56 to 1.24)	0.96 (0.82 to 1.08)	0.96 (0.46 to 1.28)	0.97 (0.74 to 1.14)	0.98 (0.81 to 1.13)	**Risperidone**	NA	NA	NA	**0.85 (0.73 to 0.96)**	NA
0.35 (0 to 1.26)	0.57 (0.13 to 1.12)	0.84 (0.35 to 1.22)	0.85 (0.35 to 1.23)	0.91 (0.36 to 1.27)	0.95 (0.35 to 1.3)	0.95 (0.44 to 1.27)	0.95 (0.28 to 1.32)	0.95 (0.44 to 1.27)	0.97 (0.45 to 1.28)	0.99 (0.47 to 1.28)	**Trifluoperazine**	1 (0.51 to 1.25)	0.93 (0.47 to 1.19)	NA	NA
0.33 (0.04 to 1.17)	**0.54 (0.25 to 0.87)**	0.8 (0.39 to 1.14)	**0.82 (0.66 to 0.96)**	0.88 (0.6 to 1.09)	0.91 (0.57 to 1.15)	0.91 (0.77 to 1.03)	0.91 (0.43 to 1.22)	0.92 (0.74 to 1.06)	0.93 (0.75 to 1.07)	0.95 (0.8 to 1.07)	0.96 (0.49 to 1.23)	**Chlorpromazine**	0.93 (0.47 to 1.19)	0.92 (0.81 to 1.01)	0.88 (0.44 to 1.1)
0.33 (0 to 1.16)	0.52 (0.15 to 1.03)	0.77 (0.33 to 1.13)	0.79 (0.33 to 1.13)	0.85 (0.35 to 1.18)	0.88 (0.35 to 1.2)	0.88 (0.41 to 1.17)	0.88 (0.27 to 1.22)	0.89 (0.41 to 1.18)	0.9 (0.43 to 1.18)	0.91 (0.45 to 1.19)	0.93 (0.47 to 1.19)	0.97 (0.54 to 1.2)	**Thioridazine**	NA	NA
0.31 (0 to 1.05)	**0.49 (0.24 to 0.77)**	0.72 (0.34 to 1.02)	**0.73 (0.56 to 0.88)**	**0.78 (0.55 to 0.97)**	0.82 (0.49 to 1.04)	**0.82 (0.72 to 0.9)**	0.82 (0.4 to 1.09)	**0.82 (0.65 to 0.96)**	**0.83 (0.72 to 0.94)**	**0.85 (0.75 to 0.94)**	0.86 (0.42 to 1.11)	**0.89 (0.8 to 0.97)**	0.93 (0.53 to 1.13)	**Clozapine**	NA
0.29 (0 to 1.08)	**0.47 (0.12 to 0.97)**	0.71 (0.17 to 1.09)	0.72 (0.25 to 1.05)	0.77 (0.29 to 1.09)	0.8 (0.29 to 1.1)	0.8 (0.33 to 1.08)	0.8 (0.21 to 1.12)	0.81 (0.33 to 1.09)	0.82 (0.33 to 1.09)	0.83 (0.36 to 1.1)	0.84 (0.25 to 1.13)	0.88 (0.44 to 1.1)	0.91 (0.33 to 1.14)	0.98 (0.57 to 1.14)	**Levomepromazine**

The original results given in OR (and their 95% CI) are transformed to RR (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column) using the formula described above. For this transformation, we assumed a sedation rate with clozapine of 47% as the control event rate (CER) for all comparisons of active antipsychotic versus clozapine.

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses

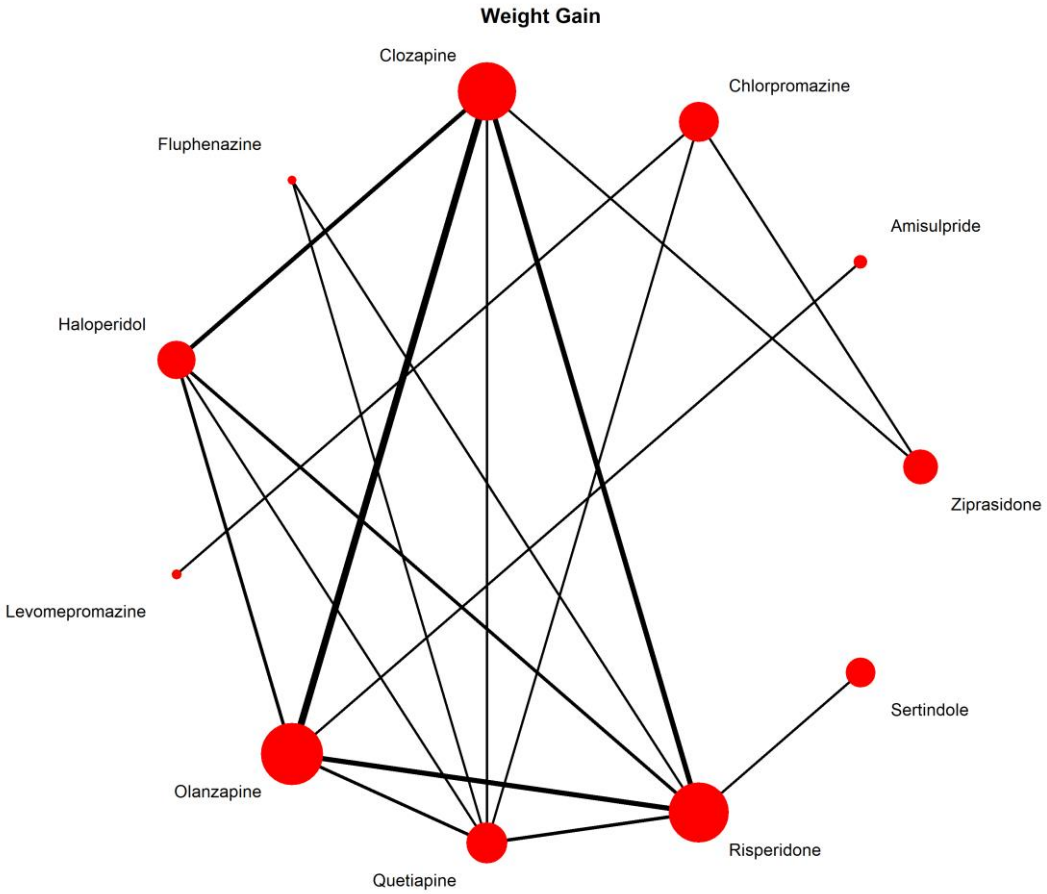




A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is OR.

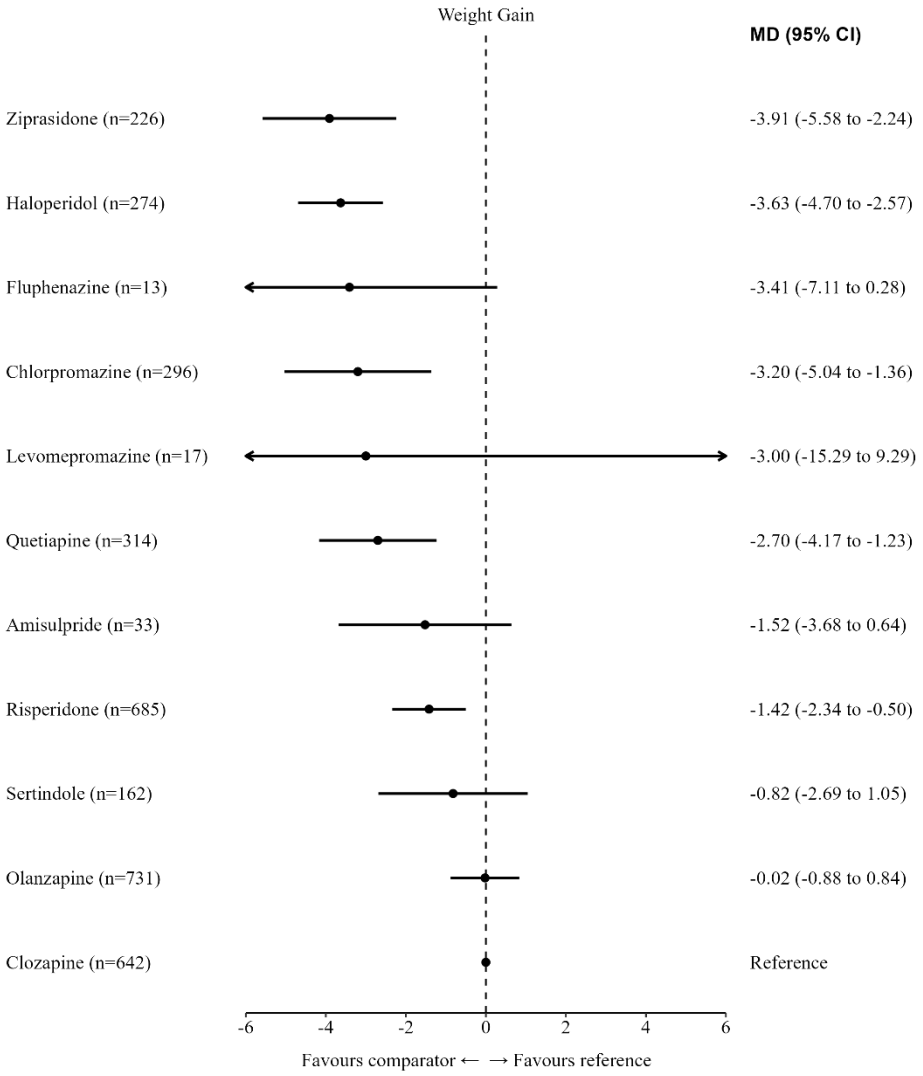
8.10 Weight gain

Network plot



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.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



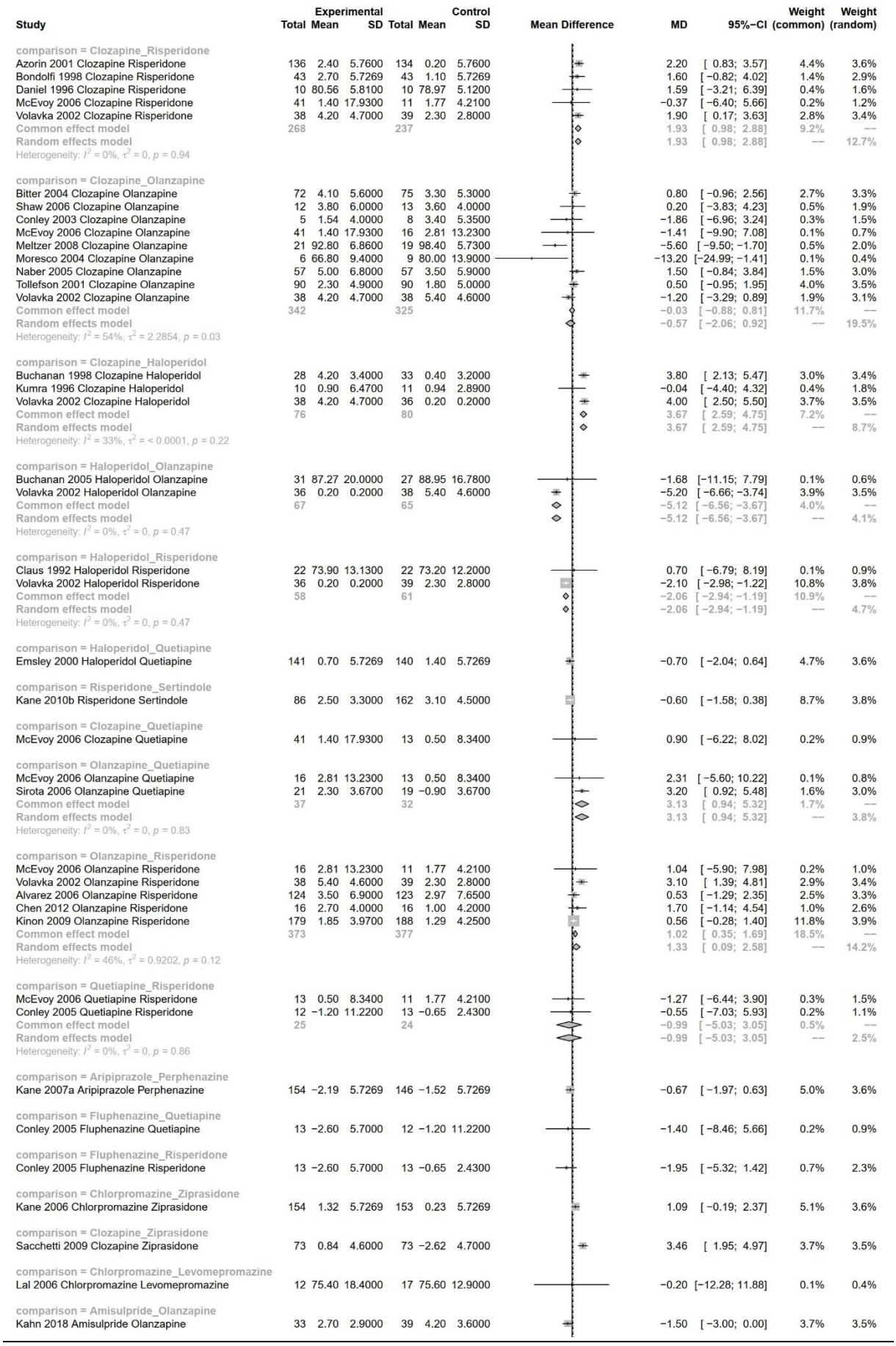
Effect sizes, measured as mean difference (MD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

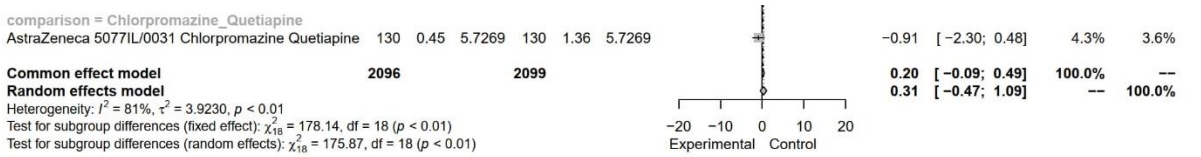
League table for the outcome: Weight gain

Ziprasidone	NA	NA	-1.09 (-2.91 to 0.73)	NA	NA	NA	NA	NA	NA	**-3.46 (-5.45 to -1.47)**
-0.28 (-2.13 to 1.58)	**Haloperidol**	NA	NA	-0.70 (-2.56 to 1.16)	NA	NA	**-1.99 (-3.52 to -0.45)**	NA	**-5.06 (-6.97 to -3.14)**	**-3.55 (-4.92 to -2.17)**
-0.50 (-4.51 to 3.52)	-0.22 (-3.97 to 3.52)	**Fluphenazine**	NA	-1.40 (-8.58 to 5.78)	NA	NA	-1.95 (-5.56 to 1.66)	NA	NA	NA
-0.71 (-2.29 to 0.87)	-0.44 (-2.34 to 1.47)	-0.22 (-4.27 to 3.84)	**Chlorpromazine**	-0.91 (-2.81 to 0.99)	-0.20 (-12.35 to 11.95)	NA	NA	NA	NA	NA
-1.21 (-3.05 to 0.63)	-0.93 (-2.33 to 0.46)	-0.71 (-4.57 to 3.15)	-0.50 (-2.13 to 1.13)	**Quetiapine**	NA	NA	-0.99 (-5.14 to 3.16)	NA	**-3.11 (-5.60 to -0.62)**	-0.90 (-8.14 to 6.34)
-0.91 (-13.17 to 11.34)	-0.64 (-12.94 to 11.66)	-0.42 (-13.22 to 12.39)	-0.20 (-12.35 to 11.95)	0.30 (-11.96 to 12.56)	**Levomepromazine**	NA	NA	NA	NA	NA
-2.39 (-5.07 to 0.29)	-2.11 (-4.39 to 0.17)	-1.89 (-6.08 to 2.29)	-1.68 (-4.42 to 1.07)	-1.18 (-3.64 to 1.29)	-1.48 (-13.93 to 10.98)	**Amisulpride**	NA	NA	-1.50 (-3.48 to 0.48)	NA
-2.49 (-4.33 to -0.65)	**-2.21 (-3.33 to -1.10)**	-1.99 (-5.58 to 1.60)	-1.78 (-3.71 to 0.16)	-1.28 (-2.79 to 0.23)	-1.58 (-13.88 to 10.73)	-0.10 (-2.27 to 2.06)	**Risperidone**	-0.60 (-2.23 to 1.03)	**-1.26 (-2.28 to -0.24)**	**-1.86 (-3.06 to -0.66)**
-3.09 (-5.54 to -0.63)	**-2.81 (-4.78 to -0.84)**	-2.59 (-6.53 to 1.35)	-2.38 (-4.90 to 0.15)	-1.88 (-4.10 to 0.34)	-2.18 (-14.59 to 10.23)	-0.70 (-3.41 to 2.00)	-0.60 (-2.23 to 1.03)	**Sertindole**	NA	NA
-3.89 (-5.70 to -2.08)	**-3.61 (-4.73 to -2.49)**	-3.39 (-7.08 to 0.29)	**-3.18 (-5.08 to -1.27)**	**-2.68 (-4.14 to -1.21)**	-2.98 (-15.28 to 9.32)	-1.50 (-3.48 to 0.48)	**-1.40 (-2.27 to -0.53)**	-0.80 (-2.64 to 1.05)	**Olanzapine**	0.20 (-0.83 to 1.22)
-3.91 (-5.58 to -2.24)	**-3.63 (-4.70 to -2.57)**	-3.41 (-7.11 to 0.28)	**-3.20 (-5.04 to -1.36)**	**-2.70 (-4.17 to -1.23)**	-3.00 (-15.29 to 9.29)	-1.52 (-3.68 to 0.64)	**-1.42 (-2.34 to -0.50)**	-0.82 (-2.69 to 1.05)	-0.02 (-0.88 to 0.84)	**Clozapine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is mean difference (MD). Bold results indicate 95% CI excluding no effect. NA=not available.

Forest plot of results of pairwise meta-analyses

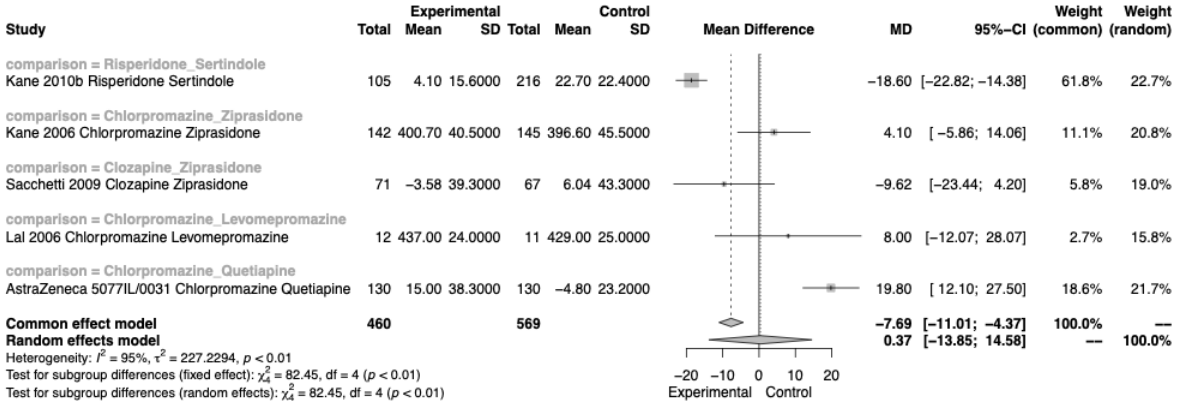




A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is mean difference (MD).

8.11 QTc prolongation

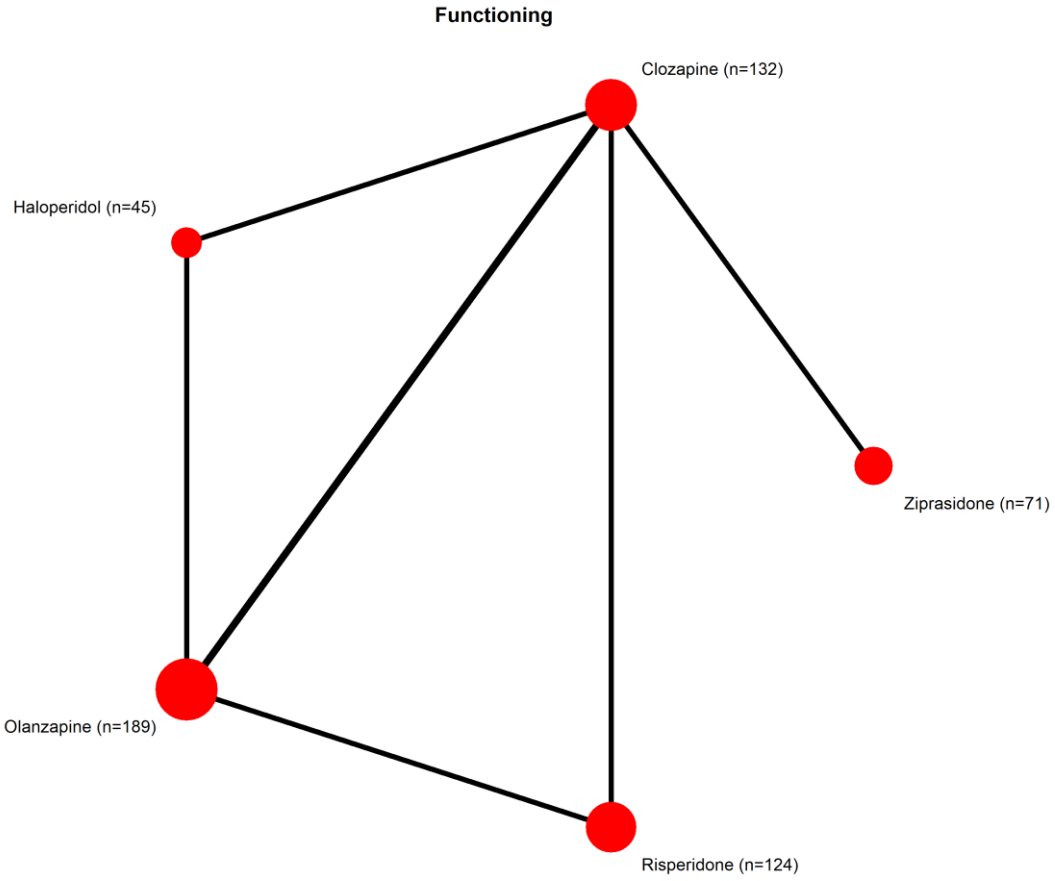
Forest plot of results of pairwise meta-analyses



A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is mean difference (MD).

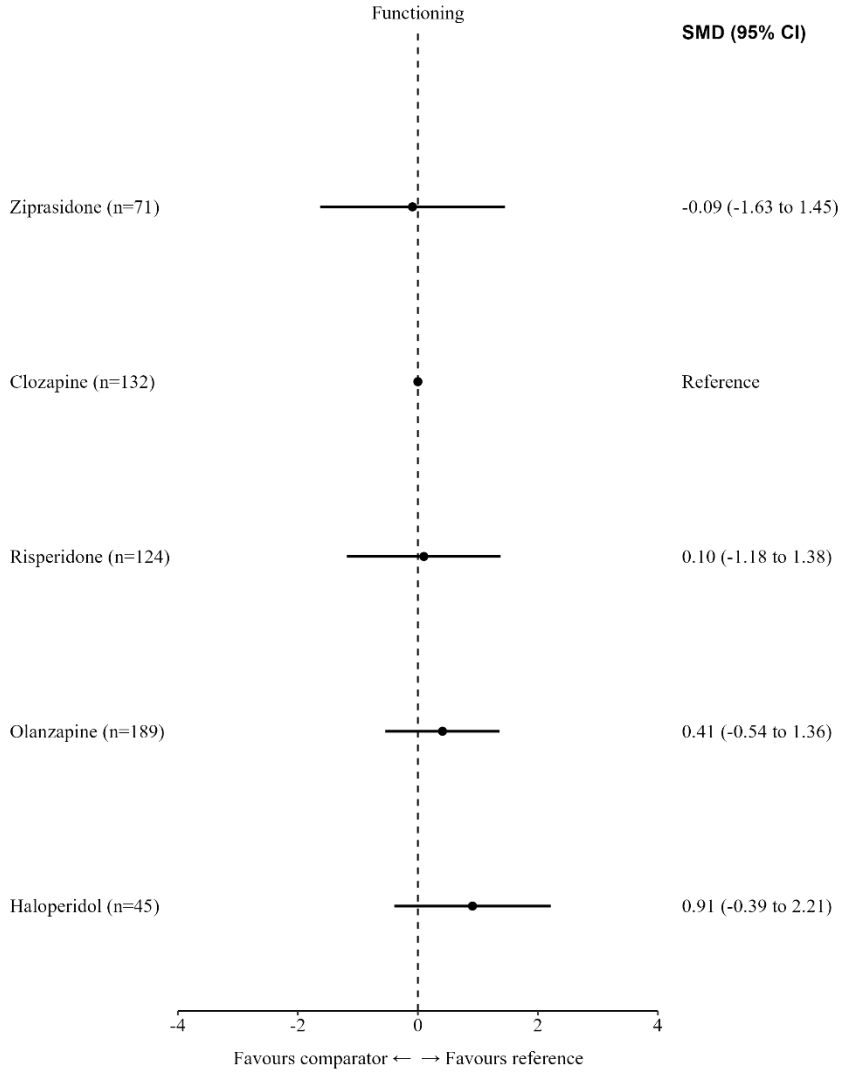
8.12 Functioning

Network plot



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.

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



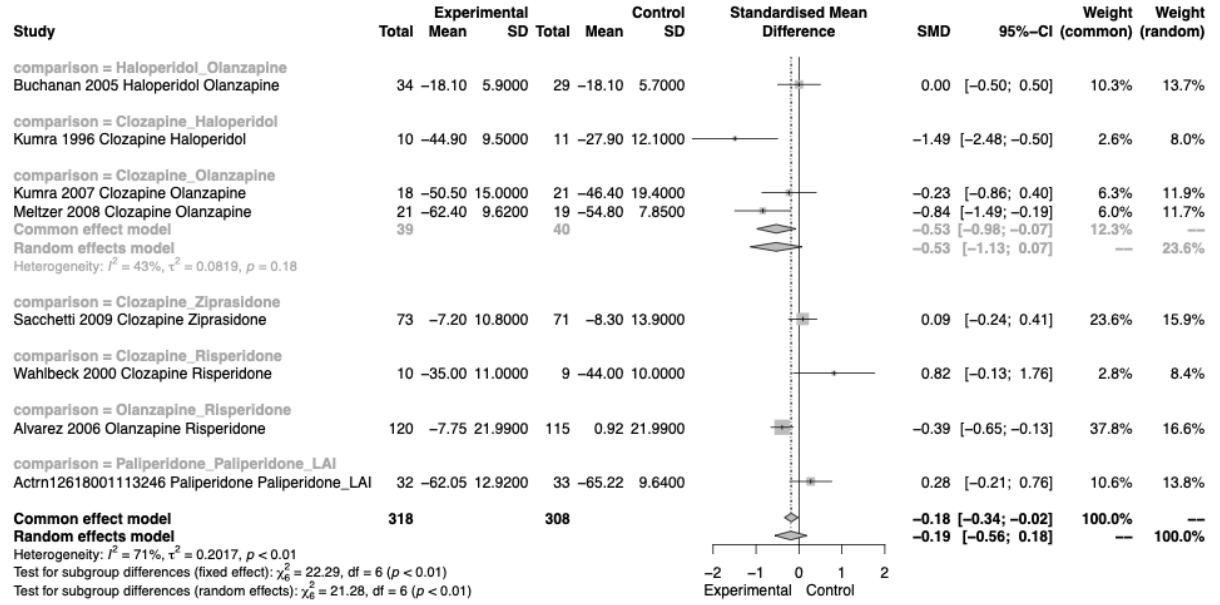
Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table for the outcome: Functioning

Clozapine	0.09 (-1.45 to 1.63)	0.85 (-0.92 to 2.63)	-0.55 (-1.70 to 0.61)	-1.55 (-3.35 to 0.24)
0.09 (-1.45 to 1.63)	**Ziprasidone**	NA	NA	NA
-0.10 (-1.38 to 1.18)	-0.19 (-2.19 to 1.82)	**Risperidone**	0.39 (-1.13 to 1.92)	NA
-0.41 (-1.36 to 0.54)	-0.50 (-2.31 to 1.31)	-0.31 (-1.54 to 0.92)	**Olanzapine**	-0.00 (-1.59 to 1.59)
-0.91 (-2.21 to 0.39)	-1.00 (-3.02 to 1.02)	-0.81 (-2.47 to 0.85)	-0.50 (-1.76 to 0.76)	**Haloperidol**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

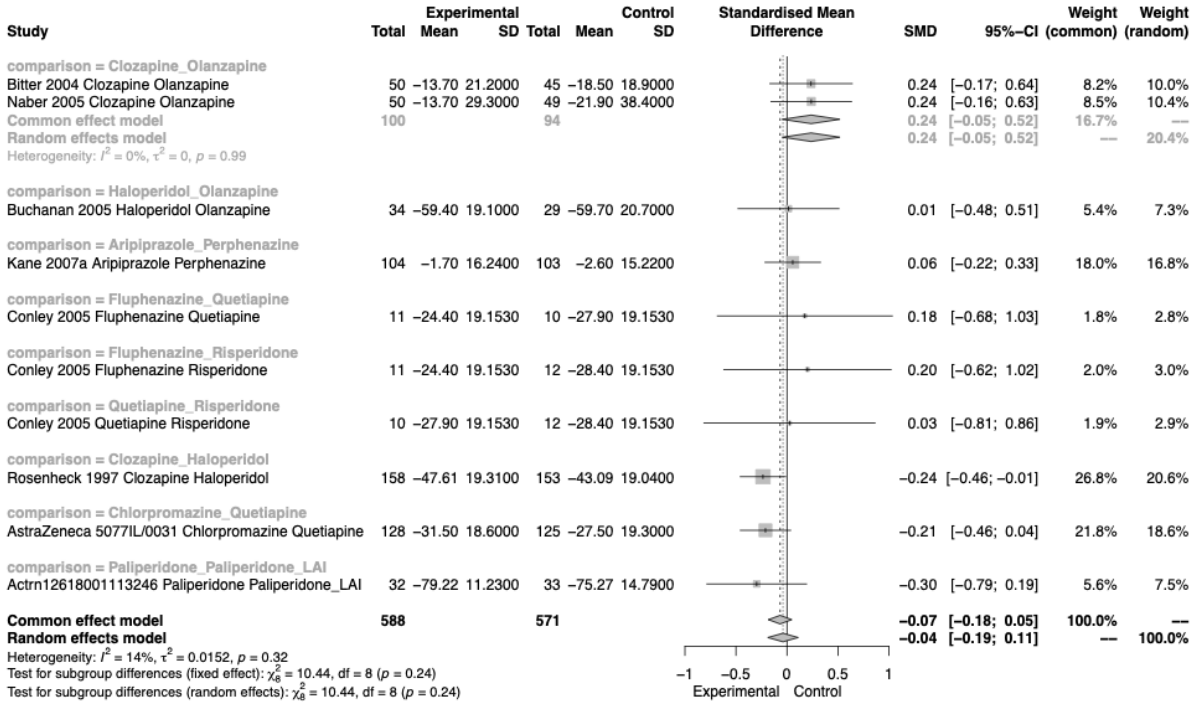
Forest plot of results of pairwise meta-analyses



A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is standardized mean difference (SMD).

8.13 Quality of life

Forest plot of results of pairwise meta-analyses



A summary effect size is calculated by pairwise meta-analyses of all studies of a specific comparison. The type of effect size measure is standardized mean difference (SMD).

9 Evaluation of heterogeneity

Outcome	Between study variance (tau)	Outcome type used as comparator	Predictive distribution of tau	Location of the estimated common tau compared to the quartiles of the empirical predictive distribution	Judgement on heterogeneity
Continuous		from Rhodes et al 2015	Median (IQR)		
Overall symptoms (SMD)	0.1804	Mental health outcome	0.19 (0.09, 0.42)	Between 25%-and 50%-quantile	low-moderate
Positive symptoms (SMD)	0.1840	Mental health outcome	0.19 (0.09, 0.42)	Between 25%-and 50%-quantile	low-moderate
Negative symptoms (SMD)	0.5014	Mental health outcome	0.19 (0.09, 0.42)	Above 75%-quantile	high
Weight gain (MD)	0.6602	General physical health and adverse event and pain and quality of life/functioning	0.18 (0.07, 0.43)	Above 75%-quantile	high
Prolactin (MD)	0	General physical health and adverse event and pain and quality of life/functioning	0.18 (0.07, 0.43)	Below 25%-quantile	low
Functioning (SMD)	0.7686	Mental health outcome	0.19 (0.09, 0.42)	Above 75%-quantile	high
Quality of life (SMD)	0	Mental health outcome	0.19 (0.09, 0.42)	Below 25%-quantile	low
Dichotomous		from Turner et al 2015	Median (IQR)		
Response (OR)	0.3783	Mental health indicators	0.31 (0.18, 0.53)	Between 50%-and 75%-quantile	moderate-high
Dropout for any reason (OR)	0.2674	Withdrawals/drop-outs	0.2 (0.11, 0.36)	Between 50%-and 75%-quantile	moderate-high
Dropout for inefficacy (OR)	0.0951	Withdrawals/drop-outs	0.2 (0.11, 0.36)	Below 25%-quantile	low
Dropout for adverse events (OR)	0	Withdrawals/drop-outs	0.2 (0.11, 0.36)	Below 25%-quantile	low
Use of antiparkinsonian medication (OR)	0.2990	Adverse events	0.35 (0.21, 0.6)	Between 50%-and 75%-quantile	moderate-high
Sedation (OR)	0	Adverse events	0.35 (0.21, 0.6)	Below 25%-quantile	low

10 Evaluation of inconsistency

Outcome	Number of studies (comparisons) [interventions]	P value of design-by-treatment interaction test	Inconsistent comparisons of detachable comparisons (%) (SIDE-test p<0.10)	Judgement
Continuous				
Overall symptoms	45 (57) [12]	< 0.0001	2 / 18 (11.11%)	Important evidence of inconsistency
Positive symptoms	39 (51) [11]	0.4937	2 / 17 (11.76%)	Little evidence of inconsistency
Negative symptoms	42 (54) [12]	0.7478	1 / 18 (5.56%)	Little evidence of inconsistency
Weight gain	28 (40) [11]	0.9701	1 / 15 (6.67%)	Little evidence of inconsistency
Prolactin	10 (17) [8]	0.4395	2 / 13 (15.38%)	Little evidence of inconsistency
QTc prolongation	5 (5) [7]	No closed loops	No closed loops	Inconsistency not estimable
Functioning	7 (7) [5]	0.0097	0 / 5 (0%)	Some evidence of inconsistency
Quality of life	8 (9) [11]	No closed loops	No closed loops	Inconsistency not estimable
Dichotomous				
Response	46 (66) [20]	0.0194	4 / 31 (12.90%)	Important evidence of inconsistency
Dropout for any reason	54 (75) [18]	0.9155	1 / 27 (3.70%)	Little evidence of inconsistency
Dropout for inefficacy	48 (67) [17]	0.7432	2 / 26 (7.69%)	Little evidence of inconsistency
Dropout for adverse events	50 (71) [19]	0.8684	0 / 29 (0%)	No evidence of inconsistency
Use of antiparkinsonian medication	24 (35) [16]	0.7994	0 / 14 (0%)	No evidence of inconsistency
Sedation	30 (44) [16]	0.5939	1 / 24 (4.17%)	Little evidence of inconsistency

11 Results of the sensitivity analyses of the primary outcome

11.1 Excluding 3 old clozapine-chlorpromazine studies

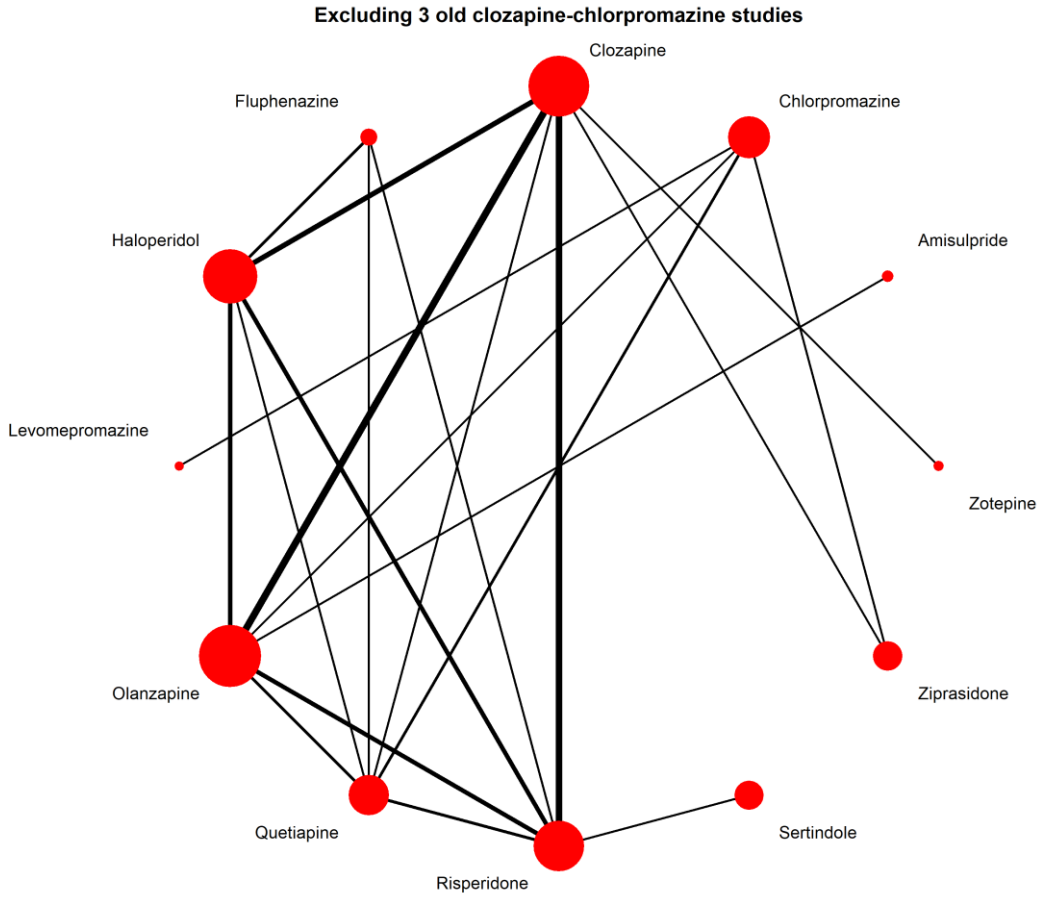
Number of studies: k = 42

Number of pairwise comparisons: m = 54

Number of treatments: n = 12

Number of designs: d = 20

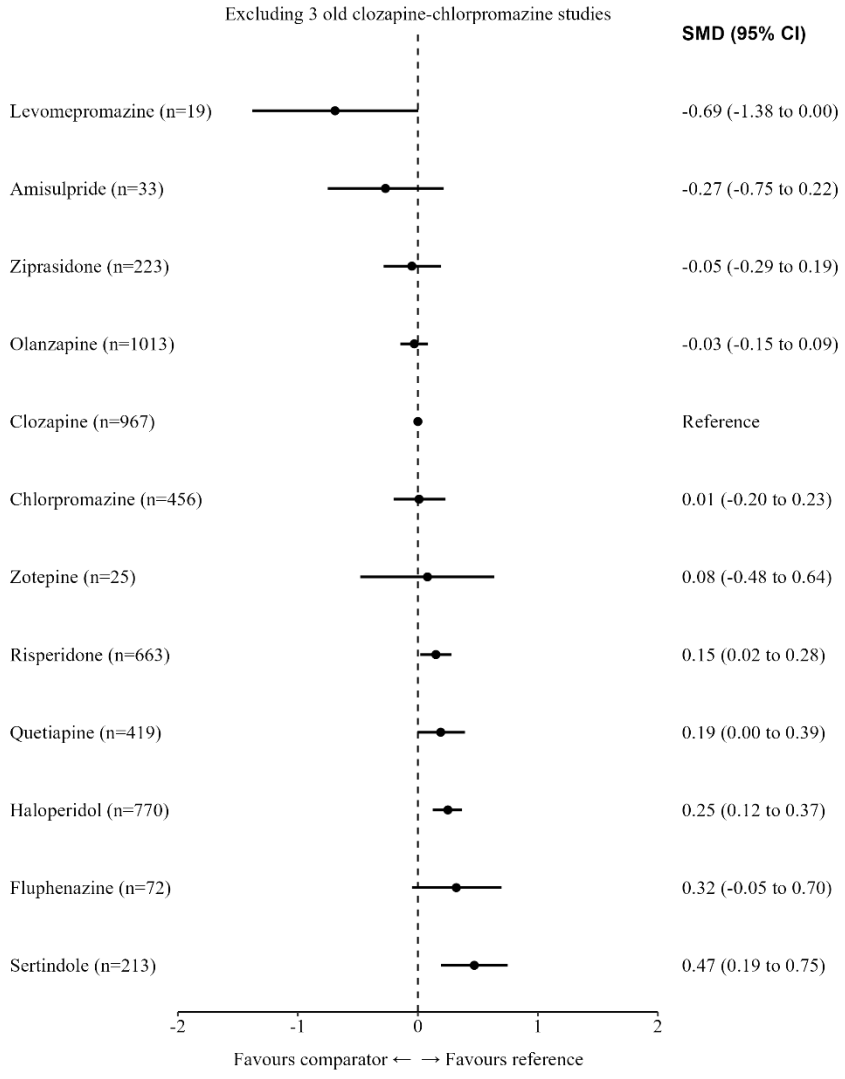
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.0325	0.2979	5.88

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Levomepromazine	NA	NA	NA	NA	**-0.70 (-1.36 to -0.04)**	NA	NA	NA	NA	NA	NA
-0.42 (-1.26 to 0.42)	**Amisulpride**	NA	-0.24 (-0.71 to 0.23)	NA	NA	NA	NA	NA	NA	NA	NA
-0.64 (-1.33 to 0.05)	-0.22 (-0.75 to 0.31)	**Ziprasidone**	NA	-0.02 (-0.36 to 0.31)	-0.07 (-0.30 to 0.16)	NA	NA	NA	NA	NA	NA
-0.66 (-1.35 to 0.03)	-0.24 (-0.71 to 0.23)	-0.02 (-0.26 to 0.23)	**Olanzapine**	-0.03 (-0.18 to 0.13)	-0.22 (-0.66 to 0.23)	NA	**-0.23 (-0.41 to -0.05)**	-0.05 (-0.57 to 0.47)	**-0.27 (-0.44 to -0.11)**	NA	NA
-0.69 (-1.38 to 0.00)	-0.27 (-0.75 to 0.22)	-0.05 (-0.29 to 0.19)	-0.03 (-0.15 to 0.09)	**Clozapine**	NA	-0.08 (-0.64 to 0.48)	-0.11 (-0.28 to 0.05)	**-1.01 (-1.81 to -0.21)**	**-0.19 (-0.35 to -0.03)**	NA	NA
-0.70 (-1.36 to -0.04)	-0.28 (-0.80 to 0.24)	-0.06 (-0.26 to 0.14)	-0.04 (-0.26 to 0.17)	-0.01 (-0.23 to 0.20)	**Chlorpromazine**	NA	NA	**-0.22 (-0.40 to -0.03)**	NA	NA	NA
-0.77 (-1.66 to 0.12)	-0.35 (-1.08 to 0.39)	-0.12 (-0.73 to 0.48)	-0.11 (-0.68 to 0.46)	-0.08 (-0.64 to 0.48)	-0.06 (-0.66 to 0.53)	**Zotepine**	NA	NA	NA	NA	NA
-0.84 (-1.54 to -0.14)	-0.42 (-0.91 to 0.07)	-0.20 (-0.46 to 0.07)	**-0.18 (-0.32 to -0.05)**	**-0.15 (-0.28 to -0.02)**	-0.14 (-0.37 to 0.10)	-0.07 (-0.65 to 0.50)	**Risperidone**	-0.06 (-0.69 to 0.57)	-0.14 (-0.42 to 0.14)	0.02 (-0.75 to 0.79)	**-0.32 (-0.57 to -0.07)**
-0.88 (-1.56 to -0.20)	-0.46 (-0.97 to 0.05)	-0.24 (-0.48 to 0.00)	**-0.22 (-0.42 to -0.03)**	-0.19 (-0.39 to 0.00)	**-0.18 (-0.35 to -0.02)**	-0.12 (-0.71 to 0.48)	-0.04 (-0.26 to 0.17)	**Quetiapine**	-0.14 (-0.38 to 0.10)	0.15 (-0.64 to 0.93)	NA
-0.93 (-1.63 to -0.24)	**-0.51 (-1.00 to -0.03)**	**-0.29 (-0.54 to -0.04)**	**-0.28 (-0.40 to -0.15)**	**-0.25 (-0.37 to -0.12)**	**-0.23 (-0.44 to -0.02)**	-0.17 (-0.74 to 0.40)	-0.10 (-0.24 to 0.05)	-0.05 (-0.24 to 0.13)	**Haloperidol**	-0.17 (-0.59 to 0.25)	NA
-1.01 (-1.79 to -0.24)	-0.59 (-1.19 to 0.01)	-0.37 (-0.80 to 0.06)	-0.35 (-0.73 to 0.02)	-0.32 (-0.70 to 0.05)	-0.31 (-0.72 to 0.10)	-0.25 (-0.92 to 0.43)	-0.17 (-0.55 to 0.21)	-0.13 (-0.52 to 0.26)	-0.08 (-0.44 to 0.28)	**Fluphenazine**	NA
-1.16 (-1.90 to -0.42)	**-0.74 (-1.28 to -0.19)**	**-0.52 (-0.88 to -0.16)**	**-0.50 (-0.78 to -0.22)**	**-0.47 (-0.75 to -0.19)**	**-0.46 (-0.80 to -0.12)**	-0.39 (-1.02 to 0.23)	**-0.32 (-0.57 to -0.07)**	-0.28 (-0.60 to 0.05)	-0.23 (-0.51 to 0.06)	-0.15 (-0.60 to 0.30)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.2 Excluding studies that included intolerant patients

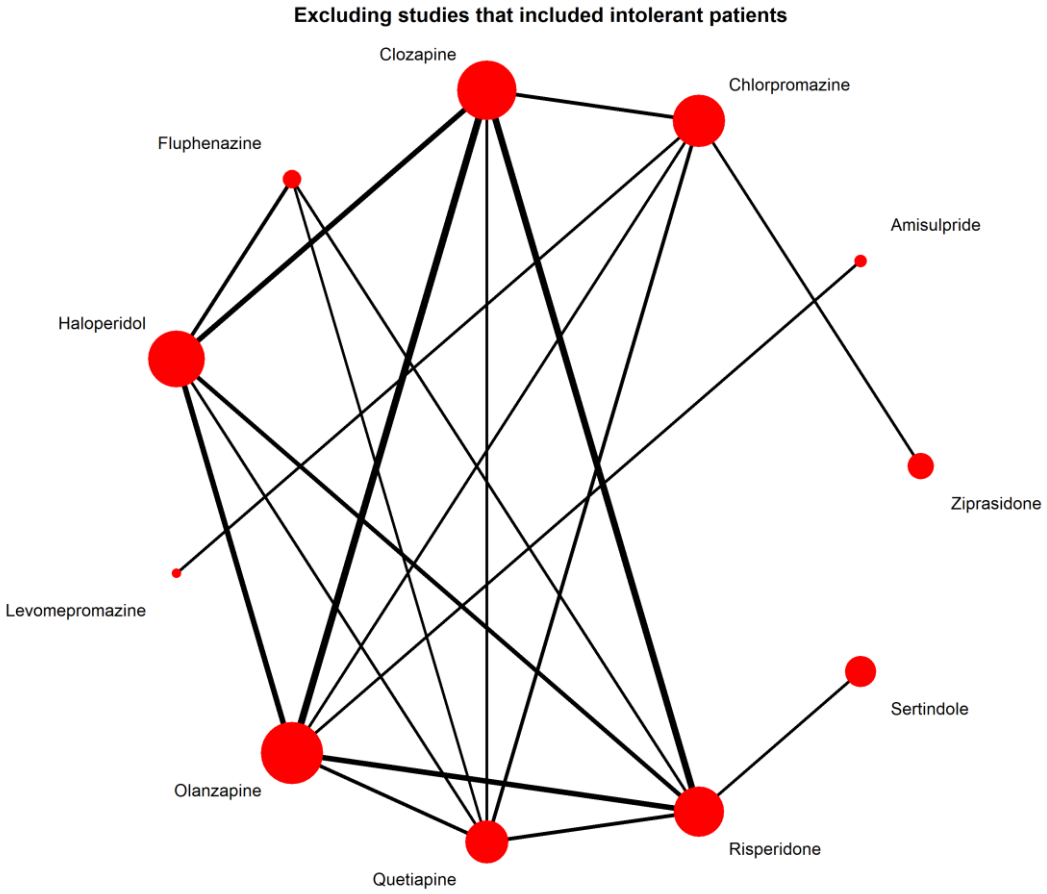
Number of studies: k = 35

Number of pairwise comparisons: m = 47

Number of treatments: n = 11

Number of designs: d = 19

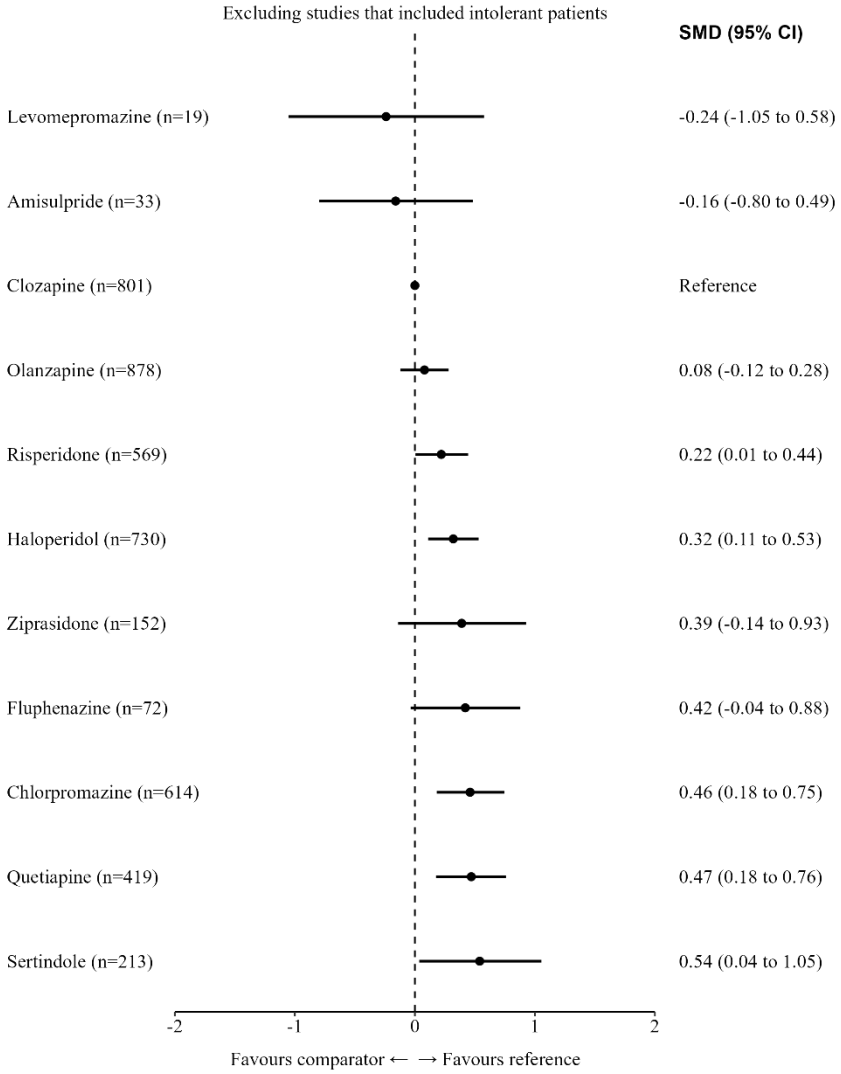
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.2007	0.0002	18.75

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Levomepromazine	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.47 to 0.06)	NA	NA
-0.08 (-1.10 to 0.94)	**Amisulpride**	NA	-0.24 (-0.85 to 0.37)	NA	NA	NA	NA	NA	NA	NA
-0.24 (-1.05 to 0.58)	-0.16 (-0.80 to 0.49)	**Clozapine**	-0.01 (-0.28 to 0.26)	-0.14 (-0.42 to 0.13)	-0.13 (-0.42 to 0.15)	NA	NA	**-0.85 (-1.24 to -0.45)**	**-1.01 (-1.90 to -0.12)**	NA
-0.32 (-1.14 to 0.50)	-0.24 (-0.85 to 0.37)	-0.08 (-0.28 to 0.12)	**Olanzapine**	-0.23 (-0.55 to 0.08)	-0.28 (-0.58 to 0.01)	NA	NA	-0.22 (-0.80 to 0.37)	-0.07 (-0.66 to 0.53)	NA
-0.46 (-1.29 to 0.37)	-0.38 (-1.03 to 0.27)	**-0.22 (-0.44 to -0.01)**	-0.14 (-0.37 to 0.09)	**Risperidone**	-0.15 (-0.56 to 0.27)	NA	0.02 (-0.84 to 0.89)	NA	-0.06 (-0.75 to 0.64)	-0.32 (-0.78 to 0.14)
-0.56 (-1.38 to 0.27)	-0.48 (-1.12 to 0.17)	**-0.32 (-0.53 to -0.11)**	**-0.24 (-0.46 to -0.03)**	-0.10 (-0.34 to 0.15)	**Haloperidol**	NA	-0.17 (-0.68 to 0.33)	NA	0.14 (-0.32 to 0.60)	NA
-0.63 (-1.52 to 0.26)	-0.55 (-1.36 to 0.27)	-0.39 (-0.93 to 0.14)	-0.31 (-0.85 to 0.23)	-0.17 (-0.73 to 0.39)	-0.07 (-0.62 to 0.47)	**Ziprasidone**	NA	-0.07 (-0.52 to 0.38)	NA	NA
-0.66 (-1.57 to 0.25)	-0.58 (-1.34 to 0.18)	-0.42 (-0.88 to 0.04)	-0.34 (-0.80 to 0.12)	-0.20 (-0.66 to 0.27)	-0.10 (-0.53 to 0.32)	-0.03 (-0.70 to 0.65)	**Fluphenazine**	NA	-0.15 (-1.02 to 0.73)	NA
-0.70 (-1.47 to 0.06)	-0.62 (-1.30 to 0.06)	**-0.46 (-0.75 to -0.18)**	**-0.38 (-0.68 to -0.09)**	-0.24 (-0.57 to 0.09)	-0.14 (-0.45 to 0.16)	-0.07 (-0.52 to 0.38)	-0.04 (-0.54 to 0.46)	**Chlorpromazine**	-0.22 (-0.55 to 0.12)	NA
-0.71 (-1.52 to 0.11)	-0.62 (-1.30 to 0.05)	**-0.47 (-0.76 to -0.18)**	**-0.39 (-0.68 to -0.09)**	-0.24 (-0.57 to 0.08)	-0.15 (-0.44 to 0.14)	-0.07 (-0.60 to 0.45)	-0.05 (-0.53 to 0.44)	-0.00 (-0.28 to 0.27)	**Quetiapine**	NA
-0.78 (-1.73 to 0.17)	-0.70 (-1.50 to 0.10)	**-0.54 (-1.05 to -0.04)**	-0.46 (-0.98 to 0.05)	-0.32 (-0.78 to 0.14)	-0.22 (-0.75 to 0.30)	-0.15 (-0.87 to 0.57)	-0.12 (-0.78 to 0.53)	-0.08 (-0.64 to 0.48)	-0.08 (-0.64 to 0.48)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.3 Double-blind studies only

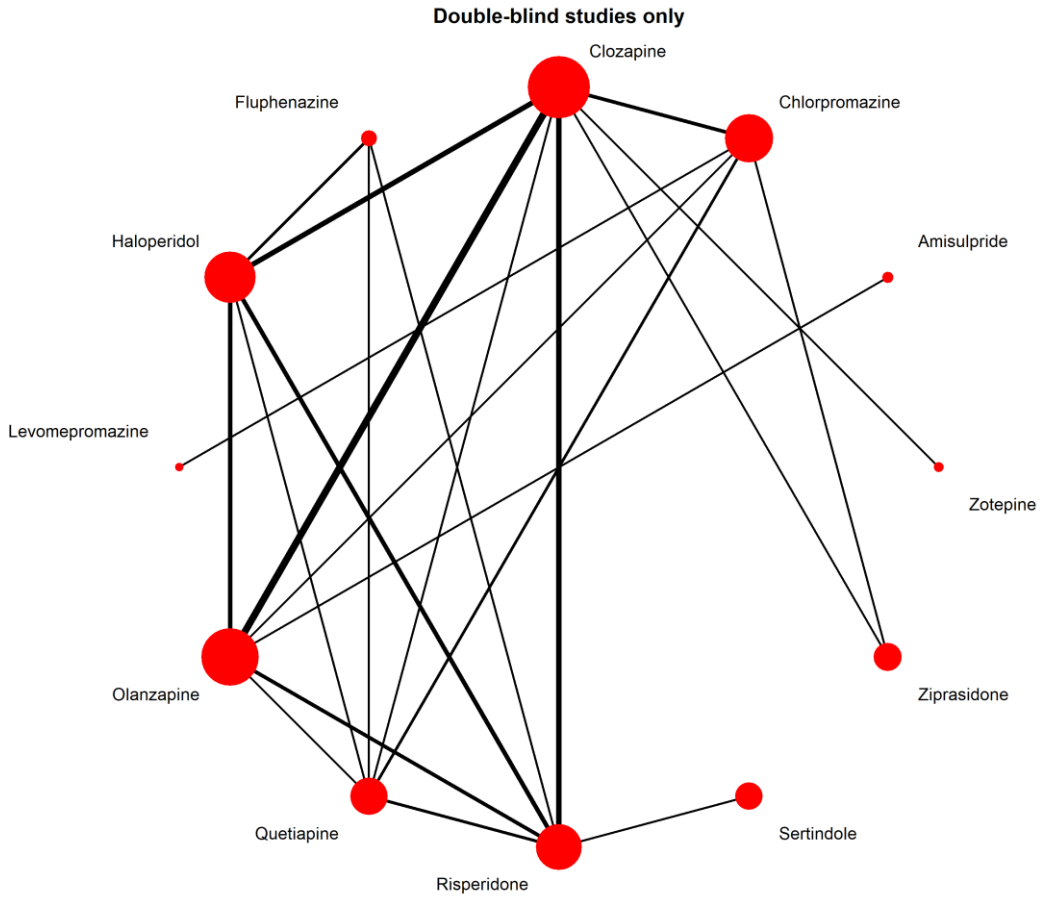
Number of studies: k = 41

Number of pairwise comparisons: m = 53

Number of treatments: n = 12

Number of designs: d = 20

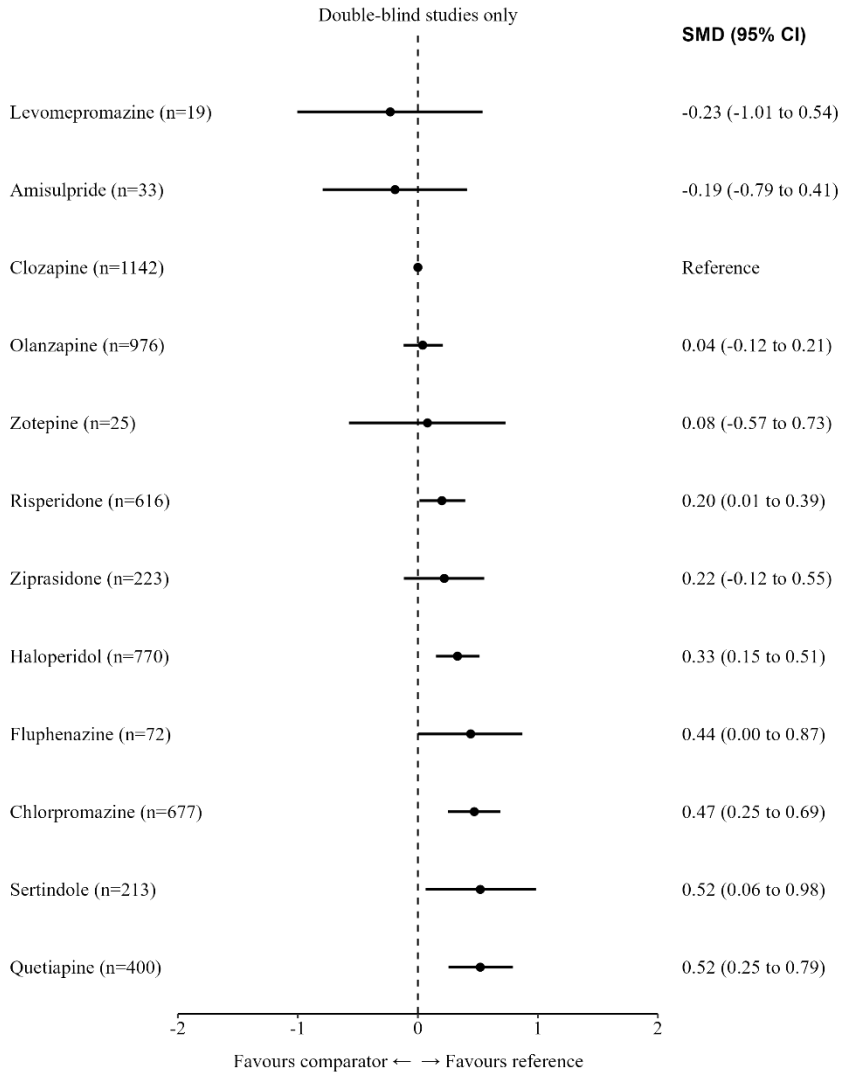
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1759	0.0001	16.67

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	NA	NA	-0.24 (-0.82 to 0.34)	NA	NA	NA	NA	NA	NA	NA	NA
0.04 (-0.93 to 1.01)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.44 to 0.04)	NA	NA
-0.19 (-0.79 to 0.41)	-0.23 (-1.01 to 0.54)	**Clozapine**	-0.01 (-0.21 to 0.19)	-0.08 (-0.73 to 0.57)	-0.13 (-0.37 to 0.11)	0.02 (-0.45 to 0.50)	-0.18 (-0.44 to 0.07)	NA	**-0.78 (-1.07 to -0.48)**	NA	**-1.01 (-1.88 to -0.14)**
-0.24 (-0.82 to 0.34)	-0.28 (-1.06 to 0.50)	-0.04 (-0.21 to 0.12)	**Olanzapine**	NA	-0.25 (-0.56 to 0.06)	NA	**-0.28 (-0.55 to -0.01)**	NA	-0.22 (-0.77 to 0.34)	NA	-0.38 (-1.37 to 0.62)
-0.27 (-1.16 to 0.62)	-0.31 (-1.32 to 0.70)	-0.08 (-0.73 to 0.57)	-0.03 (-0.71 to 0.64)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA
-0.40 (-1.01 to 0.22)	-0.44 (-1.23 to 0.35)	**-0.20 (-0.39 to -0.01)**	-0.16 (-0.37 to 0.05)	-0.13 (-0.81 to 0.55)	**Risperidone**	NA	-0.15 (-0.48 to 0.19)	0.02 (-0.82 to 0.86)	NA	-0.32 (-0.74 to 0.10)	-0.06 (-0.74 to 0.62)
-0.41 (-1.09 to 0.27)	-0.45 (-1.26 to 0.36)	-0.22 (-0.55 to 0.12)	-0.17 (-0.54 to 0.19)	-0.14 (-0.87 to 0.59)	-0.01 (-0.39 to 0.36)	**Ziprasidone**	NA	NA	-0.07 (-0.48 to 0.34)	NA	NA
-0.52 (-1.14 to 0.09)	-0.57 (-1.35 to 0.22)	**-0.33 (-0.51 to -0.15)**	**-0.29 (-0.48 to -0.09)**	-0.25 (-0.93 to 0.42)	-0.13 (-0.34 to 0.09)	-0.11 (-0.48 to 0.26)	**Haloperidol**	-0.17 (-0.66 to 0.31)	NA	NA	0.14 (-0.27 to 0.56)
-0.63 (-1.36 to 0.10)	-0.67 (-1.54 to 0.21)	-0.44 (-0.87 to 0.00)	-0.39 (-0.83 to 0.05)	-0.36 (-1.14 to 0.43)	-0.23 (-0.67 to 0.21)	-0.22 (-0.76 to 0.32)	-0.10 (-0.51 to 0.31)	**Fluphenazine**	NA	NA	-0.15 (-1.00 to 0.71)
-0.66 (-1.29 to -0.03)	-0.70 (-1.44 to 0.04)	**-0.47 (-0.69 to -0.25)**	**-0.42 (-0.67 to -0.18)**	-0.39 (-1.08 to 0.30)	-0.27 (-0.54 to 0.01)	-0.25 (-0.58 to 0.07)	-0.14 (-0.39 to 0.12)	-0.03 (-0.50 to 0.43)	**Chlorpromazine**	NA	-0.22 (-0.52 to 0.09)
-0.72 (-1.46 to 0.03)	-0.76 (-1.65 to 0.14)	**-0.52 (-0.98 to -0.06)**	**-0.48 (-0.95 to -0.01)**	-0.45 (-1.25 to 0.35)	-0.32 (-0.74 to 0.10)	-0.31 (-0.87 to 0.26)	-0.19 (-0.66 to 0.28)	-0.09 (-0.70 to 0.52)	-0.06 (-0.56 to 0.44)	**Sertindole**	NA
-0.72 (-1.36 to -0.07)	-0.76 (-1.54 to 0.02)	**-0.52 (-0.79 to -0.25)**	**-0.48 (-0.77 to -0.19)**	-0.45 (-1.15 to 0.26)	**-0.32 (-0.62 to -0.02)**	-0.31 (-0.69 to 0.08)	-0.19 (-0.46 to 0.08)	-0.09 (-0.55 to 0.38)	-0.05 (-0.30 to 0.19)	0.00 (-0.51 to 0.52)	**Quetiapine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available

11.4 Excluding studies that presented only completer analyses

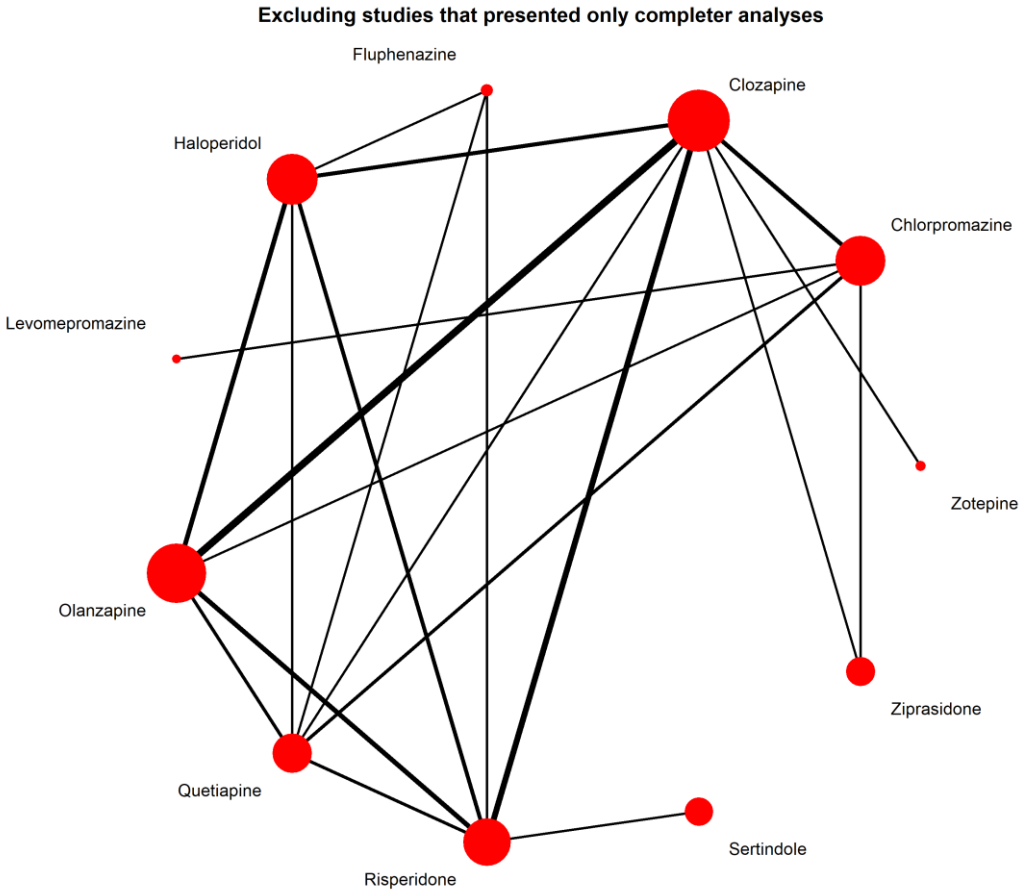
Number of studies: k = 37

Number of pairwise comparisons: m = 49

Number of treatments: n = 11

Number of designs: d = 20

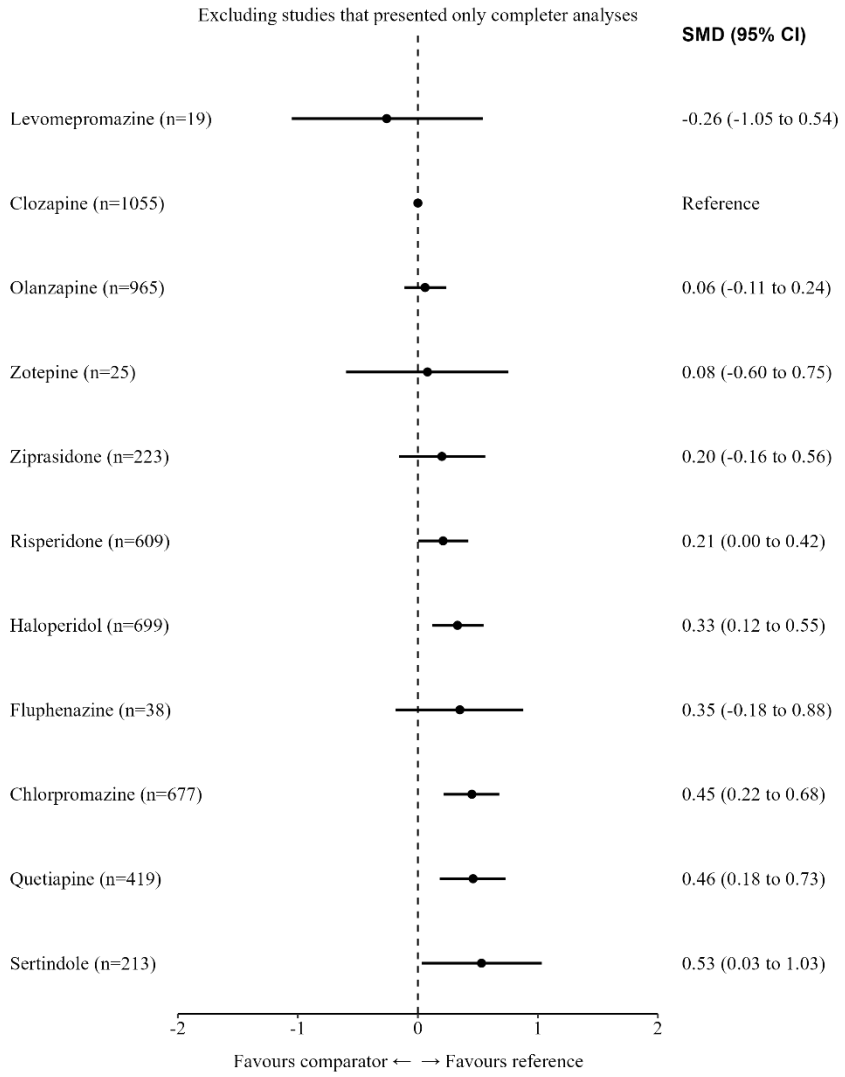
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1979	0.0007	11.11

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Levomepromazine	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.46 to 0.06)	NA	NA
-0.26 (-1.05 to 0.54)	**Clozapine**	-0.00 (-0.22 to 0.21)	-0.08 (-0.75 to 0.60)	0.02 (-0.48 to 0.53)	-0.10 (-0.36 to 0.17)	NA	-0.18 (-0.51 to 0.14)	**-0.77 (-1.09 to -0.46)**	**-1.01 (-1.89 to -0.13)**	NA
-0.32 (-1.12 to 0.49)	-0.06 (-0.24 to 0.11)	**Olanzapine**	NA	NA	-0.23 (-0.54 to 0.07)	NA	-0.28 (-0.57 to 0.01)	-0.22 (-0.80 to 0.37)	-0.07 (-0.66 to 0.52)	NA
-0.33 (-1.38 to 0.71)	-0.08 (-0.75 to 0.60)	-0.02 (-0.71 to 0.68)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA
-0.46 (-1.29 to 0.38)	-0.20 (-0.56 to 0.16)	-0.14 (-0.53 to 0.25)	-0.12 (-0.89 to 0.64)	**Ziprasidone**	NA	NA	NA	-0.07 (-0.52 to 0.38)	NA	NA
-0.47 (-1.28 to 0.35)	-0.21 (-0.42 to 0.00)	-0.15 (-0.37 to 0.07)	-0.13 (-0.84 to 0.57)	-0.01 (-0.42 to 0.40)	**Risperidone**	0.02 (-0.84 to 0.88)	-0.07 (-0.44 to 0.30)	NA	-0.06 (-0.75 to 0.64)	-0.32 (-0.78 to 0.13)
-0.60 (-1.54 to 0.34)	-0.35 (-0.88 to 0.18)	-0.28 (-0.82 to 0.25)	-0.27 (-1.13 to 0.59)	-0.15 (-0.78 to 0.48)	-0.13 (-0.67 to 0.40)	**Fluphenazine**	0.09 (-0.58 to 0.77)	NA	-0.15 (-1.02 to 0.73)	NA
-0.59 (-1.40 to 0.22)	**-0.33 (-0.55 to -0.12)**	**-0.27 (-0.48 to -0.06)**	-0.26 (-0.97 to 0.45)	-0.13 (-0.54 to 0.27)	-0.12 (-0.36 to 0.12)	0.01 (-0.50 to 0.52)	**Haloperidol**	NA	0.14 (-0.31 to 0.60)	NA
-0.70 (-1.46 to 0.06)	**-0.45 (-0.68 to -0.22)**	**-0.38 (-0.64 to -0.13)**	-0.37 (-1.08 to 0.35)	-0.25 (-0.60 to 0.11)	-0.23 (-0.53 to 0.06)	-0.10 (-0.66 to 0.46)	-0.11 (-0.40 to 0.17)	**Chlorpromazine**	-0.22 (-0.54 to 0.11)	NA
-0.71 (-1.52 to 0.09)	**-0.46 (-0.73 to -0.18)**	**-0.39 (-0.68 to -0.11)**	-0.38 (-1.11 to 0.35)	-0.26 (-0.67 to 0.16)	-0.24 (-0.55 to 0.06)	-0.11 (-0.65 to 0.43)	-0.12 (-0.41 to 0.16)	-0.01 (-0.27 to 0.25)	**Quetiapine**	NA
-0.79 (-1.72 to 0.15)	**-0.53 (-1.03 to -0.03)**	-0.47 (-0.97 to 0.03)	-0.45 (-1.30 to 0.39)	-0.33 (-0.94 to 0.28)	-0.32 (-0.78 to 0.13)	-0.19 (-0.89 to 0.51)	-0.20 (-0.71 to 0.32)	-0.09 (-0.63 to 0.45)	-0.08 (-0.62 to 0.47)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.5 Excluding studies that did not use operationalized criteria to diagnose schizophrenia

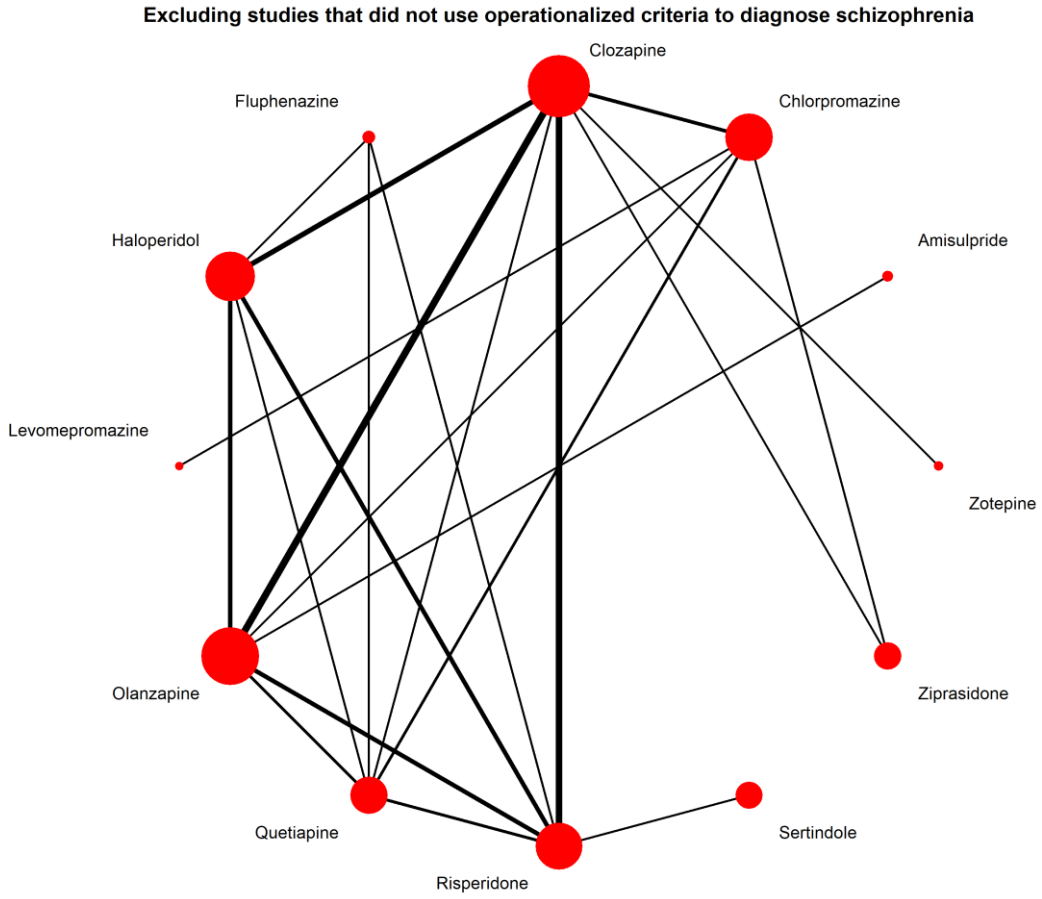
Number of studies: k = 44

Number of pairwise comparisons: m = 56

Number of treatments: n = 12

Number of designs: d = 21

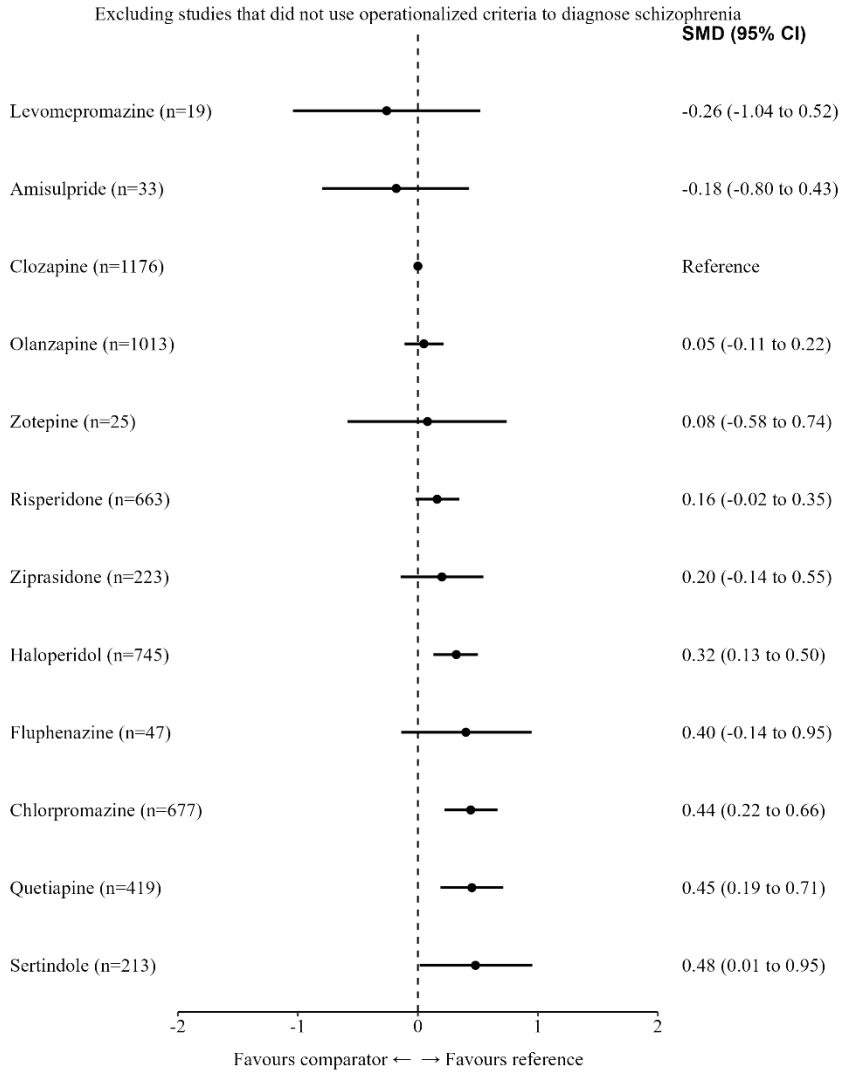
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1848	< 0.0001	11.11

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Levomepromazine	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.45 to 0.05)	NA
-0.08 (-1.06 to 0.91)	**Amisulpride**	NA	-0.24 (-0.83 to 0.35)	NA	NA	NA	NA	NA	NA	NA	NA
-0.26 (-1.04 to 0.52)	-0.18 (-0.80 to 0.43)	**Clozapine**	-0.01 (-0.22 to 0.19)	-0.08 (-0.74 to 0.58)	-0.08 (-0.30 to 0.15)	0.02 (-0.47 to 0.51)	-0.18 (-0.45 to 0.08)	NA	NA	**-0.78 (-1.08 to -0.47)**	**-1.01 (-1.88 to -0.14)**
-0.31 (-1.10 to 0.48)	-0.24 (-0.83 to 0.35)	-0.05 (-0.22 to 0.11)	**Olanzapine**	NA	-0.23 (-0.53 to 0.06)	NA	-0.28 (-0.56 to 0.00)	NA	NA	-0.22 (-0.78 to 0.35)	-0.07 (-0.65 to 0.52)
-0.34 (-1.36 to 0.69)	-0.26 (-1.16 to 0.64)	-0.08 (-0.74 to 0.58)	-0.03 (-0.71 to 0.66)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA
-0.42 (-1.22 to 0.37)	-0.35 (-0.97 to 0.27)	-0.16 (-0.35 to 0.02)	-0.11 (-0.31 to 0.09)	-0.09 (-0.77 to 0.60)	**Risperidone**	NA	-0.15 (-0.49 to 0.19)	0.02 (-0.83 to 0.87)	-0.32 (-0.75 to 0.11)	NA	-0.06 (-0.74 to 0.63)
-0.46 (-1.28 to 0.36)	-0.39 (-1.08 to 0.31)	-0.20 (-0.55 to 0.14)	-0.15 (-0.52 to 0.22)	-0.12 (-0.87 to 0.62)	-0.04 (-0.42 to 0.35)	**Ziprasidone**	NA	NA	NA	-0.07 (-0.50 to 0.36)	NA
-0.58 (-1.37 to 0.22)	-0.50 (-1.12 to 0.12)	**-0.32 (-0.50 to -0.13)**	**-0.26 (-0.46 to -0.07)**	-0.24 (-0.92 to 0.45)	-0.15 (-0.37 to 0.06)	-0.11 (-0.49 to 0.27)	**Haloperidol**	-0.27 (-1.01 to 0.46)	NA	NA	0.14 (-0.29 to 0.57)
-0.67 (-1.60 to 0.27)	-0.59 (-1.39 to 0.22)	-0.40 (-0.95 to 0.14)	-0.35 (-0.90 to 0.19)	-0.33 (-1.18 to 0.53)	-0.24 (-0.79 to 0.30)	-0.20 (-0.84 to 0.43)	-0.09 (-0.62 to 0.44)	**Fluphenazine**	NA	NA	-0.15 (-1.01 to 0.72)
-0.74 (-1.65 to 0.16)	-0.67 (-1.43 to 0.09)	**-0.48 (-0.95 to -0.01)**	-0.43 (-0.91 to 0.05)	-0.41 (-1.22 to 0.41)	-0.32 (-0.75 to 0.11)	-0.28 (-0.86 to 0.30)	-0.17 (-0.65 to 0.31)	-0.08 (-0.77 to 0.62)	**Sertindole**	NA	NA
-0.70 (-1.45 to 0.05)	-0.63 (-1.27 to 0.01)	**-0.44 (-0.66 to -0.22)**	**-0.39 (-0.64 to -0.14)**	-0.36 (-1.06 to 0.33)	**-0.28 (-0.55 to -0.01)**	-0.24 (-0.58 to 0.09)	-0.13 (-0.39 to 0.14)	-0.04 (-0.60 to 0.53)	0.04 (-0.47 to 0.55)	**Chlorpromazine**	-0.22 (-0.53 to 0.10)
-0.71 (-1.50 to 0.08)	-0.63 (-1.28 to 0.01)	**-0.45 (-0.71 to -0.19)**	**-0.40 (-0.67 to -0.13)**	-0.37 (-1.08 to 0.34)	-0.29 (-0.58 to 0.00)	-0.25 (-0.64 to 0.15)	-0.13 (-0.40 to 0.13)	-0.04 (-0.60 to 0.51)	0.03 (-0.49 to 0.56)	-0.01 (-0.26 to 0.24)	**Quetiapine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.6 Excluding studies at high risk of bias

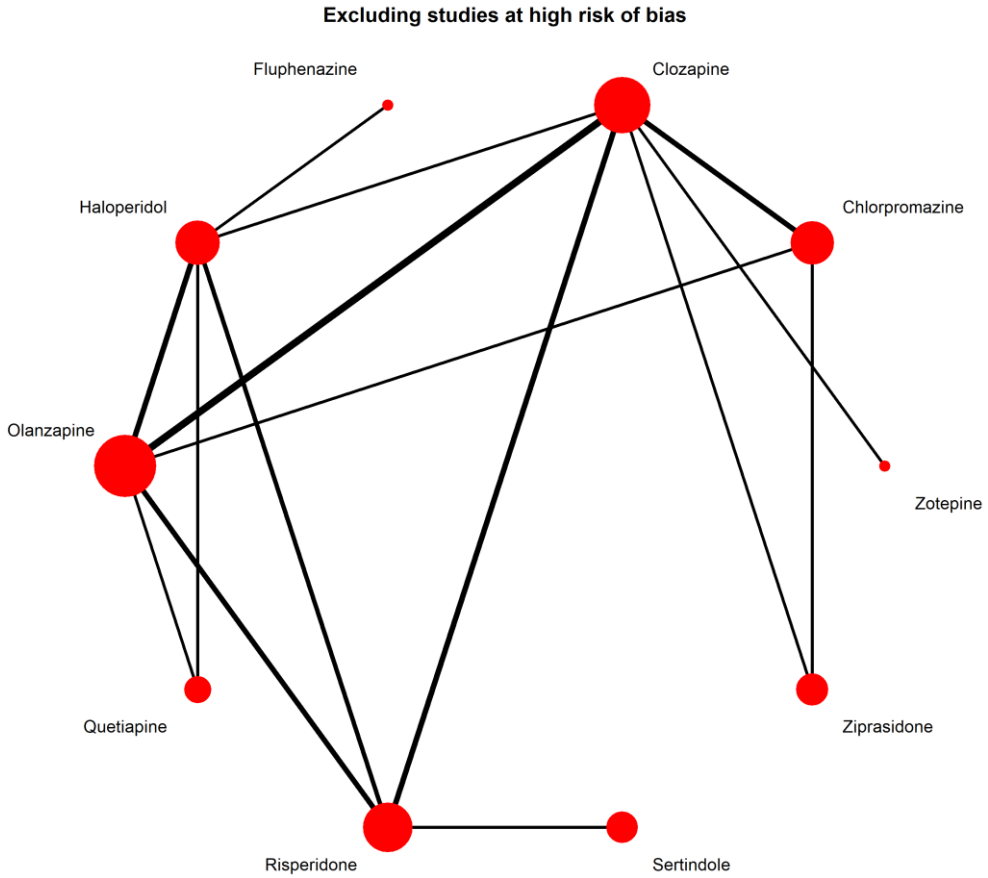
Number of studies: k = 23

Number of pairwise comparisons: m = 28

Number of treatments: n = 10

Number of designs: d = 15

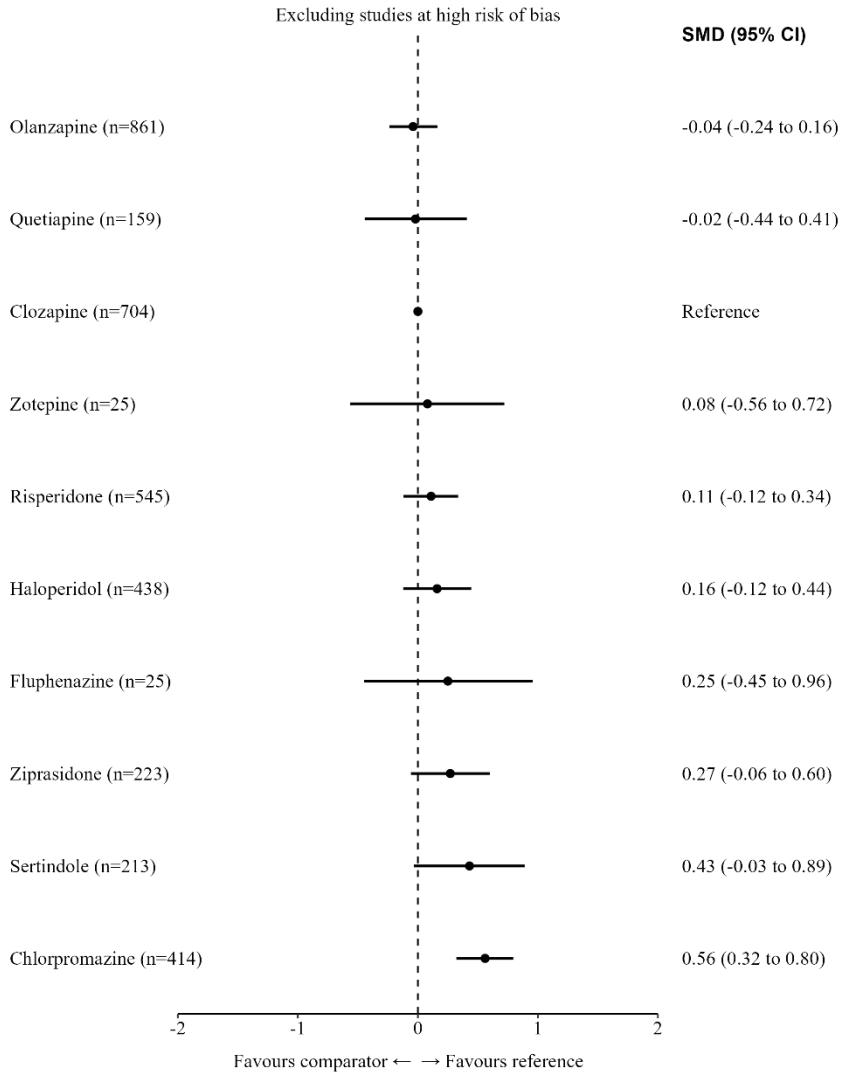
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1655	0.0093	25.0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Olanzapine	-0.11 (-0.36 to 0.14)	0.09 (-0.61 to 0.79)	NA	-0.22 (-0.51 to 0.07)	-0.24 (-0.51 to 0.04)	NA	NA	NA	-0.22 (-0.76 to 0.33)
-0.04 (-0.24 to 0.16)	**Clozapine**	NA	-0.08 (-0.72 to 0.56)	-0.04 (-0.32 to 0.24)	0.12 (-0.44 to 0.67)	NA	0.02 (-0.44 to 0.48)	NA	**-0.78 (-1.07 to -0.49)**
-0.02 (-0.41 to 0.37)	0.02 (-0.41 to 0.44)	**Quetiapine**	NA	NA	-0.14 (-0.54 to 0.26)	NA	NA	NA	NA
-0.11 (-0.79 to 0.56)	-0.08 (-0.72 to 0.56)	-0.10 (-0.87 to 0.67)	**Zotepine**	NA	NA	NA	NA	NA	NA
-0.14 (-0.37 to 0.08)	-0.11 (-0.34 to 0.12)	-0.13 (-0.55 to 0.30)	-0.03 (-0.71 to 0.65)	**Risperidone**	-0.14 (-0.55 to 0.27)	NA	NA	-0.32 (-0.72 to 0.08)	NA
-0.20 (-0.43 to 0.04)	-0.16 (-0.44 to 0.12)	-0.18 (-0.53 to 0.17)	-0.08 (-0.79 to 0.62)	-0.05 (-0.34 to 0.23)	**Haloperidol**	-0.09 (-0.74 to 0.55)	NA	NA	NA
-0.29 (-0.97 to 0.39)	-0.25 (-0.96 to 0.45)	-0.27 (-1.00 to 0.46)	-0.18 (-1.13 to 0.78)	-0.15 (-0.85 to 0.56)	-0.09 (-0.74 to 0.55)	**Fluphenazine**	NA	NA	NA
-0.31 (-0.68 to 0.07)	-0.27 (-0.60 to 0.06)	-0.29 (-0.82 to 0.24)	-0.19 (-0.92 to 0.53)	-0.16 (-0.56 to 0.23)	-0.11 (-0.54 to 0.32)	-0.02 (-0.79 to 0.75)	**Ziprasidone**	NA	-0.07 (-0.47 to 0.32)
-0.46 (-0.92 to 0.00)	-0.43 (-0.89 to 0.03)	-0.45 (-1.03 to 0.14)	-0.35 (-1.14 to 0.44)	-0.32 (-0.72 to 0.08)	-0.27 (-0.76 to 0.22)	-0.17 (-0.98 to 0.63)	-0.16 (-0.72 to 0.41)	**Sertindole**	NA
-0.59 (-0.88 to -0.31)	**-0.56 (-0.80 to -0.32)**	**-0.58 (-1.05 to -0.10)**	-0.48 (-1.16 to 0.21)	**-0.45 (-0.77 to -0.13)**	**-0.40 (-0.75 to -0.04)**	-0.30 (-1.04 to 0.43)	-0.29 (-0.60 to 0.03)	-0.13 (-0.64 to 0.38)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.7 Excluding studies that only included children and/or adolescents

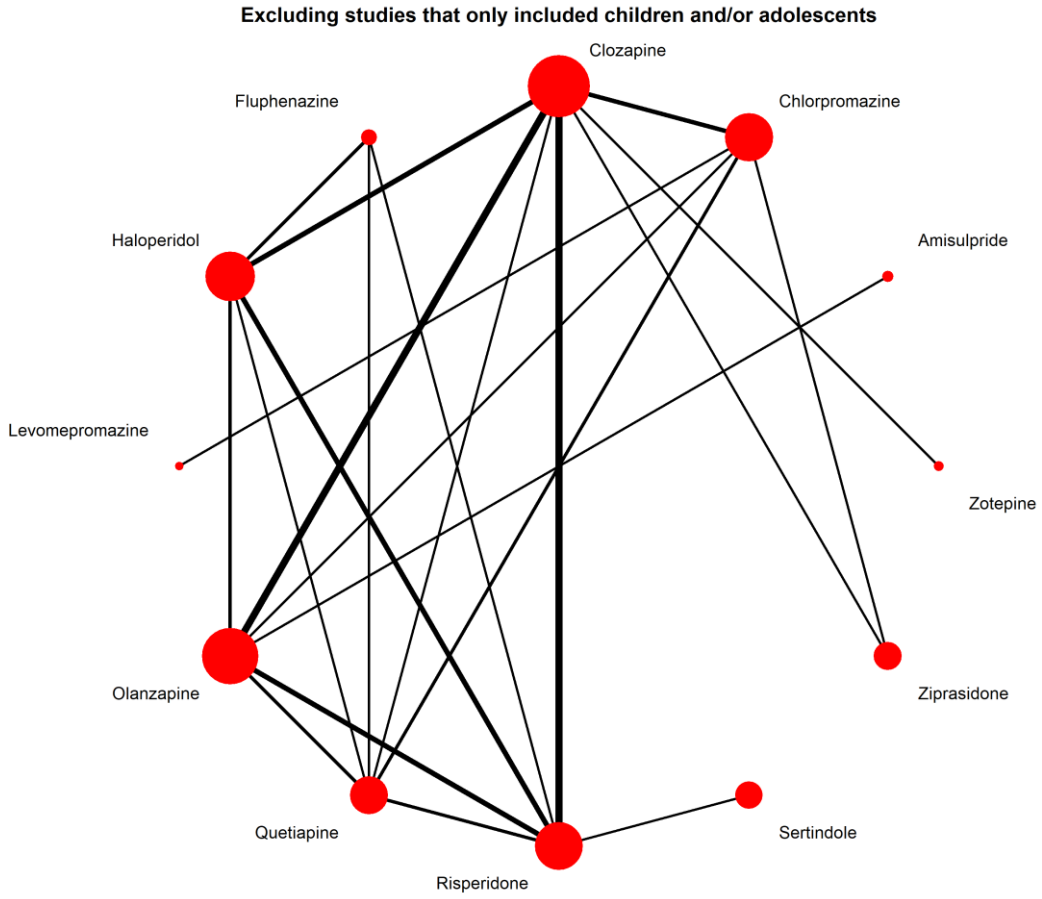
Number of studies: k = 40

Number of pairwise comparisons: m = 52

Number of treatments: n = 12

Number of designs: d = 21

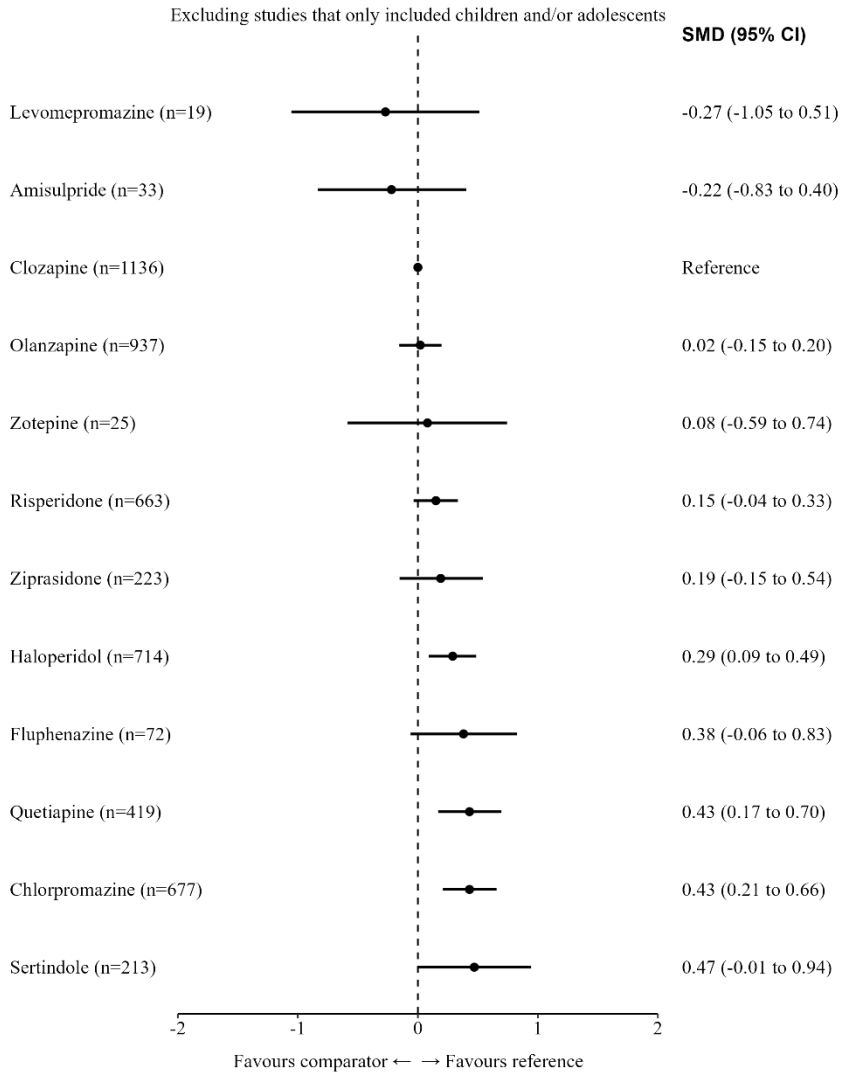
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1874	< 0.0001	16.67

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	NA	NA	-0.24 (-0.83 to 0.36)	NA	NA	NA	NA	NA	NA	NA	NA
0.05 (-0.94 to 1.04)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.45 to 0.05)
-0.22 (-0.83 to 0.40)	-0.27 (-1.05 to 0.51)	**Clozapine**	0.03 (-0.19 to 0.25)	-0.08 (-0.74 to 0.59)	-0.08 (-0.30 to 0.15)	0.02 (-0.47 to 0.51)	-0.13 (-0.41 to 0.14)	NA	NA	**-1.01 (-1.89 to -0.13)**	**-0.78 (-1.08 to -0.47)**
-0.24 (-0.83 to 0.36)	-0.29 (-1.08 to 0.50)	-0.02 (-0.20 to 0.15)	**Olanzapine**	NA	-0.23 (-0.53 to 0.06)	NA	-0.30 (-0.64 to 0.04)	NA	NA	-0.07 (-0.65 to 0.52)	-0.22 (-0.79 to 0.36)
-0.29 (-1.20 to 0.61)	-0.35 (-1.38 to 0.68)	-0.08 (-0.74 to 0.59)	-0.06 (-0.75 to 0.63)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA
-0.36 (-0.99 to 0.26)	-0.42 (-1.22 to 0.38)	-0.15 (-0.33 to 0.04)	-0.13 (-0.34 to 0.08)	-0.07 (-0.76 to 0.62)	**Risperidone**	NA	-0.15 (-0.49 to 0.19)	0.02 (-0.83 to 0.87)	-0.32 (-0.76 to 0.12)	-0.06 (-0.74 to 0.63)	NA
-0.41 (-1.11 to 0.29)	-0.47 (-1.29 to 0.36)	-0.19 (-0.54 to 0.15)	-0.17 (-0.55 to 0.20)	-0.12 (-0.87 to 0.63)	-0.05 (-0.43 to 0.34)	**Ziprasidone**	NA	NA	NA	NA	-0.07 (-0.50 to 0.36)
-0.50 (-1.14 to 0.13)	-0.56 (-1.36 to 0.24)	**-0.29 (-0.49 to -0.09)**	**-0.27 (-0.48 to -0.05)**	-0.21 (-0.90 to 0.48)	-0.14 (-0.36 to 0.08)	-0.09 (-0.48 to 0.29)	**Haloperidol**	-0.17 (-0.67 to 0.32)	NA	0.14 (-0.29 to 0.58)	NA
-0.60 (-1.34 to 0.15)	-0.65 (-1.54 to 0.24)	-0.38 (-0.83 to 0.06)	-0.36 (-0.81 to 0.09)	-0.30 (-1.10 to 0.50)	-0.23 (-0.68 to 0.21)	-0.19 (-0.74 to 0.37)	-0.09 (-0.51 to 0.32)	**Fluphenazine**	NA	-0.15 (-1.01 to 0.72)	NA
-0.69 (-1.45 to 0.08)	-0.74 (-1.65 to 0.17)	-0.47 (-0.94 to 0.01)	-0.45 (-0.93 to 0.04)	-0.39 (-1.21 to 0.43)	-0.32 (-0.76 to 0.12)	-0.27 (-0.86 to 0.31)	-0.18 (-0.67 to 0.31)	-0.09 (-0.71 to 0.54)	**Sertindole**	NA	NA
-0.65 (-1.30 to 0.01)	-0.70 (-1.50 to 0.09)	**-0.43 (-0.70 to -0.17)**	**-0.41 (-0.69 to -0.13)**	-0.35 (-1.07 to 0.36)	-0.28 (-0.58 to 0.01)	-0.24 (-0.64 to 0.16)	-0.14 (-0.42 to 0.13)	-0.05 (-0.52 to 0.42)	0.04 (-0.49 to 0.56)	**Quetiapine**	0.22 (-0.10 to 0.53)
-0.65 (-1.29 to 0.00)	-0.70 (-1.45 to 0.05)	**-0.43 (-0.66 to -0.21)**	**-0.41 (-0.67 to -0.16)**	-0.35 (-1.06 to 0.35)	**-0.28 (-0.56 to -0.01)**	-0.24 (-0.58 to 0.10)	-0.14 (-0.41 to 0.13)	-0.05 (-0.52 to 0.43)	0.04 (-0.48 to 0.55)	0.00 (-0.25 to 0.25)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.8 Excluding low clozapine doses (<400 mg)

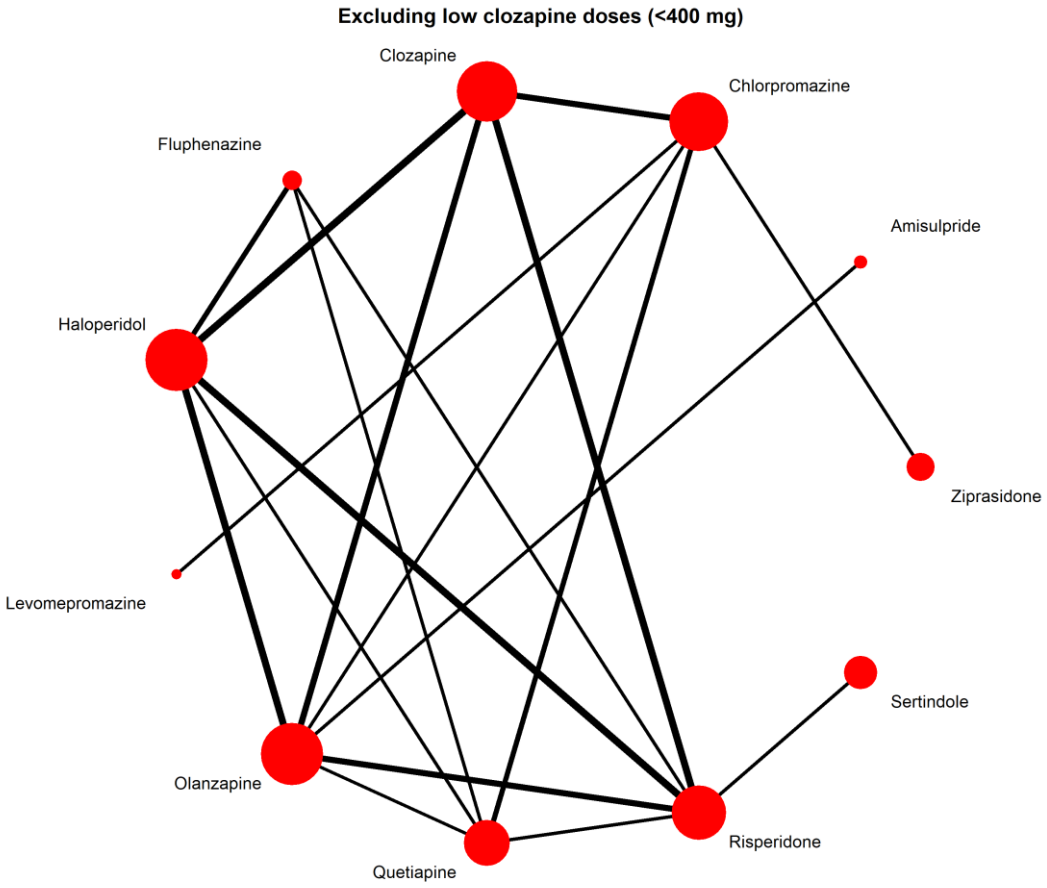
Number of studies: k = 32

Number of pairwise comparisons: m = 39

Number of treatments: n = 11

Number of designs: d = 18

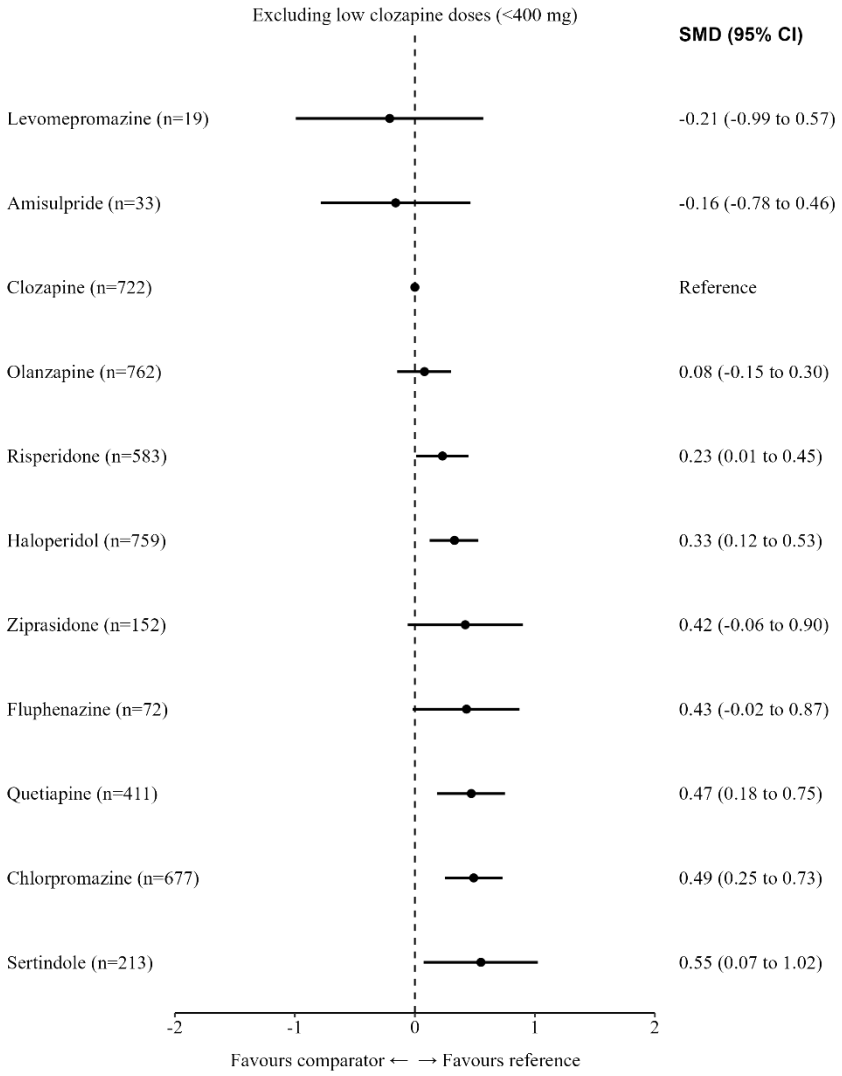
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1786	0.0003	26.67

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	NA	NA	-0.24 (-0.82 to 0.35)	NA	NA	NA	NA	NA	NA	NA
0.05 (-0.93 to 1.03)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.45 to 0.04)	NA
-0.16 (-0.78 to 0.46)	-0.21 (-0.99 to 0.57)	**Clozapine**	0.15 (-0.22 to 0.53)	-0.13 (-0.41 to 0.15)	-0.14 (-0.40 to 0.13)	NA	NA	NA	**-0.78 (-1.07 to -0.48)**	NA
-0.24 (-0.82 to 0.35)	-0.29 (-1.08 to 0.50)	-0.08 (-0.30 to 0.15)	**Olanzapine**	-0.22 (-0.52 to 0.09)	**-0.28 (-0.55 to -0.01)**	NA	NA	0.09 (-0.62 to 0.81)	-0.22 (-0.78 to 0.34)	NA
-0.39 (-1.01 to 0.24)	-0.44 (-1.24 to 0.36)	**-0.23 (-0.45 to -0.01)**	-0.15 (-0.38 to 0.07)	**Risperidone**	-0.15 (-0.48 to 0.19)	NA	0.02 (-0.82 to 0.87)	-0.12 (-0.98 to 0.74)	NA	-0.32 (-0.74 to 0.10)
-0.49 (-1.10 to 0.13)	-0.54 (-1.33 to 0.25)	**-0.33 (-0.53 to -0.12)**	**-0.25 (-0.46 to -0.04)**	-0.10 (-0.32 to 0.13)	**Haloperidol**	NA	-0.17 (-0.66 to 0.31)	0.14 (-0.28 to 0.56)	NA	NA
-0.58 (-1.35 to 0.19)	-0.63 (-1.48 to 0.22)	-0.42 (-0.90 to 0.06)	-0.34 (-0.84 to 0.16)	-0.19 (-0.70 to 0.32)	-0.09 (-0.59 to 0.40)	**Ziprasidone**	NA	NA	-0.07 (-0.49 to 0.34)	NA
-0.59 (-1.32 to 0.15)	-0.64 (-1.52 to 0.24)	-0.43 (-0.87 to 0.02)	-0.35 (-0.80 to 0.10)	-0.20 (-0.64 to 0.25)	-0.10 (-0.51 to 0.31)	-0.01 (-0.64 to 0.62)	**Fluphenazine**	-0.15 (-1.01 to 0.71)	NA	NA
-0.63 (-1.28 to 0.02)	-0.68 (-1.46 to 0.11)	**-0.47 (-0.75 to -0.18)**	**-0.39 (-0.68 to -0.10)**	-0.24 (-0.55 to 0.07)	-0.14 (-0.42 to 0.13)	-0.05 (-0.53 to 0.44)	-0.04 (-0.51 to 0.43)	**Quetiapine**	0.22 (-0.09 to 0.52)	NA
-0.65 (-1.30 to -0.01)	-0.70 (-1.45 to 0.04)	**-0.49 (-0.73 to -0.25)**	**-0.41 (-0.69 to -0.14)**	-0.26 (-0.56 to 0.03)	-0.17 (-0.44 to 0.10)	-0.07 (-0.49 to 0.34)	-0.06 (-0.54 to 0.41)	-0.02 (-0.28 to 0.23)	**Chlorpromazine**	NA
-0.71 (-1.46 to 0.05)	-0.76 (-1.66 to 0.14)	**-0.55 (-1.02 to -0.07)**	-0.47 (-0.95 to 0.01)	-0.32 (-0.74 to 0.10)	-0.22 (-0.70 to 0.25)	-0.13 (-0.79 to 0.53)	-0.12 (-0.74 to 0.49)	-0.08 (-0.61 to 0.44)	-0.06 (-0.57 to 0.46)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.9 Excluding studies from clozapine's manufacturer

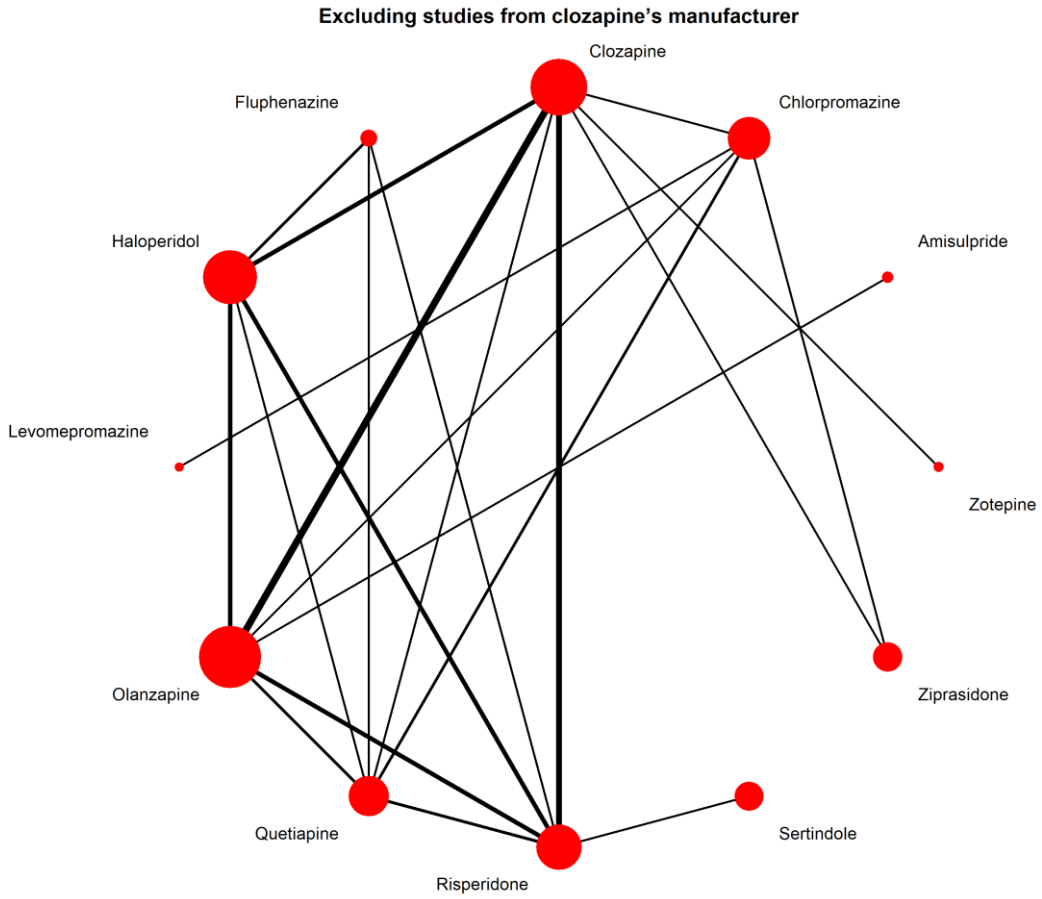
Number of studies: k = 41

Number of pairwise comparisons: m = 53

Number of treatments: n = 12

Number of designs: d = 21

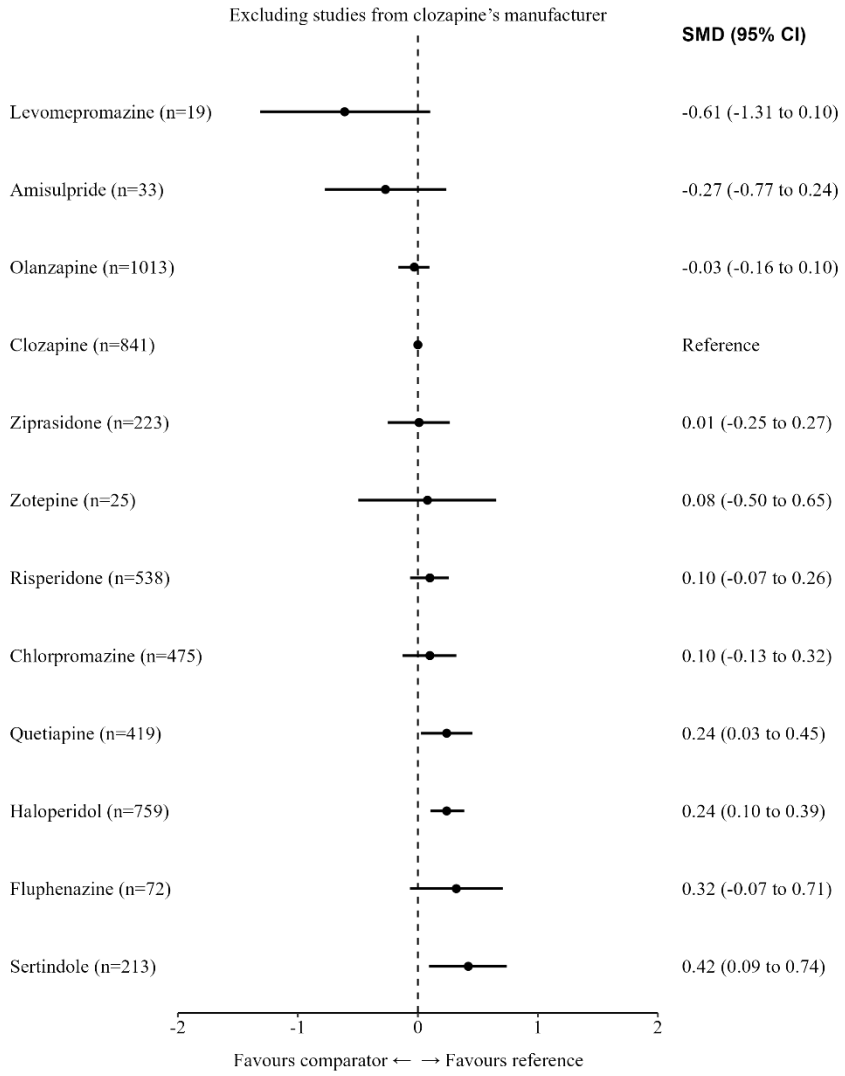
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.0768	**0.0804**	**16.67**

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Levomepromazine	NA	NA	NA	NA	NA	**-0.70 (-1.37 to -0.03)**	NA	NA	NA	NA	NA
-0.34 (-1.20 to 0.52)	**Amisulpride**	-0.24 (-0.73 to 0.25)	NA	NA	NA	NA	NA	NA	NA	NA	NA
-0.57 (-1.28 to 0.14)	-0.24 (-0.73 to 0.25)	**Olanzapine**	-0.02 (-0.19 to 0.14)	NA	NA	-0.22 (-0.68 to 0.25)	**-0.23 (-0.44 to -0.02)**	-0.05 (-0.58 to 0.48)	**-0.27 (-0.46 to -0.08)**	NA	NA
-0.61 (-1.31 to 0.10)	-0.27 (-0.77 to 0.24)	-0.03 (-0.16 to 0.10)	**Clozapine**	0.02 (-0.34 to 0.38)	-0.08 (-0.65 to 0.50)	**-0.76 (-1.42 to -0.10)**	0.04 (-0.19 to 0.26)	**-1.01 (-1.82 to -0.20)**	-0.18 (-0.37 to 0.01)	NA	NA
-0.61 (-1.32 to 0.10)	-0.28 (-0.84 to 0.28)	-0.04 (-0.31 to 0.23)	-0.01 (-0.27 to 0.25)	**Ziprasidone**	NA	-0.07 (-0.34 to 0.20)	NA	NA	NA	NA	NA
-0.68 (-1.60 to 0.23)	-0.35 (-1.11 to 0.42)	-0.11 (-0.70 to 0.48)	-0.08 (-0.65 to 0.50)	-0.07 (-0.70 to 0.56)	**Zotepine**	NA	NA	NA	NA	NA	NA
-0.70 (-1.37 to -0.03)	-0.37 (-0.90 to 0.17)	-0.13 (-0.36 to 0.10)	-0.10 (-0.32 to 0.13)	-0.09 (-0.32 to 0.14)	-0.02 (-0.64 to 0.60)	**Chlorpromazine**	NA	**-0.22 (-0.42 to -0.01)**	NA	NA	NA
-0.70 (-1.42 to 0.02)	-0.37 (-0.88 to 0.15)	-0.13 (-0.29 to 0.03)	-0.10 (-0.26 to 0.07)	-0.09 (-0.38 to 0.20)	-0.02 (-0.62 to 0.58)	-0.00 (-0.25 to 0.25)	**Risperidone**	-0.06 (-0.70 to 0.58)	-0.14 (-0.43 to 0.15)	0.02 (-0.76 to 0.81)	**-0.32 (-0.60 to -0.04)**
-0.85 (-1.54 to -0.15)	-0.51 (-1.04 to 0.02)	**-0.27 (-0.49 to -0.06)**	**-0.24 (-0.45 to -0.03)**	-0.23 (-0.50 to 0.04)	-0.16 (-0.78 to 0.45)	-0.14 (-0.33 to 0.04)	-0.14 (-0.38 to 0.09)	**Quetiapine**	-0.14 (-0.42 to 0.14)	0.15 (-0.65 to 0.95)	NA
-0.85 (-1.56 to -0.14)	**-0.51 (-1.02 to -0.01)**	**-0.28 (-0.42 to -0.14)**	**-0.24 (-0.39 to -0.10)**	-0.24 (-0.51 to 0.04)	-0.17 (-0.76 to 0.42)	-0.15 (-0.38 to 0.08)	-0.15 (-0.32 to 0.02)	-0.00 (-0.21 to 0.20)	**Haloperidol**	-0.17 (-0.60 to 0.26)	NA
-0.93 (-1.72 to -0.13)	-0.59 (-1.21 to 0.03)	-0.35 (-0.74 to 0.03)	-0.32 (-0.71 to 0.07)	-0.31 (-0.76 to 0.14)	-0.24 (-0.94 to 0.45)	-0.22 (-0.64 to 0.20)	-0.22 (-0.62 to 0.17)	-0.08 (-0.48 to 0.32)	-0.08 (-0.44 to 0.29)	**Fluphenazine**	NA
-1.02 (-1.79 to -0.25)	**-0.69 (-1.27 to -0.10)**	**-0.45 (-0.77 to -0.13)**	**-0.42 (-0.74 to -0.09)**	-0.41 (-0.81 to 0.00)	-0.34 (-1.00 to 0.32)	-0.32 (-0.70 to 0.06)	**-0.32 (-0.60 to -0.04)**	-0.18 (-0.55 to 0.19)	-0.17 (-0.50 to 0.16)	-0.10 (-0.58 to 0.39)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.10 Excluding studies from olanzapine's manufacturer

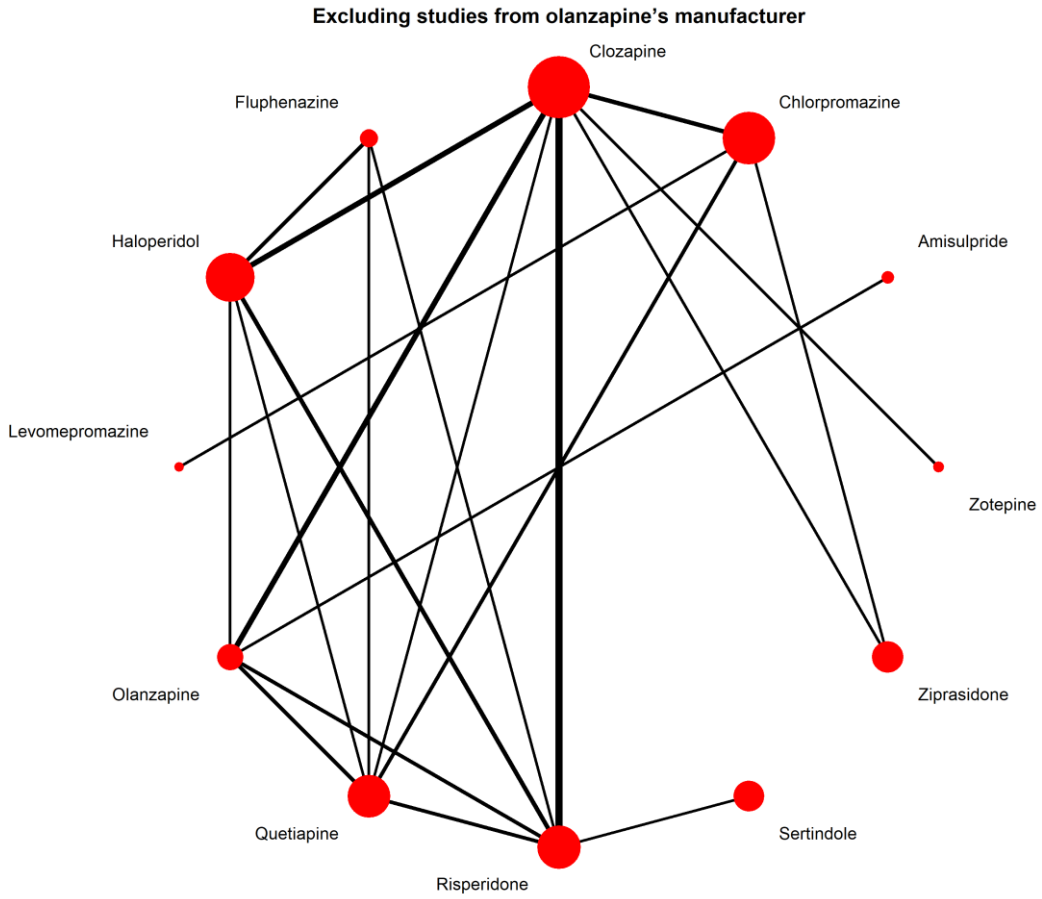
Number of studies: k = 35

Number of pairwise comparisons: m = 42

Number of treatments: n = 12

Number of designs: d = 19

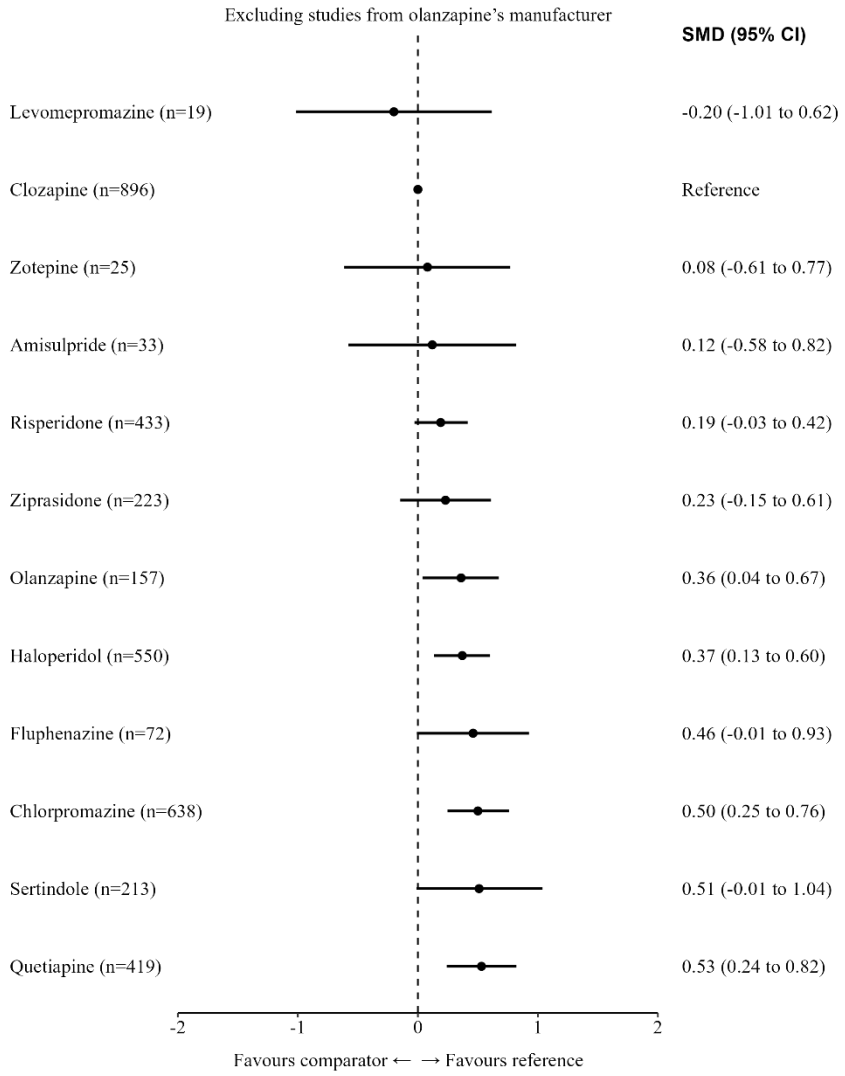
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.2106	0.0004	11.76

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Levomepromazine	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.48 to 0.07)	NA
-0.20 (-1.01 to 0.62)	**Clozapine**	-0.08 (-0.77 to 0.61)	NA	-0.13 (-0.40 to 0.13)	0.02 (-0.50 to 0.55)	-0.43 (-0.88 to 0.01)	-0.27 (-0.58 to 0.05)	NA	NA	**-0.77 (-1.10 to -0.45)**	**-1.01 (-1.91 to -0.11)**
-0.28 (-1.35 to 0.79)	-0.08 (-0.77 to 0.61)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA	NA	NA
-0.32 (-1.38 to 0.75)	-0.12 (-0.82 to 0.58)	-0.04 (-1.03 to 0.94)	**Amisulpride**	NA	NA	-0.24 (-0.86 to 0.39)	NA	NA	NA	NA	NA
-0.39 (-1.23 to 0.45)	-0.19 (-0.42 to 0.03)	-0.12 (-0.84 to 0.61)	-0.07 (-0.79 to 0.64)	**Risperidone**	NA	0.25 (-0.40 to 0.90)	-0.17 (-0.61 to 0.27)	0.02 (-0.85 to 0.89)	-0.32 (-0.80 to 0.16)	NA	-0.05 (-0.75 to 0.64)
-0.43 (-1.29 to 0.43)	-0.23 (-0.61 to 0.15)	-0.15 (-0.94 to 0.64)	-0.11 (-0.90 to 0.68)	-0.04 (-0.47 to 0.39)	**Ziprasidone**	NA	NA	NA	NA	-0.07 (-0.54 to 0.40)	NA
-0.56 (-1.42 to 0.31)	**-0.36 (-0.67 to -0.04)**	-0.28 (-1.04 to 0.48)	-0.24 (-0.86 to 0.39)	-0.16 (-0.51 to 0.19)	-0.13 (-0.61 to 0.36)	**Olanzapine**	-0.02 (-0.66 to 0.63)	NA	NA	NA	-0.07 (-0.67 to 0.53)
-0.57 (-1.40 to 0.27)	**-0.37 (-0.60 to -0.13)**	-0.29 (-1.02 to 0.44)	-0.25 (-0.96 to 0.46)	-0.17 (-0.44 to 0.09)	-0.14 (-0.57 to 0.29)	-0.01 (-0.35 to 0.33)	**Haloperidol**	-0.17 (-0.69 to 0.34)	NA	NA	0.14 (-0.33 to 0.62)
-0.66 (-1.58 to 0.27)	-0.46 (-0.93 to 0.01)	-0.38 (-1.22 to 0.45)	-0.34 (-1.16 to 0.48)	-0.27 (-0.74 to 0.21)	-0.23 (-0.82 to 0.36)	-0.10 (-0.63 to 0.43)	-0.09 (-0.52 to 0.34)	**Fluphenazine**	NA	NA	-0.15 (-1.03 to 0.74)
-0.71 (-1.68 to 0.25)	-0.51 (-1.04 to 0.01)	-0.44 (-1.30 to 0.43)	-0.39 (-1.25 to 0.46)	-0.32 (-0.80 to 0.16)	-0.28 (-0.93 to 0.36)	-0.16 (-0.75 to 0.43)	-0.15 (-0.69 to 0.40)	-0.06 (-0.73 to 0.62)	**Sertindole**	NA	NA
-0.70 (-1.48 to 0.07)	**-0.50 (-0.76 to -0.25)**	-0.43 (-1.16 to 0.31)	-0.38 (-1.11 to 0.35)	-0.31 (-0.63 to 0.01)	-0.27 (-0.64 to 0.10)	-0.15 (-0.53 to 0.24)	-0.14 (-0.45 to 0.18)	-0.04 (-0.55 to 0.46)	0.01 (-0.57 to 0.59)	**Chlorpromazine**	-0.22 (-0.56 to 0.13)
-0.73 (-1.55 to 0.09)	**-0.53 (-0.82 to -0.24)**	-0.45 (-1.20 to 0.30)	-0.41 (-1.13 to 0.31)	**-0.34 (-0.67 to -0.01)**	-0.30 (-0.73 to 0.13)	-0.17 (-0.55 to 0.20)	-0.16 (-0.46 to 0.14)	-0.07 (-0.56 to 0.42)	-0.02 (-0.60 to 0.56)	-0.03 (-0.31 to 0.25)	**Quetiapine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.11 Excluding off-label dose olanzapine (>20mg/d)

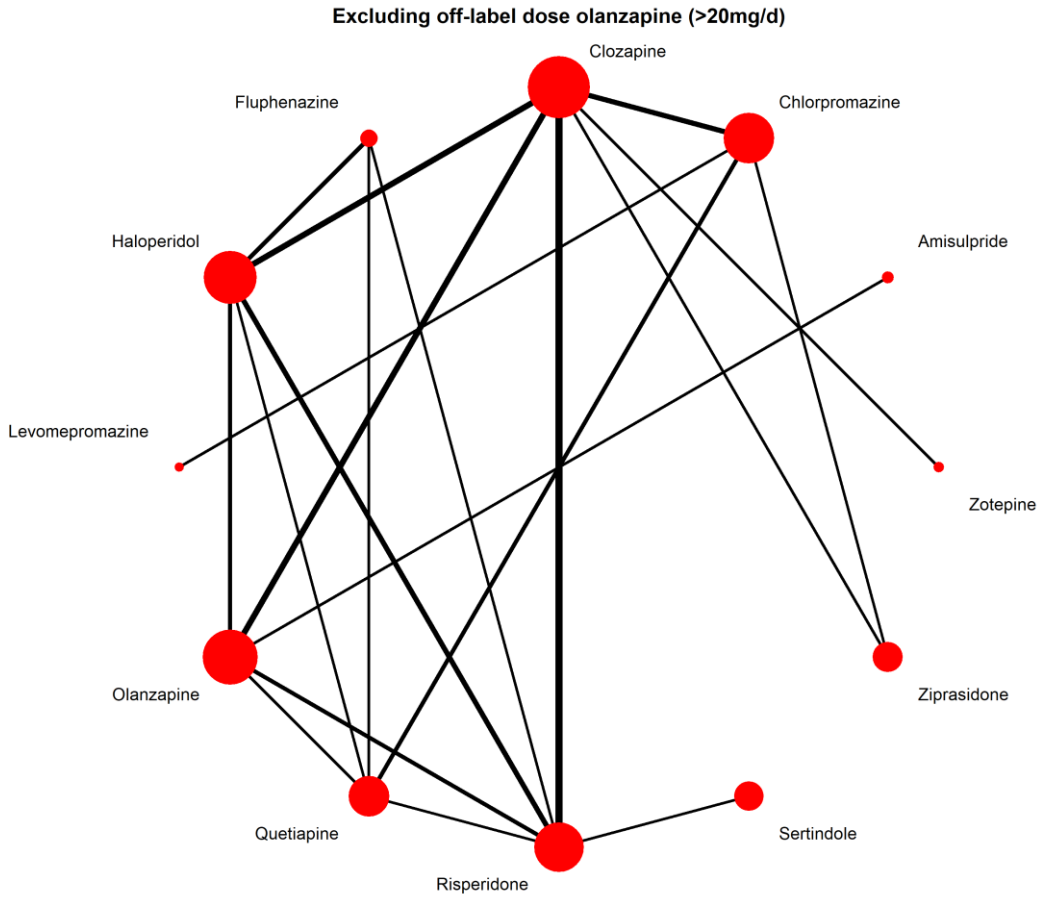
Number of studies: k = 37

Number of pairwise comparisons: m = 39

Number of treatments: n = 12

Number of designs: d = 18

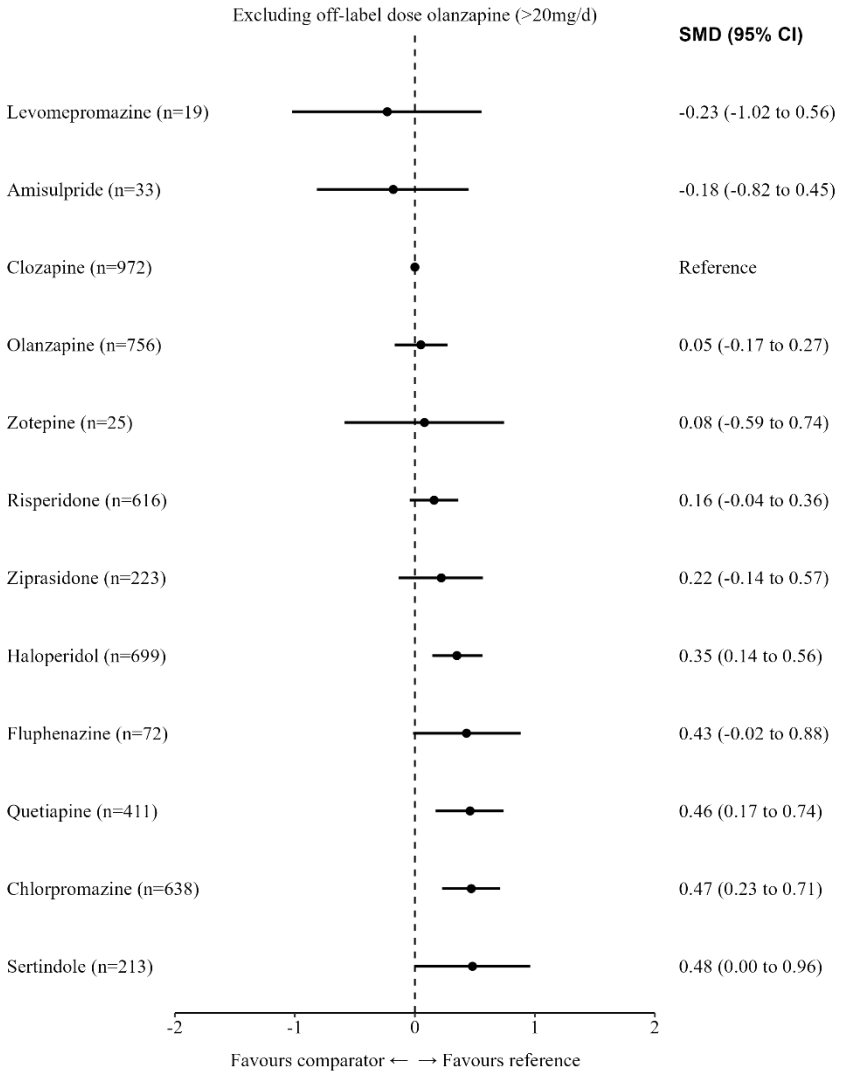
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1874	**0.0001**	**12.5**

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	NA	NA	-0.24 (-0.83 to 0.36)	NA	NA	NA	NA	NA	NA	NA	NA
0.05 (-0.96 to 1.05)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.45 to 0.05)
-0.18 (-0.82 to 0.45)	-0.23 (-1.02 to 0.56)	**Clozapine**	-0.06 (-0.38 to 0.26)	-0.08 (-0.74 to 0.59)	-0.07 (-0.33 to 0.19)	0.02 (-0.47 to 0.51)	-0.26 (-0.56 to 0.03)	NA	NA	NA	**-0.78 (-1.08 to -0.47)**
-0.24 (-0.83 to 0.36)	-0.29 (-1.10 to 0.53)	-0.05 (-0.27 to 0.17)	**Olanzapine**	NA	-0.21 (-0.58 to 0.16)	NA	-0.35 (-0.72 to 0.03)	NA	NA	0.09 (-0.63 to 0.82)	NA
-0.26 (-1.18 to 0.66)	-0.31 (-1.34 to 0.72)	-0.08 (-0.74 to 0.59)	-0.03 (-0.73 to 0.67)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA
-0.34 (-0.98 to 0.30)	-0.39 (-1.20 to 0.42)	-0.16 (-0.36 to 0.04)	-0.11 (-0.35 to 0.13)	-0.08 (-0.78 to 0.61)	**Risperidone**	NA	-0.16 (-0.59 to 0.26)	0.02 (-0.83 to 0.87)	-0.32 (-0.76 to 0.12)	-0.12 (-0.99 to 0.74)	NA
-0.40 (-1.12 to 0.32)	-0.45 (-1.27 to 0.38)	-0.22 (-0.57 to 0.14)	-0.16 (-0.57 to 0.24)	-0.14 (-0.89 to 0.62)	-0.06 (-0.46 to 0.34)	**Ziprasidone**	NA	NA	NA	NA	-0.07 (-0.50 to 0.36)
-0.54 (-1.18 to 0.10)	-0.59 (-1.39 to 0.22)	**-0.35 (-0.56 to -0.14)**	**-0.30 (-0.54 to -0.06)**	-0.28 (-0.97 to 0.42)	-0.19 (-0.43 to 0.04)	-0.14 (-0.53 to 0.26)	**Haloperidol**	-0.17 (-0.67 to 0.32)	NA	0.14 (-0.29 to 0.58)	NA
-0.62 (-1.37 to 0.14)	-0.67 (-1.56 to 0.23)	-0.43 (-0.88 to 0.02)	-0.38 (-0.85 to 0.08)	-0.35 (-1.16 to 0.45)	-0.27 (-0.73 to 0.18)	-0.22 (-0.78 to 0.34)	-0.08 (-0.50 to 0.34)	**Fluphenazine**	NA	-0.15 (-1.01 to 0.72)	NA
-0.66 (-1.44 to 0.11)	-0.71 (-1.63 to 0.21)	-0.48 (-0.96 to 0.00)	-0.43 (-0.93 to 0.07)	-0.40 (-1.22 to 0.42)	-0.32 (-0.76 to 0.12)	-0.26 (-0.86 to 0.33)	-0.13 (-0.62 to 0.37)	-0.05 (-0.68 to 0.58)	**Sertindole**	NA	NA
-0.64 (-1.31 to 0.03)	-0.69 (-1.49 to 0.11)	**-0.46 (-0.74 to -0.17)**	**-0.40 (-0.72 to -0.09)**	-0.38 (-1.10 to 0.35)	-0.30 (-0.61 to 0.02)	-0.24 (-0.65 to 0.16)	-0.10 (-0.39 to 0.18)	-0.02 (-0.50 to 0.45)	0.02 (-0.52 to 0.56)	**Quetiapine**	0.22 (-0.10 to 0.53)
-0.65 (-1.32 to 0.02)	-0.70 (-1.45 to 0.05)	**-0.47 (-0.71 to -0.23)**	**-0.42 (-0.72 to -0.11)**	-0.39 (-1.10 to 0.32)	**-0.31 (-0.61 to -0.01)**	-0.25 (-0.59 to 0.09)	-0.11 (-0.40 to 0.18)	-0.04 (-0.52 to 0.45)	0.01 (-0.52 to 0.54)	-0.01 (-0.27 to 0.25)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

11.12 A most extreme sensitivity analysis including only situations in which clozapine may be most superior

In this sensitivity analysis, open-label studies, studies in which clozapine doses below 400mg/day, studies with intolerant patients and studies with low and intermediate cut-off stringency of criteria for treatment resistance were excluded.

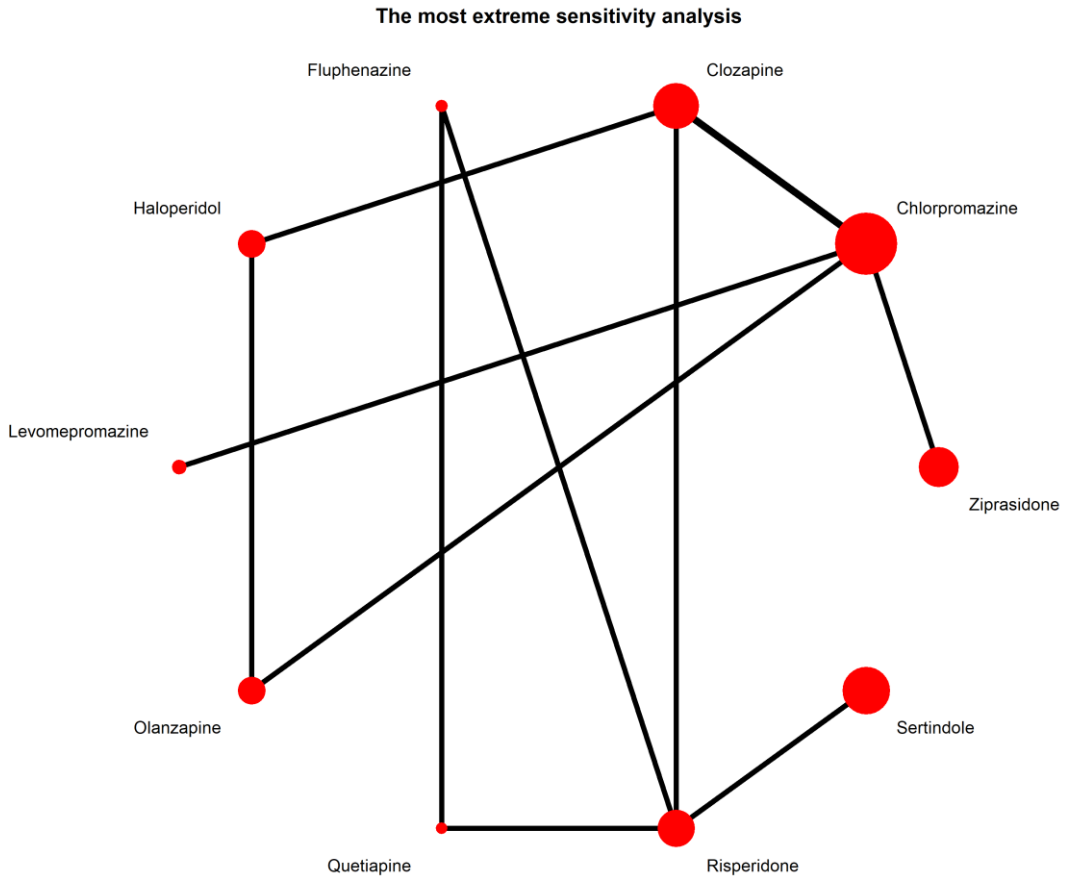
Number of studies: k = 10

Number of pairwise comparisons: m = 12

Number of treatments: n = 10

Number of designs: d = 9

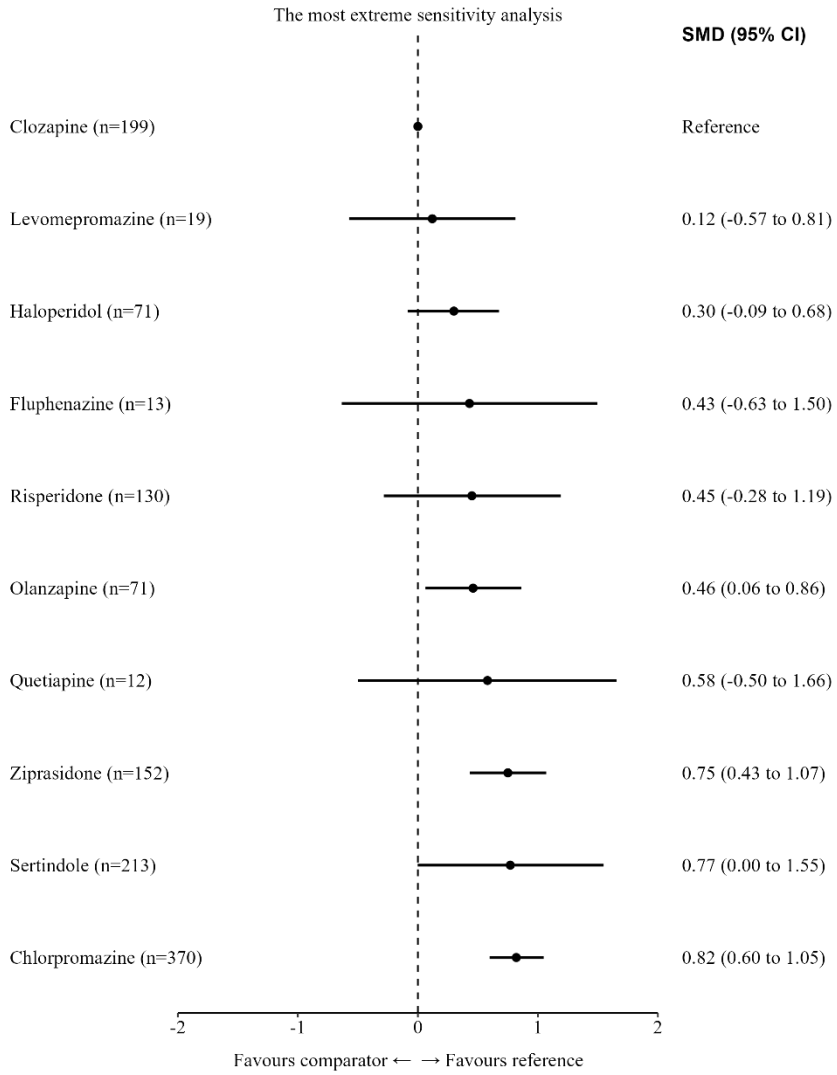
Network plot



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.

τ	P-value	Inconsistency loop (%)
0	0.2145	0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	NA	-0.14 (-0.59 to 0.31)	-0.45 (-1.19 to 0.28)	NA	NA	NA	NA	NA	**-0.86 (-1.10 to -0.63)**
-0.12 (-0.81 to 0.57)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	**-0.70 (-1.36 to -0.05)**
-0.30 (-0.68 to 0.09)	-0.18 (-0.94 to 0.59)	**Haloperidol**	NA	NA	0.02 (-0.48 to 0.51)	NA	NA	NA	NA
-0.45 (-1.19 to 0.28)	-0.33 (-1.35 to 0.68)	-0.16 (-0.99 to 0.67)	**Risperidone**	0.02 (-0.75 to 0.79)	NA	-0.12 (-0.91 to 0.66)	NA	**-0.32 (-0.56 to -0.08)**	NA
-0.43 (-1.50 to 0.63)	-0.31 (-1.58 to 0.96)	-0.14 (-1.27 to 1.00)	0.02 (-0.75 to 0.79)	**Fluphenazine**	NA	-0.15 (-0.93 to 0.64)	NA	NA	NA
-0.46 (-0.86 to -0.06)	-0.34 (-1.10 to 0.41)	-0.17 (-0.57 to 0.23)	-0.01 (-0.85 to 0.83)	-0.03 (-1.17 to 1.11)	**Olanzapine**	NA	NA	NA	-0.22 (-0.65 to 0.22)
-0.58 (-1.66 to 0.50)	-0.46 (-1.74 to 0.82)	-0.28 (-1.42 to 0.86)	-0.12 (-0.91 to 0.66)	-0.15 (-0.93 to 0.64)	-0.12 (-1.26 to 1.03)	**Quetiapine**	NA	NA	NA
-0.75 (-1.07 to -0.43)	-0.63 (-1.32 to 0.06)	-0.46 (-0.92 to 0.01)	-0.30 (-1.10 to 0.50)	-0.32 (-1.43 to 0.79)	-0.29 (-0.72 to 0.15)	-0.17 (-1.30 to 0.95)	**Ziprasidone**	NA	-0.07 (-0.29 to 0.15)
-0.77 (-1.55 to 0.00)	-0.65 (-1.69 to 0.39)	-0.48 (-1.34 to 0.38)	**-0.32 (-0.56 to -0.08)**	-0.34 (-1.15 to 0.46)	-0.31 (-1.18 to 0.56)	-0.20 (-1.02 to 0.62)	-0.02 (-0.86 to 0.82)	**Sertindole**	NA
-0.82 (-1.05 to -0.60)	**-0.70 (-1.36 to -0.05)**	**-0.53 (-0.93 to -0.12)**	-0.37 (-1.14 to 0.40)	-0.39 (-1.48 to 0.70)	-0.36 (-0.73 to 0.01)	-0.24 (-1.35 to 0.86)	-0.07 (-0.29 to 0.15)	-0.05 (-0.86 to 0.76)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

12 Results of the subgroup analyses of the primary outcome

12.1 The criteria of treatment-resistant definitions

12.1.1 The criteria of treatment-resistant definitions

The criteria are a modified version of the previous network meta-analysis from Samara et al.[81] Additionally, we did a subgroup analysis using Samara's criteria and presented the results in Appendix 12.1.2.

a Low cut-off

Definition

Non-response or intolerant to antipsychotics without a specification and studies that do not meet intermediate or high cut-off criteria.

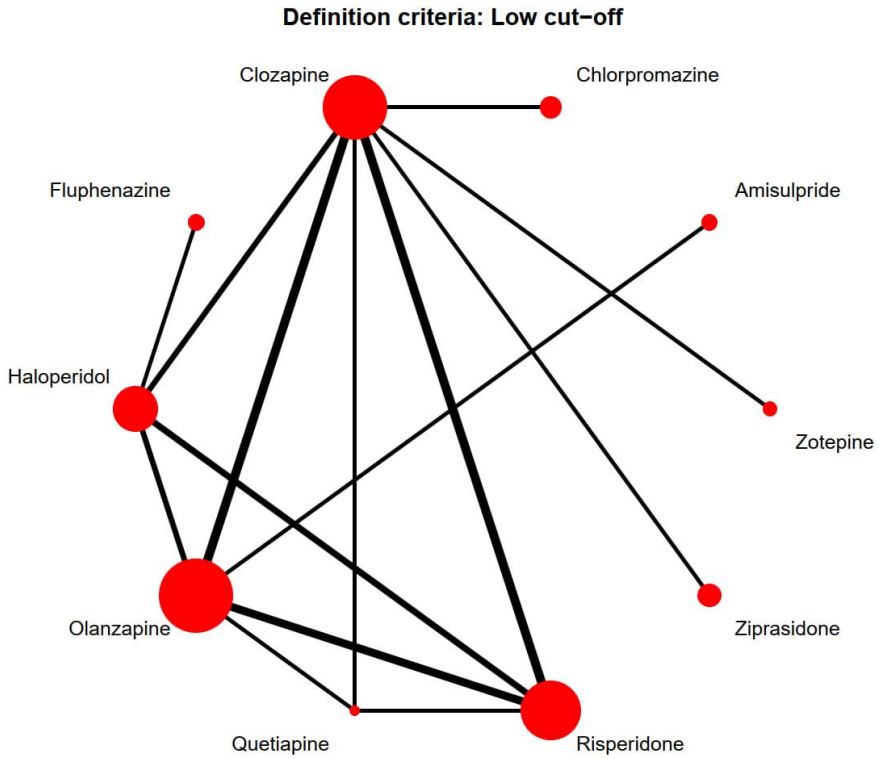
Number of studies: k = 19

Number of pairwise comparisons: m = 29

Number of treatments: n = 10

Number of designs: d = 13

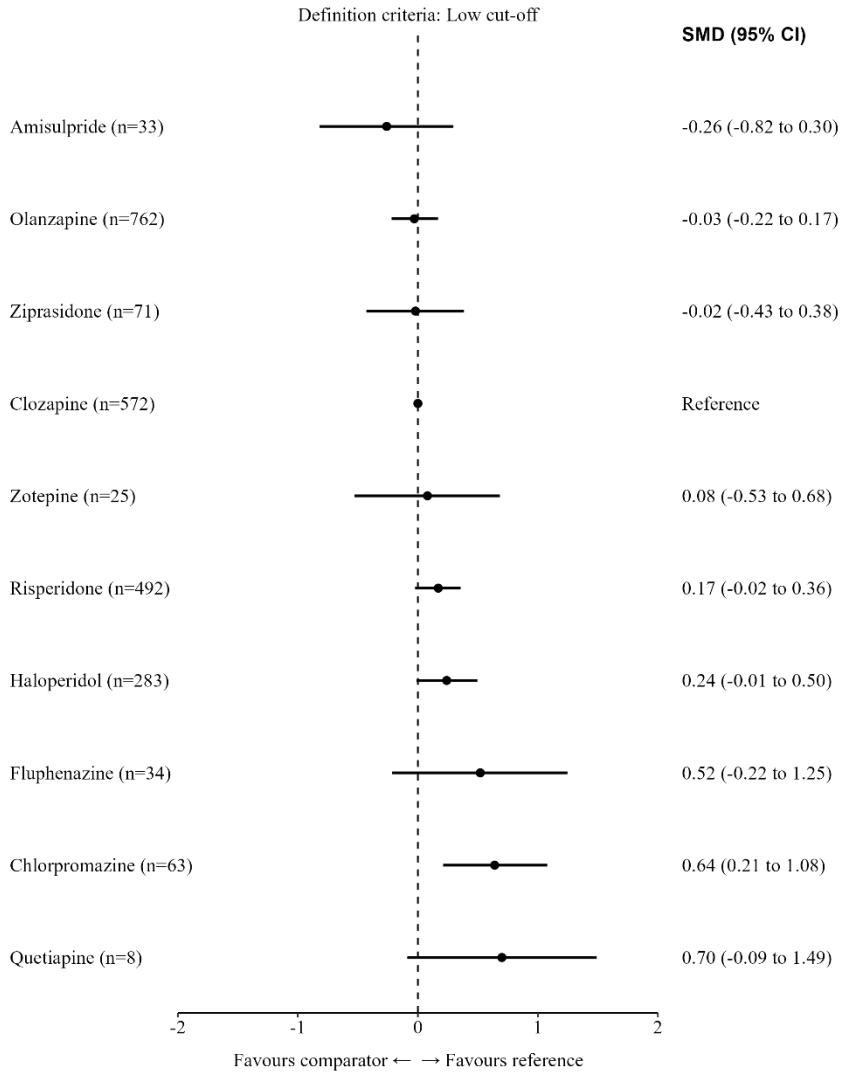
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1235	0.1370	11.11

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	-0.24 (-0.76 to 0.29)	NA	NA	NA	NA	NA	NA	NA	NA
-0.24 (-0.76 to 0.29)	**Olanzapine**	-0.03 (-0.27 to 0.20)	NA	NA	-0.23 (-0.48 to 0.01)	**-0.29 (-0.55 to -0.03)**	NA	-0.38 (-1.34 to 0.59)	NA
-0.26 (-0.82 to 0.30)	-0.03 (-0.22 to 0.17)	**Clozapine**	0.02 (-0.38 to 0.43)	-0.08 (-0.68 to 0.53)	-0.11 (-0.34 to 0.11)	-0.09 (-0.54 to 0.35)	NA	**-1.01 (-1.84 to -0.18)**	**-0.64 (-1.08 to -0.21)**
-0.24 (-0.93 to 0.45)	-0.00 (-0.45 to 0.45)	0.02 (-0.38 to 0.43)	**Ziprasidone**	NA	NA	NA	NA	NA	NA
-0.34 (-1.16 to 0.48)	-0.10 (-0.74 to 0.53)	-0.08 (-0.68 to 0.53)	-0.10 (-0.83 to 0.63)	**Zotepine**	NA	NA	NA	NA	NA
-0.43 (-0.99 to 0.13)	-0.19 (-0.38 to 0.00)	-0.17 (-0.36 to 0.02)	-0.19 (-0.64 to 0.26)	-0.09 (-0.72 to 0.55)	**Risperidone**	-0.07 (-0.40 to 0.26)	NA	0.06 (-1.03 to 1.14)	NA
-0.50 (-1.07 to 0.06)	**-0.27 (-0.49 to -0.05)**	-0.24 (-0.50 to 0.01)	-0.26 (-0.74 to 0.21)	-0.16 (-0.82 to 0.49)	-0.08 (-0.32 to 0.16)	**Haloperidol**	-0.27 (-0.96 to 0.41)	NA	NA
-0.78 (-1.67 to 0.11)	-0.54 (-1.26 to 0.18)	-0.52 (-1.25 to 0.22)	-0.54 (-1.37 to 0.30)	-0.44 (-1.39 to 0.51)	-0.35 (-1.08 to 0.38)	-0.27 (-0.96 to 0.41)	**Fluphenazine**	NA	NA
-0.96 (-1.92 to -0.01)	-0.73 (-1.52 to 0.07)	-0.70 (-1.49 to 0.09)	-0.72 (-1.61 to 0.16)	-0.62 (-1.62 to 0.37)	-0.53 (-1.33 to 0.26)	-0.46 (-1.28 to 0.36)	-0.19 (-1.25 to 0.88)	**Quetiapine**	NA
-0.91 (-1.61 to -0.20)	**-0.67 (-1.14 to -0.20)**	**-0.64 (-1.08 to -0.21)**	**-0.67 (-1.26 to -0.07)**	-0.57 (-1.31 to 0.18)	-0.48 (-0.95 to 0.00)	-0.40 (-0.90 to 0.10)	-0.13 (-0.98 to 0.72)	0.06 (-0.84 to 0.96)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

b Intermediate cut-off

Definition

Failure of response to at least 2 trials with antipsychotics at dosage in the therapeutic range and adequate duration and persistent at least moderate symptoms assessed with standardized rating scales.

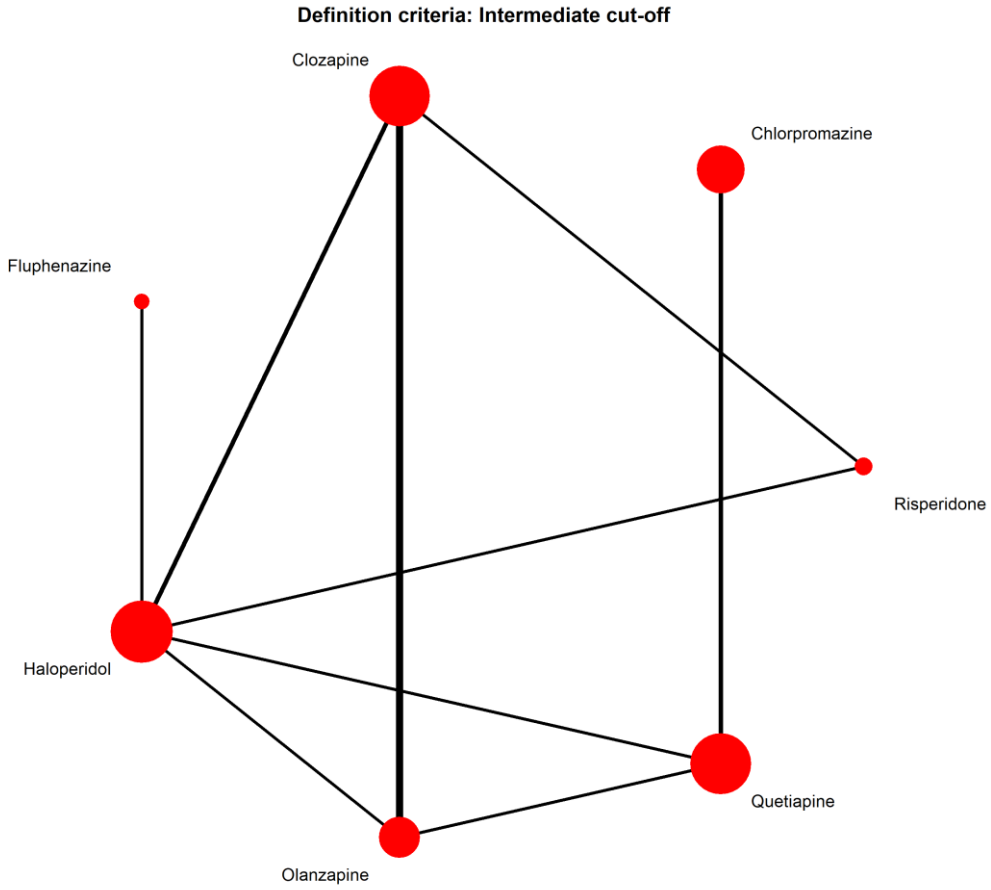
Number of studies: k = 15

Number of pairwise comparisons: m = 15

Number of treatments: n = 7

Number of designs: d = 9

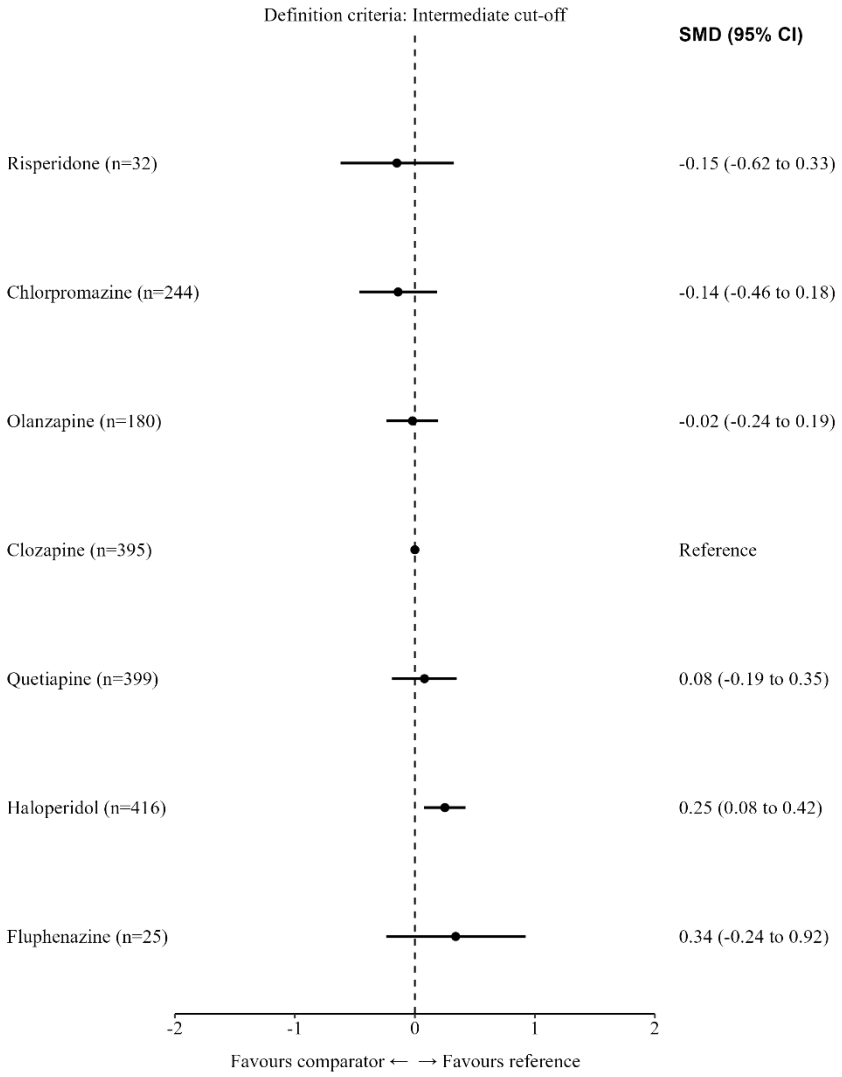
Network plot



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.

τ	P-value	Inconsistency loop (%)
0	0.5108	0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Chlorpromazine	NA	NA	NA	**-0.22 (-0.40 to -0.04)**	NA	NA
0.01 (-0.55 to 0.57)	**Risperidone**	NA	-0.03 (-0.58 to 0.52)	NA	NA	-0.72 (-1.62 to 0.19)
-0.12 (-0.48 to 0.24)	-0.13 (-0.64 to 0.39)	**Olanzapine**	-0.01 (-0.25 to 0.22)	0.09 (-0.53 to 0.72)	NA	-0.73 (-1.55 to 0.10)
-0.14 (-0.46 to 0.18)	-0.15 (-0.62 to 0.33)	-0.02 (-0.24 to 0.19)	**Clozapine**	NA	NA	**-0.23 (-0.41 to -0.04)**
-0.22 (-0.40 to -0.04)	-0.23 (-0.76 to 0.31)	-0.10 (-0.41 to 0.21)	-0.08 (-0.35 to 0.19)	**Quetiapine**	NA	-0.14 (-0.38 to 0.09)
-0.48 (-1.10 to 0.14)	-0.49 (-1.23 to 0.25)	-0.36 (-0.97 to 0.25)	-0.34 (-0.92 to 0.24)	-0.26 (-0.86 to 0.33)	**Fluphenazine**	0.09 (-0.46 to 0.65)
-0.39 (-0.67 to -0.10)	-0.40 (-0.88 to 0.09)	**-0.27 (-0.53 to -0.01)**	**-0.25 (-0.42 to -0.08)**	-0.17 (-0.39 to 0.05)	0.09 (-0.46 to 0.65)	**Haloperidol**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

c High cut-off

Definition

Failure of response to at least two antipsychotic drug trials at dosage in the therapeutic range and adequate duration and at least one of them was prospective, also persistent at least moderate symptoms assessed with standardized rating scales at an assessment at the end of the prospective trial.

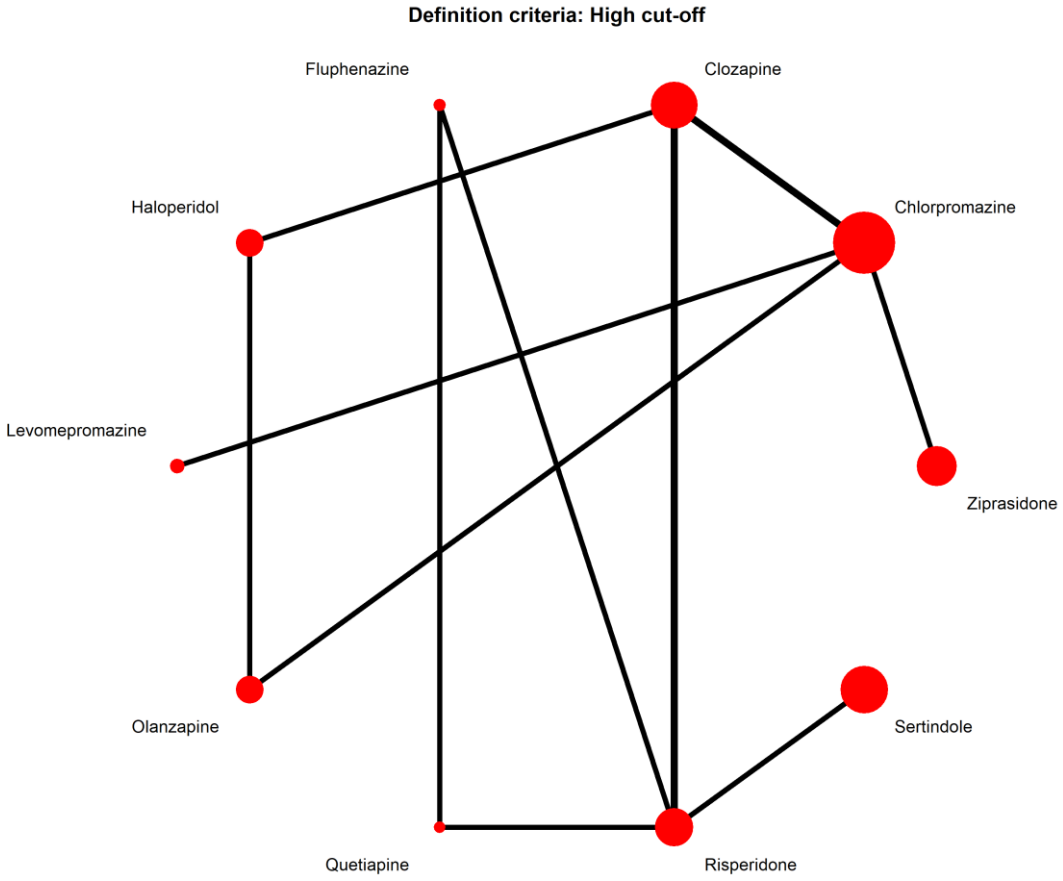
Number of studies: k = 11

Number of pairwise comparisons: m = 13

Number of treatments: n = 10

Number of designs: d = 9

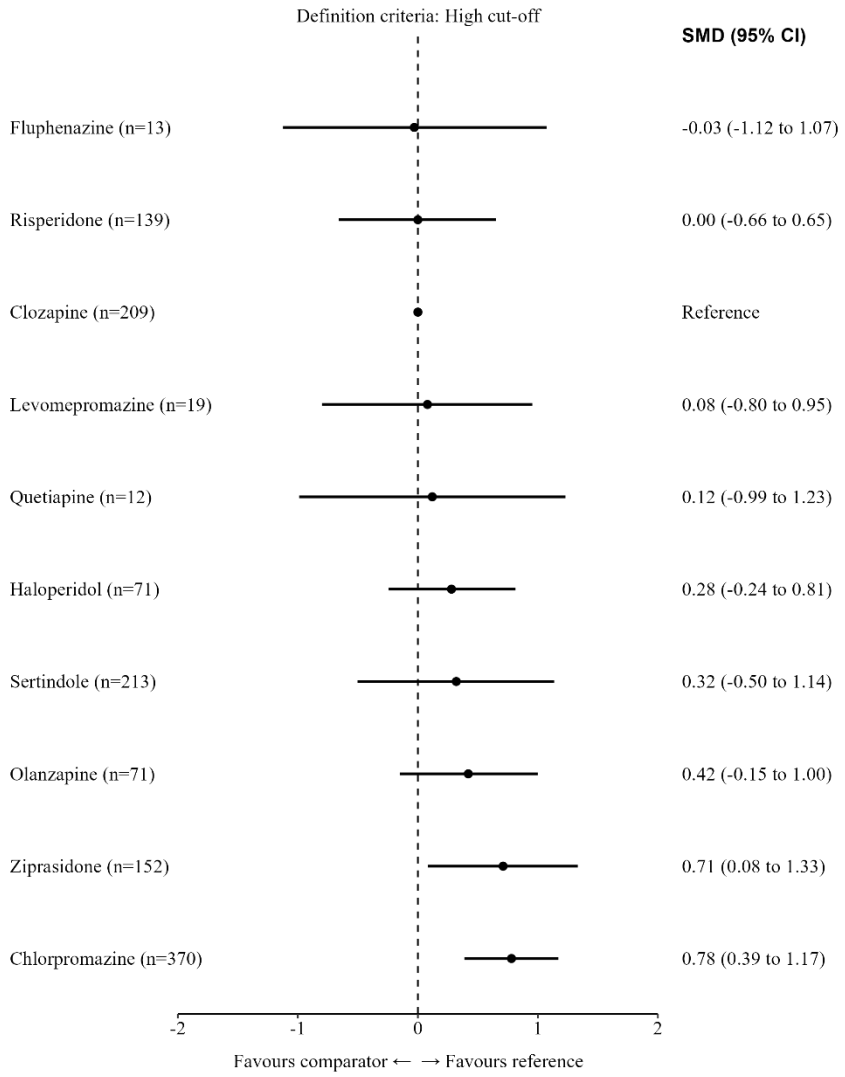
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.2199	0.4439	0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	0.00 (-0.65 to 0.66)	NA	NA	NA	-0.14 (-0.77 to 0.49)	NA	NA	NA	**-0.84 (-1.26 to -0.42)**
0.00 (-0.65 to 0.66)	**Risperidone**	0.02 (-0.86 to 0.90)	NA	-0.12 (-1.02 to 0.77)	NA	-0.32 (-0.81 to 0.17)	NA	NA	NA
0.03 (-1.07 to 1.12)	0.02 (-0.86 to 0.90)	**Fluphenazine**	NA	-0.15 (-1.04 to 0.75)	NA	NA	NA	NA	NA
-0.08 (-0.95 to 0.80)	-0.08 (-1.18 to 1.01)	-0.10 (-1.51 to 1.30)	**Levomepromazine**	NA	NA	NA	NA	NA	-0.70 (-1.49 to 0.08)
-0.12 (-1.23 to 0.99)	-0.12 (-1.02 to 0.77)	-0.15 (-1.04 to 0.75)	-0.04 (-1.46 to 1.37)	**Quetiapine**	NA	NA	NA	NA	NA
-0.28 (-0.81 to 0.24)	-0.29 (-1.13 to 0.55)	-0.31 (-1.53 to 0.91)	-0.21 (-1.18 to 0.77)	-0.16 (-1.39 to 1.07)	**Haloperidol**	NA	0.02 (-0.64 to 0.68)	NA	NA
-0.32 (-1.14 to 0.50)	-0.32 (-0.81 to 0.17)	-0.34 (-1.35 to 0.67)	-0.24 (-1.44 to 0.96)	-0.20 (-1.22 to 0.83)	-0.03 (-1.01 to 0.94)	**Sertindole**	NA	NA	NA
-0.42 (-1.00 to 0.15)	-0.43 (-1.30 to 0.44)	-0.45 (-1.69 to 0.79)	-0.35 (-1.29 to 0.60)	-0.30 (-1.55 to 0.95)	-0.14 (-0.68 to 0.40)	-0.11 (-1.11 to 0.89)	**Olanzapine**	NA	-0.22 (-0.83 to 0.40)
-0.71 (-1.33 to -0.08)	-0.71 (-1.62 to 0.19)	-0.73 (-2.00 to 0.53)	-0.63 (-1.55 to 0.29)	-0.59 (-1.86 to 0.68)	-0.42 (-1.18 to 0.33)	-0.39 (-1.42 to 0.64)	-0.28 (-1.00 to 0.43)	**Ziprasidone**	-0.07 (-0.56 to 0.41)
-0.78 (-1.17 to -0.39)	**-0.78 (-1.55 to -0.02)**	-0.81 (-1.97 to 0.36)	-0.70 (-1.49 to 0.08)	-0.66 (-1.84 to 0.52)	-0.49 (-1.07 to 0.08)	-0.46 (-1.37 to 0.44)	-0.35 (-0.88 to 0.17)	-0.07 (-0.56 to 0.41)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

12.1.2 The criteria from Samara et al[81]

a No response to 1 previous antipsychotic

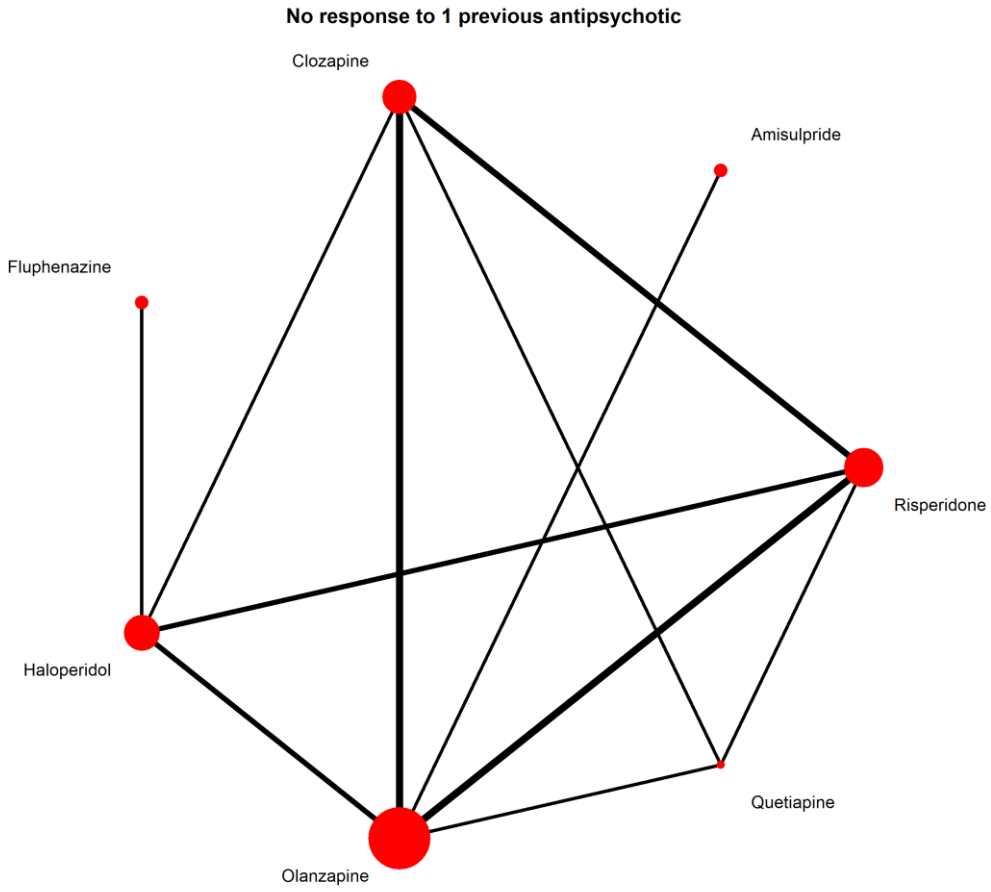
Number of studies: k = 11

Number of pairwise comparisons: m = 21

Number of treatments: n = 7

Number of designs: d = 9

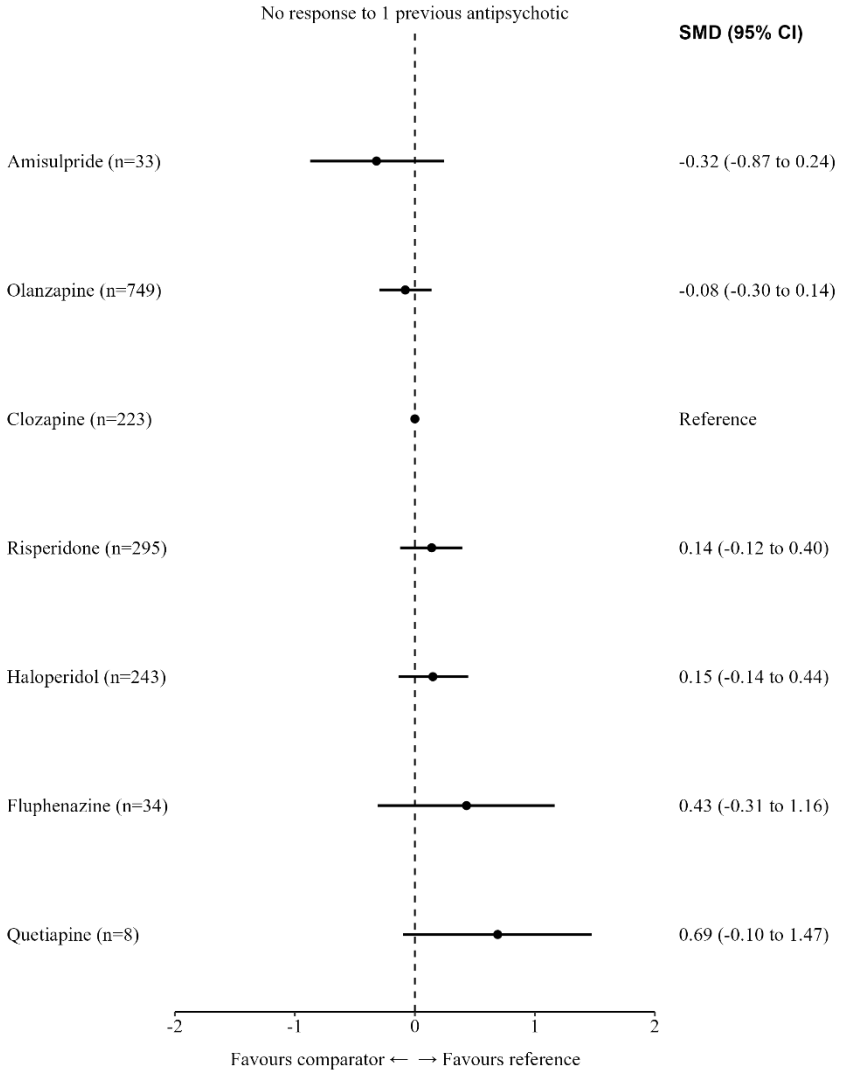
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1111	0.1312	22.22

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	-0.24 (-0.75 to 0.28)	NA	NA	NA	NA	NA
-0.24 (-0.75 to 0.28)	**Olanzapine**	-0.07 (-0.31 to 0.17)	-0.23 (-0.47 to 0.00)	**-0.29 (-0.54 to -0.04)**	NA	-0.38 (-1.34 to 0.58)
-0.32 (-0.87 to 0.24)	-0.08 (-0.30 to 0.14)	**Clozapine**	-0.04 (-0.39 to 0.31)	0.12 (-0.38 to 0.61)	NA	**-1.01 (-1.83 to -0.19)**
-0.45 (-1.01 to 0.10)	**-0.21 (-0.42 to -0.01)**	-0.14 (-0.40 to 0.12)	**Risperidone**	-0.03 (-0.42 to 0.36)	NA	0.06 (-1.02 to 1.14)
-0.47 (-1.03 to 0.09)	**-0.23 (-0.46 to -0.01)**	-0.15 (-0.44 to 0.14)	-0.02 (-0.29 to 0.25)	**Haloperidol**	-0.27 (-0.95 to 0.40)	NA
-0.74 (-1.62 to 0.14)	-0.51 (-1.22 to 0.21)	-0.43 (-1.16 to 0.31)	-0.29 (-1.02 to 0.44)	-0.27 (-0.95 to 0.40)	**Fluphenazine**	NA
-1.00 (-1.95 to -0.06)	-0.77 (-1.56 to 0.03)	-0.69 (-1.47 to 0.10)	-0.55 (-1.36 to 0.25)	-0.53 (-1.35 to 0.29)	-0.26 (-1.32 to 0.80)	**Quetiapine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

b No response to at least 2 retrospective periods of antipsychotic treatment

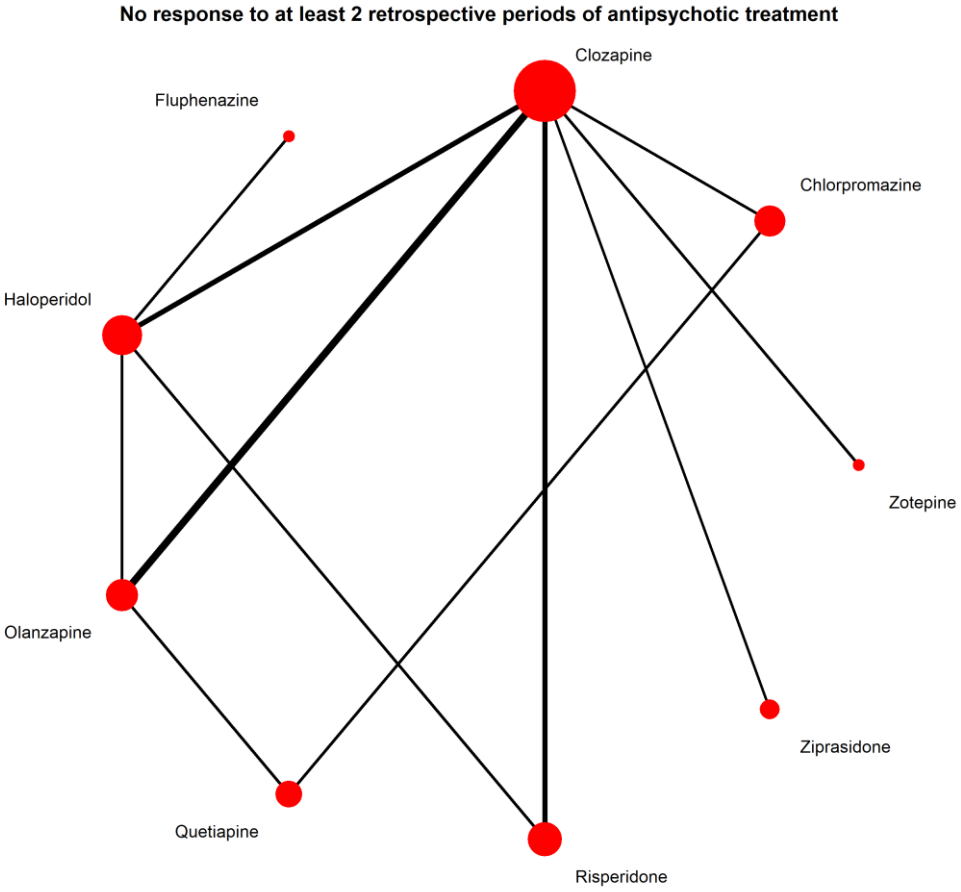
Number of studies: k = 20

Number of pairwise comparisons: m = 20

Number of treatments: n = 9

Number of designs: d = 11

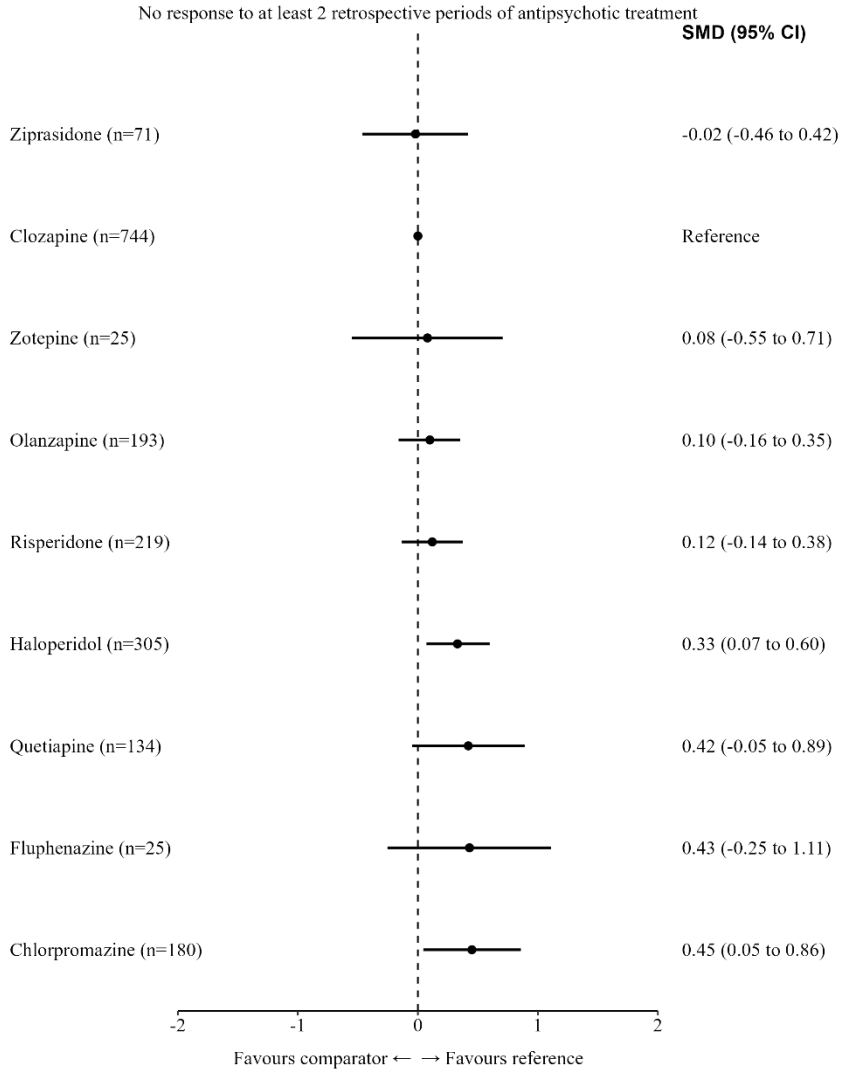
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1506	0.2017	0.375

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	0.02 (-0.42 to 0.46)	-0.08 (-0.35 to 0.20)	-0.08 (-0.71 to 0.55)	-0.11 (-0.39 to 0.17)	-0.29 (-0.59 to 0.01)	NA	NA	**-0.64 (-1.11 to -0.18)**
0.02 (-0.42 to 0.46)	**Ziprasidone**	NA	NA	NA	NA	NA	NA	NA
-0.10 (-0.35 to 0.16)	-0.12 (-0.63 to 0.39)	**Olanzapine**	NA	NA	-0.73 (-1.61 to 0.15)	NA	0.09 (-0.59 to 0.78)	NA
-0.08 (-0.71 to 0.55)	-0.10 (-0.87 to 0.67)	0.02 (-0.66 to 0.70)	**Zotepine**	NA	NA	NA	NA	NA
-0.12 (-0.38 to 0.14)	-0.14 (-0.65 to 0.37)	-0.02 (-0.38 to 0.33)	-0.04 (-0.72 to 0.64)	**Risperidone**	-0.16 (-0.76 to 0.43)	NA	NA	NA
-0.33 (-0.60 to -0.07)	-0.36 (-0.87 to 0.16)	-0.24 (-0.59 to 0.11)	-0.26 (-0.94 to 0.42)	-0.21 (-0.55 to 0.12)	**Haloperidol**	-0.09 (-0.72 to 0.54)	NA	NA
-0.43 (-1.11 to 0.25)	-0.45 (-1.26 to 0.36)	-0.33 (-1.05 to 0.39)	-0.35 (-1.28 to 0.58)	-0.31 (-1.02 to 0.40)	-0.09 (-0.72 to 0.54)	**Fluphenazine**	NA	NA
-0.42 (-0.89 to 0.05)	-0.44 (-1.09 to 0.20)	-0.33 (-0.80 to 0.15)	-0.34 (-1.13 to 0.44)	-0.30 (-0.83 to 0.23)	-0.09 (-0.62 to 0.45)	0.01 (-0.82 to 0.83)	**Quetiapine**	0.11 (-0.29 to 0.50)
-0.45 (-0.86 to -0.05)	-0.47 (-1.07 to 0.12)	-0.36 (-0.80 to 0.09)	-0.37 (-1.12 to 0.37)	-0.33 (-0.81 to 0.15)	-0.12 (-0.60 to 0.36)	-0.02 (-0.82 to 0.77)	-0.03 (-0.39 to 0.33)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

c No response to a combination of retrospective and prospective criteria for treatment resistance

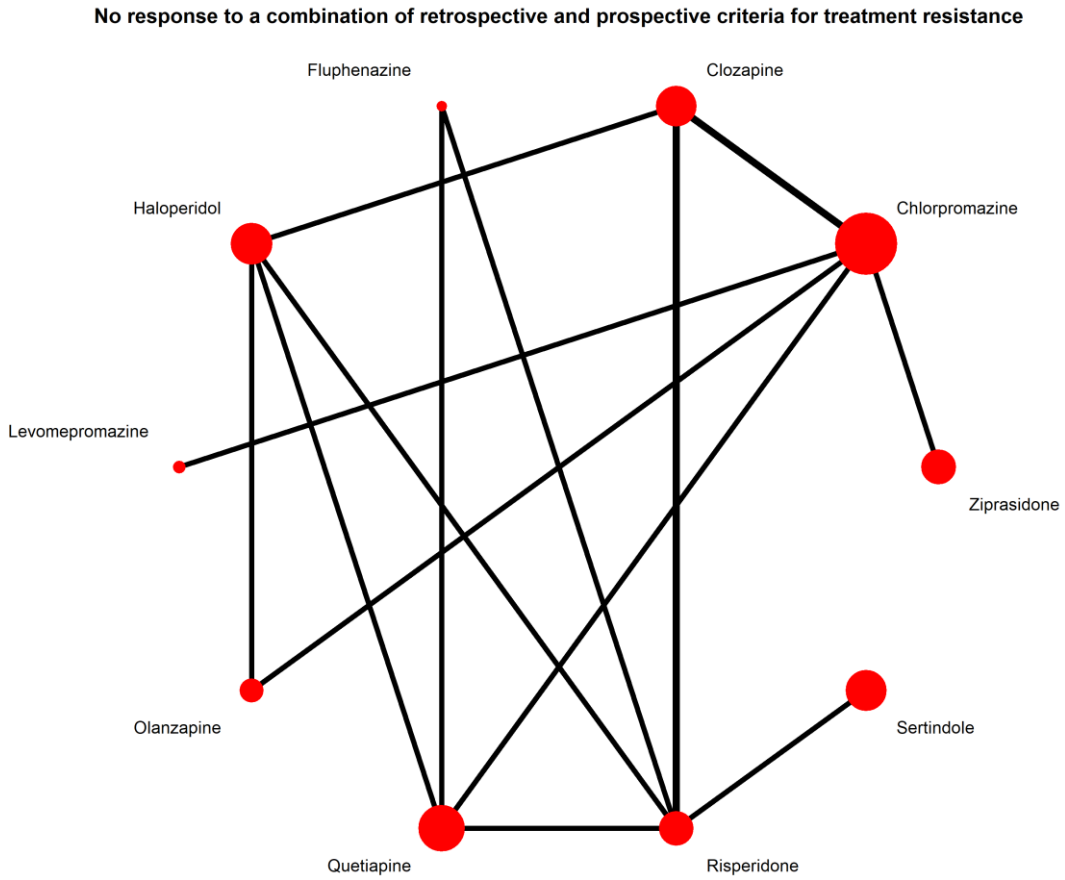
Number of studies: k = 14

Number of pairwise comparisons: m = 16

Number of treatments: n = 10

Number of designs: d = 12

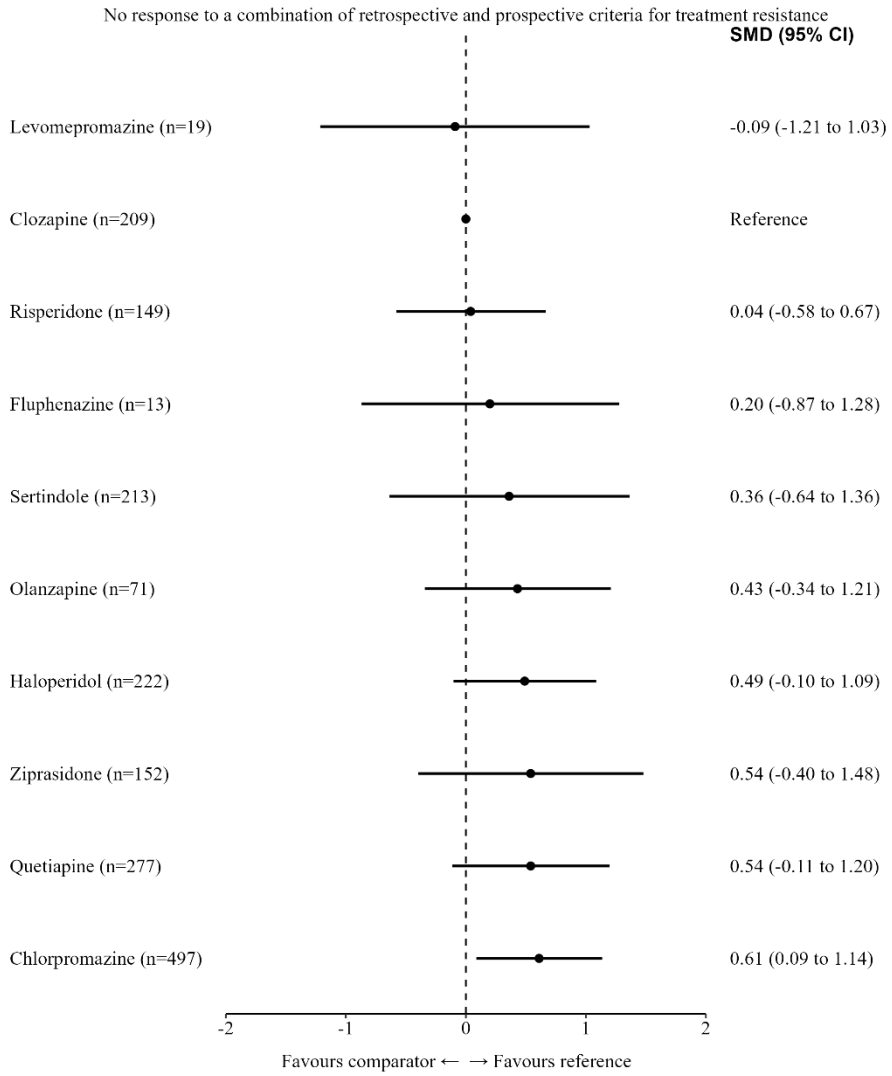
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.38	0.2853	0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	NA	0.03 (-0.75 to 0.82)	NA	NA	NA	-0.14 (-1.01 to 0.73)	NA	NA	**-0.83 (-1.45 to -0.22)**
0.09 (-1.03 to 1.21)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.69 to 0.29)
-0.04 (-0.67 to 0.58)	-0.13 (-1.36 to 1.09)	**Risperidone**	0.02 (-1.05 to 1.09)	-0.32 (-1.10 to 0.46)	NA	-0.72 (-1.89 to 0.45)	NA	-0.12 (-1.21 to 0.96)	NA
-0.20 (-1.28 to 0.87)	-0.29 (-1.77 to 1.18)	-0.16 (-1.15 to 0.83)	**Fluphenazine**	NA	NA	NA	NA	-0.15 (-1.23 to 0.94)	NA
-0.36 (-1.36 to 0.64)	-0.45 (-1.91 to 1.00)	-0.32 (-1.10 to 0.46)	-0.16 (-1.42 to 1.10)	**Sertindole**	NA	NA	NA	NA	NA
-0.43 (-1.21 to 0.34)	-0.52 (-1.73 to 0.69)	-0.39 (-1.27 to 0.49)	-0.23 (-1.44 to 0.98)	-0.07 (-1.25 to 1.11)	**Olanzapine**	-0.02 (-0.91 to 0.88)	NA	NA	-0.22 (-1.08 to 0.65)
-0.49 (-1.09 to 0.10)	-0.58 (-1.76 to 0.59)	-0.45 (-1.13 to 0.23)	-0.29 (-1.36 to 0.79)	-0.13 (-1.17 to 0.91)	-0.06 (-0.76 to 0.64)	**Haloperidol**	NA	0.14 (-0.64 to 0.92)	NA
-0.54 (-1.48 to 0.40)	-0.63 (-1.89 to 0.63)	-0.50 (-1.56 to 0.56)	-0.34 (-1.67 to 1.00)	-0.18 (-1.49 to 1.14)	-0.11 (-1.15 to 0.93)	-0.05 (-1.05 to 0.95)	**Ziprasidone**	NA	-0.07 (-0.85 to 0.71)
-0.54 (-1.20 to 0.11)	-0.63 (-1.79 to 0.53)	-0.50 (-1.20 to 0.20)	-0.34 (-1.33 to 0.66)	-0.18 (-1.23 to 0.87)	-0.11 (-0.91 to 0.69)	-0.05 (-0.64 to 0.54)	-0.00 (-0.99 to 0.98)	**Quetiapine**	0.32 (-0.46 to 1.11)
-0.61 (-1.14 to -0.09)	-0.70 (-1.69 to 0.29)	-0.57 (-1.29 to 0.15)	-0.41 (-1.50 to 0.68)	-0.25 (-1.31 to 0.81)	-0.18 (-0.87 to 0.51)	-0.12 (-0.75 to 0.51)	-0.07 (-0.85 to 0.71)	-0.07 (-0.67 to 0.53)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available

12.2 Mean age

a More than 18 years old

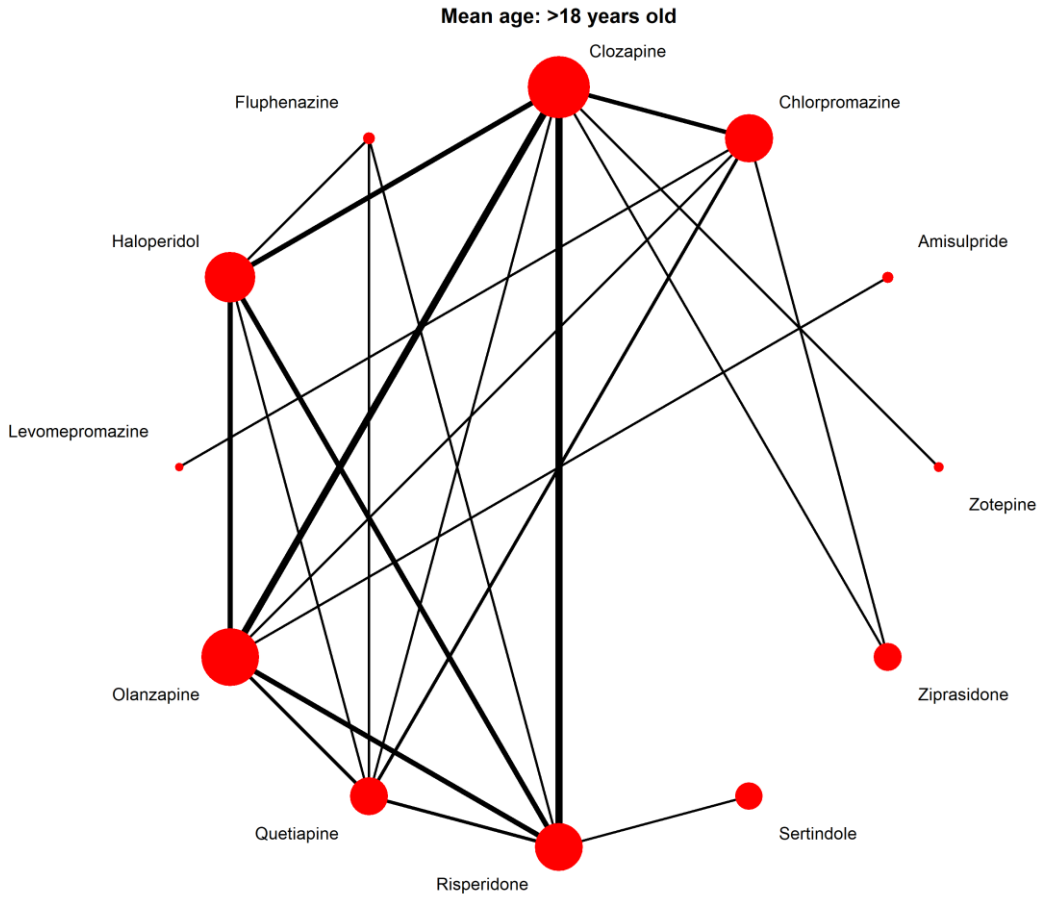
Number of studies: k = 41

Number of pairwise comparisons: m = 53

Number of treatments: n = 12

Number of designs: d = 21

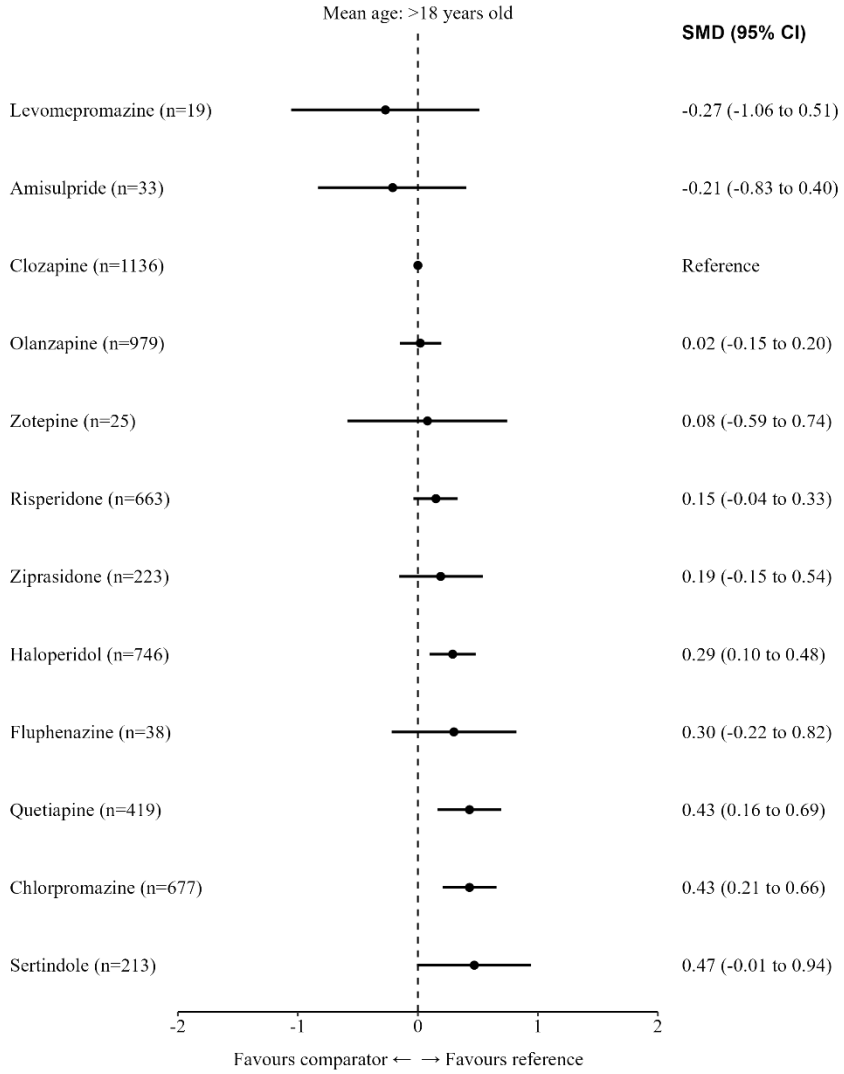
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1882	< 0.0001	11.11

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	NA	NA	-0.24 (-0.83 to 0.36)	NA	NA	NA	NA	NA	NA	NA	NA
0.06 (-0.93 to 1.05)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	NA	NA	NA	-0.70 (-1.45 to 0.05)
-0.21 (-0.83 to 0.40)	-0.27 (-1.06 to 0.51)	**Clozapine**	0.03 (-0.19 to 0.25)	-0.08 (-0.74 to 0.59)	-0.08 (-0.30 to 0.15)	0.02 (-0.47 to 0.52)	NA	-0.13 (-0.41 to 0.14)	NA	**-1.01 (-1.89 to -0.13)**	**-0.78 (-1.08 to -0.47)**
-0.24 (-0.83 to 0.36)	-0.29 (-1.09 to 0.50)	-0.02 (-0.20 to 0.15)	**Olanzapine**	NA	-0.23 (-0.53 to 0.07)	NA	NA	-0.28 (-0.56 to 0.00)	NA	-0.07 (-0.65 to 0.52)	-0.22 (-0.79 to 0.36)
-0.29 (-1.20 to 0.62)	-0.35 (-1.38 to 0.68)	-0.08 (-0.74 to 0.59)	-0.06 (-0.74 to 0.63)	**Zotepine**	NA	NA	NA	NA	NA	NA	NA
-0.36 (-0.99 to 0.27)	-0.42 (-1.22 to 0.38)	-0.15 (-0.33 to 0.04)	-0.12 (-0.33 to 0.08)	-0.07 (-0.76 to 0.62)	**Risperidone**	NA	0.02 (-0.83 to 0.87)	-0.15 (-0.49 to 0.19)	-0.32 (-0.76 to 0.12)	-0.06 (-0.74 to 0.63)	NA
-0.41 (-1.11 to 0.30)	-0.47 (-1.29 to 0.36)	-0.19 (-0.54 to 0.15)	-0.17 (-0.55 to 0.21)	-0.12 (-0.87 to 0.64)	-0.05 (-0.43 to 0.34)	**Ziprasidone**	NA	NA	NA	NA	-0.07 (-0.50 to 0.36)
-0.52 (-1.31 to 0.28)	-0.57 (-1.50 to 0.36)	-0.30 (-0.82 to 0.22)	-0.28 (-0.80 to 0.25)	-0.22 (-1.07 to 0.62)	-0.15 (-0.68 to 0.37)	-0.11 (-0.72 to 0.51)	**Fluphenazine**	0.09 (-0.57 to 0.76)	NA	-0.15 (-1.01 to 0.72)	NA
-0.50 (-1.13 to 0.12)	-0.56 (-1.36 to 0.24)	**-0.29 (-0.48 to -0.10)**	**-0.27 (-0.47 to -0.07)**	-0.21 (-0.90 to 0.48)	-0.14 (-0.36 to 0.07)	-0.10 (-0.48 to 0.29)	0.01 (-0.49 to 0.52)	**Haloperidol**	NA	0.14 (-0.29 to 0.58)	NA
-0.68 (-1.45 to 0.08)	-0.74 (-1.65 to 0.17)	-0.47 (-0.94 to 0.01)	-0.44 (-0.93 to 0.04)	-0.39 (-1.21 to 0.43)	-0.32 (-0.76 to 0.12)	-0.27 (-0.86 to 0.31)	-0.17 (-0.85 to 0.51)	-0.18 (-0.67 to 0.31)	**Sertindole**	NA	NA
-0.64 (-1.30 to 0.01)	-0.70 (-1.49 to 0.09)	**-0.43 (-0.69 to -0.16)**	**-0.41 (-0.68 to -0.13)**	-0.35 (-1.07 to 0.37)	-0.28 (-0.57 to 0.01)	-0.23 (-0.63 to 0.16)	-0.13 (-0.66 to 0.41)	-0.14 (-0.41 to 0.13)	0.04 (-0.49 to 0.57)	**Quetiapine**	0.22 (-0.10 to 0.53)
-0.64 (-1.29 to 0.00)	-0.70 (-1.45 to 0.05)	**-0.43 (-0.66 to -0.21)**	**-0.41 (-0.66 to -0.15)**	-0.35 (-1.06 to 0.35)	**-0.28 (-0.56 to -0.01)**	-0.24 (-0.58 to 0.10)	-0.13 (-0.67 to 0.42)	-0.14 (-0.41 to 0.13)	0.04 (-0.48 to 0.55)	-0.00 (-0.25 to 0.25)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

b Less than 18 years old

No closed loops

12.3 Dose of the antipsychotics in chlorpromazine-equivalents

For the purpose of this analysis the median number of dose in chlorpromazine-equivalents was used.

a High dose

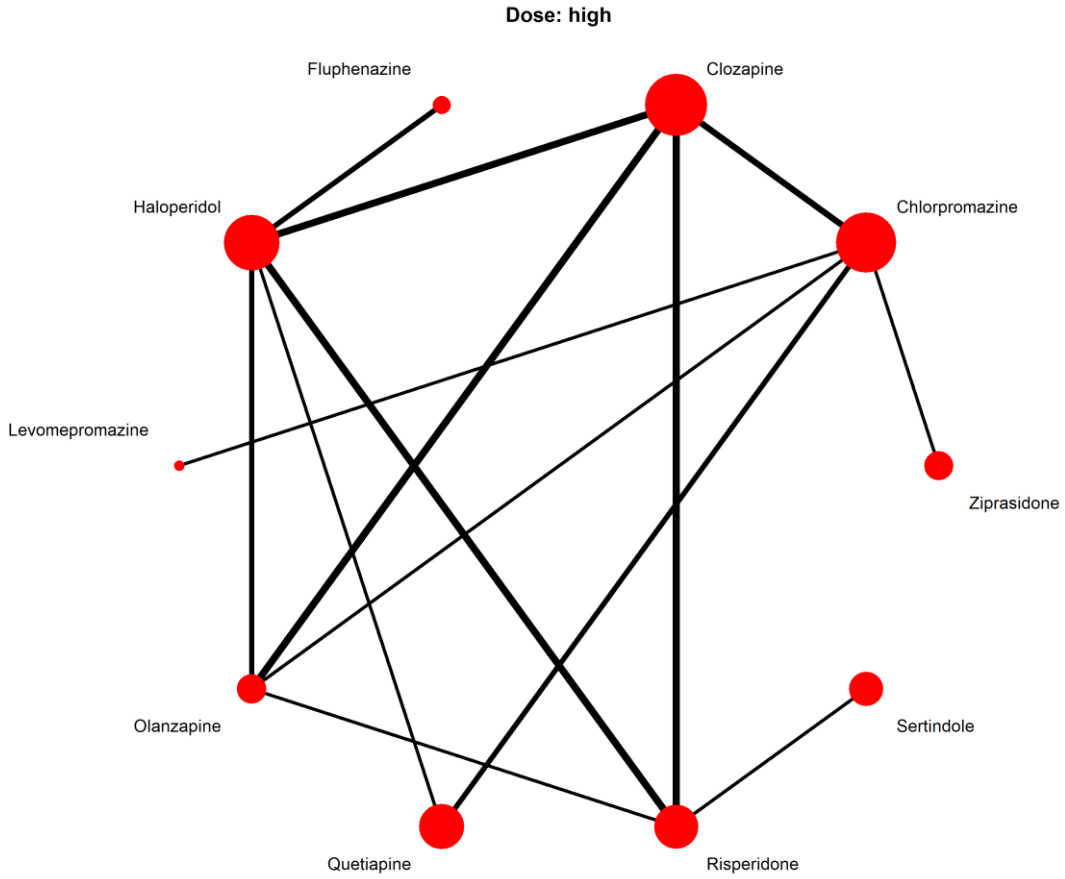
Number of studies: k = 26

Number of pairwise comparisons: m = 31

Number of treatments: n = 10

Number of designs: d = 14

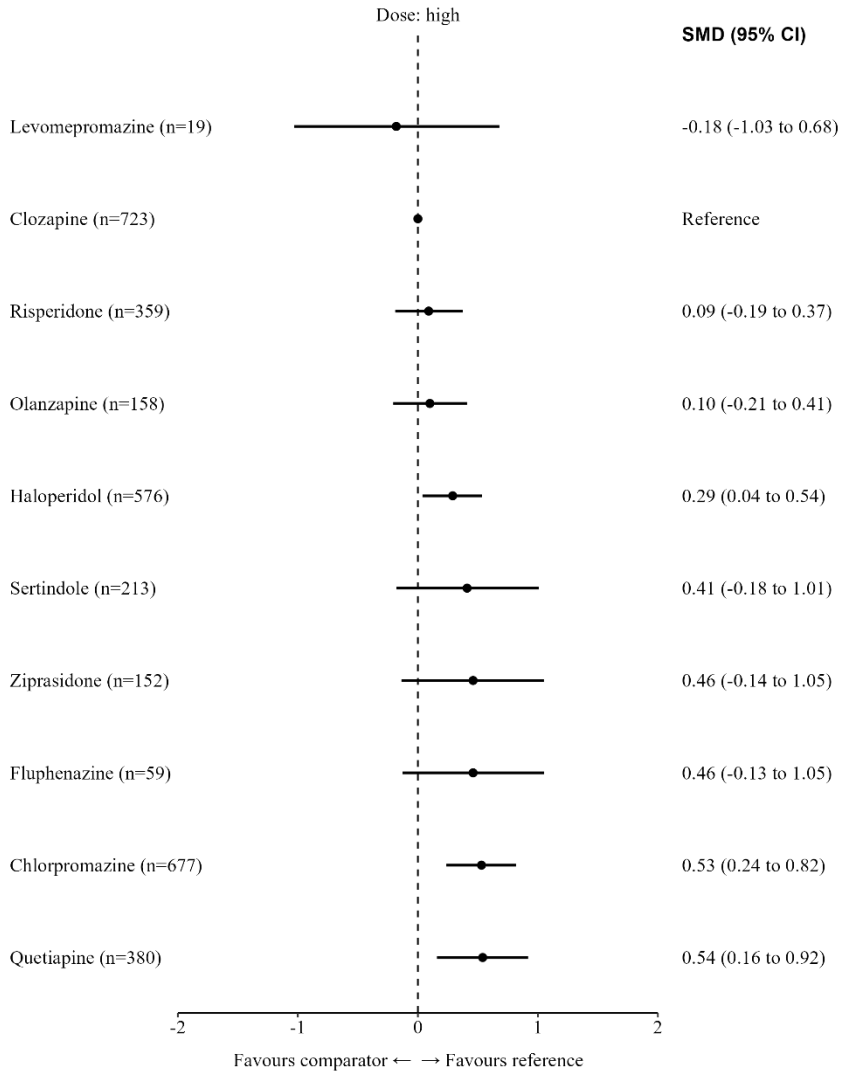
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.2378	< 0.0001	30.0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	NA	0.01 (-0.33 to 0.34)	0.07 (-0.33 to 0.46)	-0.13 (-0.45 to 0.19)	NA	NA	NA	**-0.77 (-1.12 to -0.42)**	NA
0.18 (-0.68 to 1.03)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	-0.70 (-1.51 to 0.10)	NA
-0.09 (-0.37 to 0.19)	-0.27 (-1.16 to 0.62)	**Risperidone**	0.24 (-0.40 to 0.88)	-0.15 (-0.53 to 0.22)	-0.32 (-0.84 to 0.20)	NA	NA	NA	NA
-0.10 (-0.41 to 0.21)	-0.28 (-1.16 to 0.61)	-0.01 (-0.38 to 0.37)	**Olanzapine**	-0.20 (-0.67 to 0.27)	NA	NA	NA	-0.22 (-0.85 to 0.42)	NA
-0.29 (-0.54 to -0.04)	-0.46 (-1.33 to 0.41)	-0.19 (-0.49 to 0.10)	-0.19 (-0.52 to 0.15)	**Haloperidol**	NA	NA	-0.18 (-0.71 to 0.36)	NA	0.14 (-0.38 to 0.66)
-0.41 (-1.01 to 0.18)	-0.59 (-1.62 to 0.44)	-0.32 (-0.84 to 0.20)	-0.31 (-0.95 to 0.33)	-0.13 (-0.73 to 0.47)	**Sertindole**	NA	NA	NA	NA
-0.46 (-1.05 to 0.14)	-0.63 (-1.59 to 0.32)	-0.36 (-1.01 to 0.28)	-0.35 (-0.99 to 0.28)	-0.17 (-0.79 to 0.45)	-0.04 (-0.87 to 0.79)	**Ziprasidone**	NA	-0.07 (-0.59 to 0.45)	NA
-0.46 (-1.05 to 0.13)	-0.64 (-1.66 to 0.39)	-0.37 (-0.98 to 0.24)	-0.36 (-0.99 to 0.27)	-0.18 (-0.71 to 0.36)	-0.05 (-0.85 to 0.76)	-0.01 (-0.82 to 0.81)	**Fluphenazine**	NA	NA
-0.53 (-0.82 to -0.24)	-0.70 (-1.51 to 0.10)	**-0.43 (-0.82 to -0.05)**	**-0.43 (-0.79 to -0.06)**	-0.24 (-0.58 to 0.10)	-0.11 (-0.76 to 0.54)	-0.07 (-0.59 to 0.45)	-0.06 (-0.70 to 0.57)	**Chlorpromazine**	-0.21 (-0.59 to 0.16)
-0.54 (-0.92 to -0.16)	-0.71 (-1.58 to 0.15)	-0.45 (-0.89 to 0.00)	-0.44 (-0.88 to 0.00)	-0.25 (-0.63 to 0.13)	-0.13 (-0.81 to 0.56)	-0.08 (-0.69 to 0.53)	-0.08 (-0.73 to 0.58)	-0.01 (-0.34 to 0.31)	**Quetiapine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

b Low dose

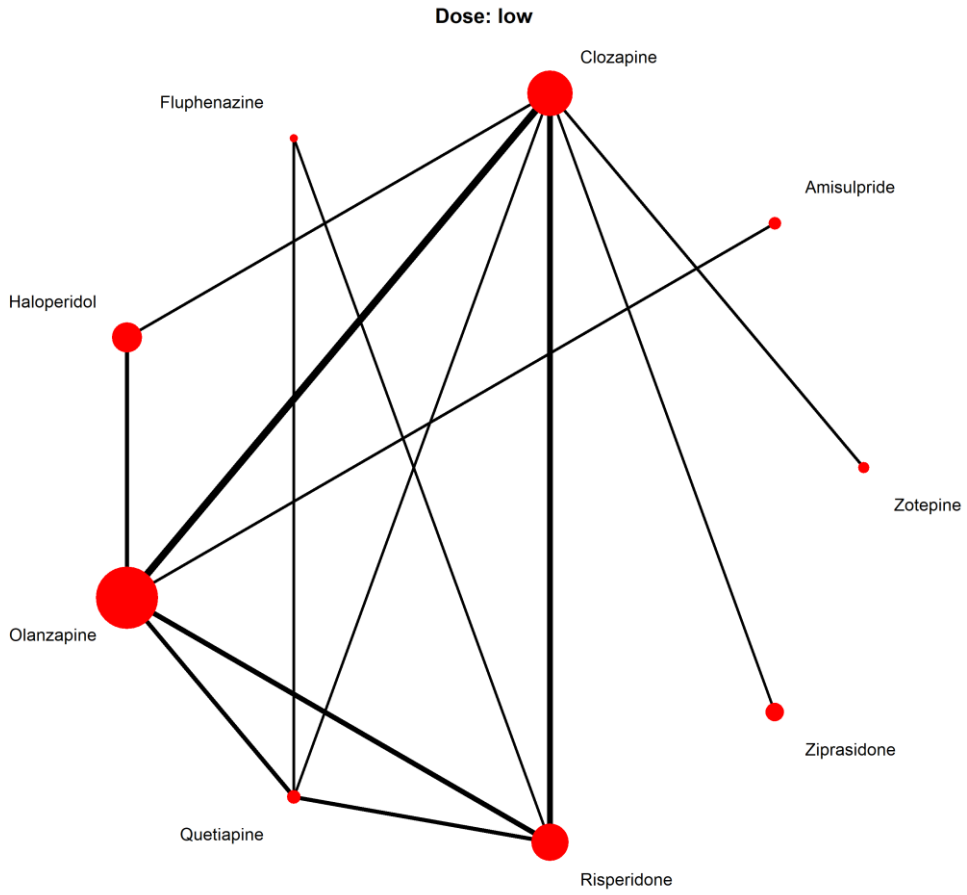
Number of studies: k = 19

Number of pairwise comparisons: m = 26

Number of treatments: n = 9

Number of designs: d = 11

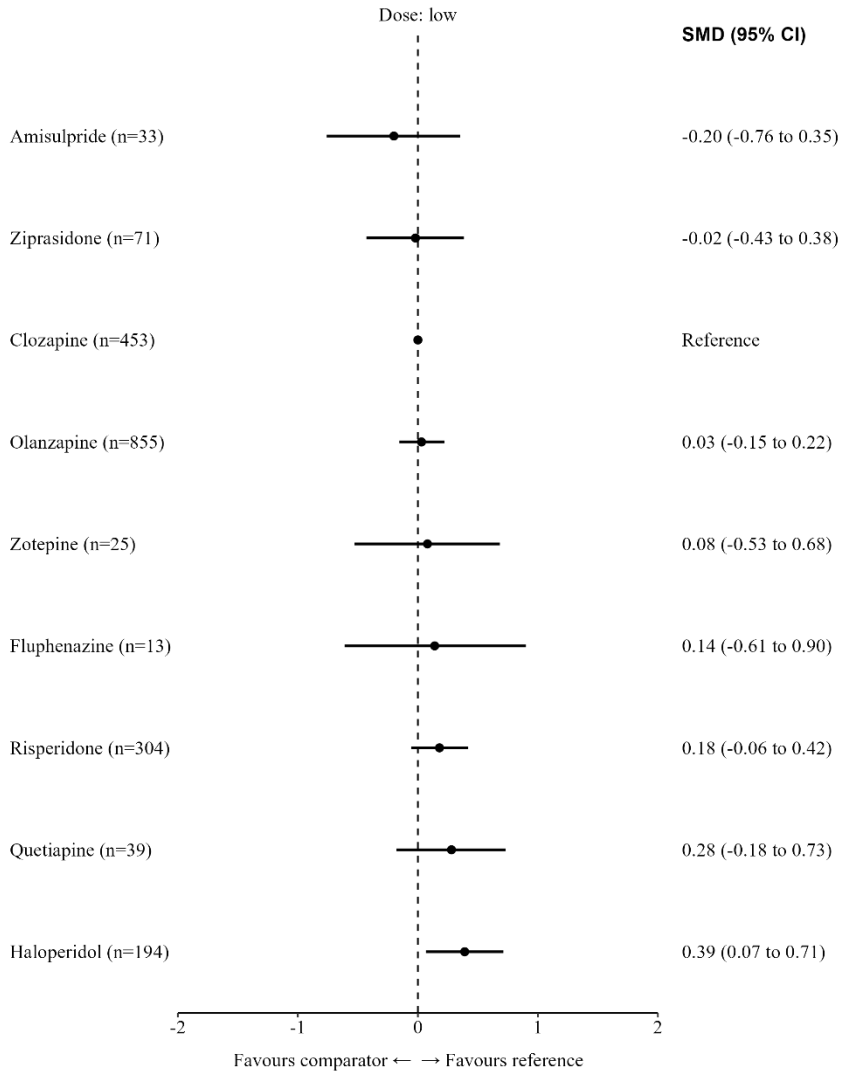
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1233	0.0817	10.0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	NA	NA	-0.24 (-0.76 to 0.29)	NA	NA	NA	NA	NA
-0.20 (-0.76 to 0.35)	**Clozapine**	0.02 (-0.38 to 0.43)	-0.03 (-0.25 to 0.18)	-0.08 (-0.68 to 0.53)	NA	-0.13 (-0.46 to 0.19)	**-1.01 (-1.84 to -0.18)**	-0.78 (-1.70 to 0.14)
-0.18 (-0.87 to 0.51)	0.02 (-0.38 to 0.43)	**Ziprasidone**	NA	NA	NA	NA	NA	NA
-0.24 (-0.76 to 0.29)	-0.03 (-0.22 to 0.15)	-0.06 (-0.50 to 0.39)	**Olanzapine**	NA	NA	-0.23 (-0.51 to 0.05)	-0.06 (-0.61 to 0.49)	**-0.32 (-0.61 to -0.03)**
-0.28 (-1.10 to 0.54)	-0.08 (-0.68 to 0.53)	-0.10 (-0.83 to 0.63)	-0.04 (-0.68 to 0.59)	**Zotepine**	NA	NA	NA	NA
-0.35 (-1.26 to 0.57)	-0.14 (-0.90 to 0.61)	-0.17 (-1.03 to 0.69)	-0.11 (-0.86 to 0.64)	-0.07 (-1.03 to 0.90)	**Fluphenazine**	-0.02 (-0.83 to 0.78)	-0.15 (-0.97 to 0.67)	NA
-0.38 (-0.96 to 0.19)	-0.18 (-0.42 to 0.06)	-0.20 (-0.67 to 0.27)	-0.15 (-0.37 to 0.08)	-0.10 (-0.75 to 0.55)	-0.04 (-0.77 to 0.70)	**Risperidone**	-0.06 (-0.71 to 0.60)	NA
-0.48 (-1.16 to 0.21)	-0.28 (-0.73 to 0.18)	-0.30 (-0.91 to 0.31)	-0.24 (-0.68 to 0.20)	-0.20 (-0.96 to 0.56)	-0.13 (-0.87 to 0.61)	-0.09 (-0.55 to 0.36)	**Quetiapine**	NA
-0.59 (-1.18 to 0.00)	**-0.39 (-0.71 to -0.07)**	-0.41 (-0.93 to 0.11)	**-0.36 (-0.63 to -0.08)**	-0.31 (-1.00 to 0.37)	-0.25 (-1.04 to 0.55)	-0.21 (-0.56 to 0.14)	-0.11 (-0.63 to 0.40)	**Haloperidol**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

12.4 Publication year

For the purpose of this analysis the median number of publication year was used.

a Early

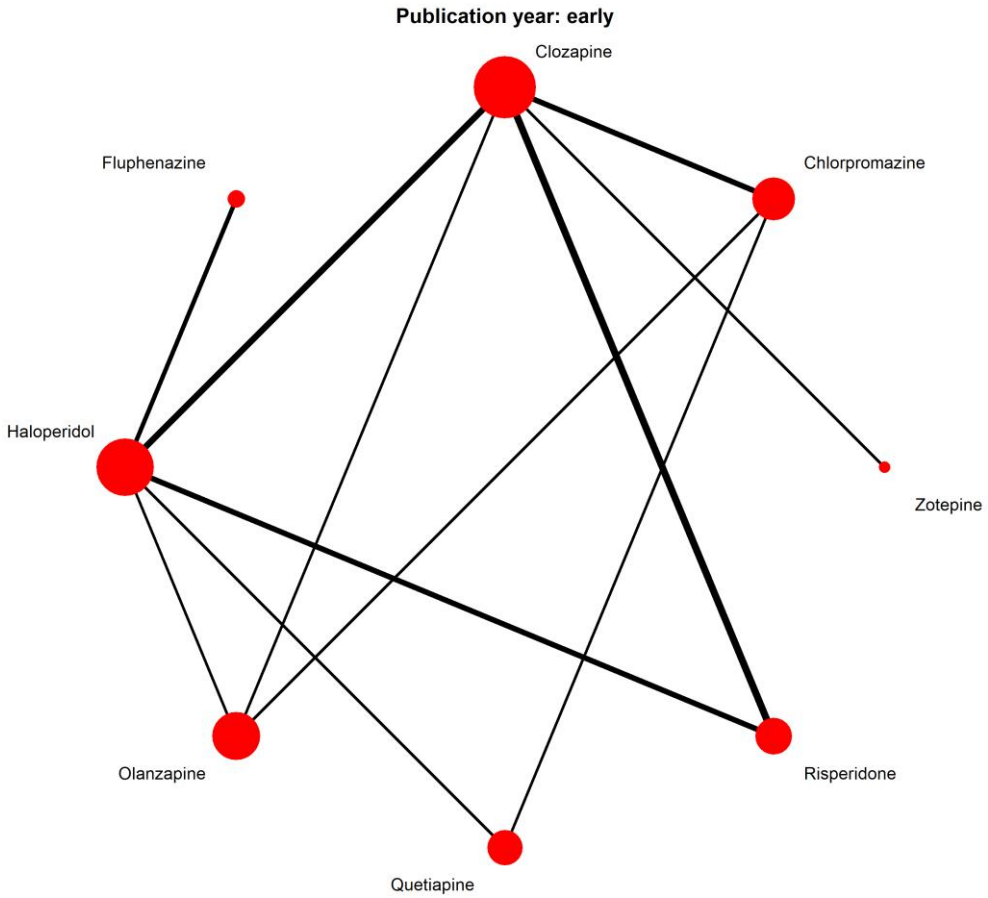
Number of studies: k = 23

Number of pairwise comparisons: m = 23

Number of treatments: n = 8

Number of designs: d = 11

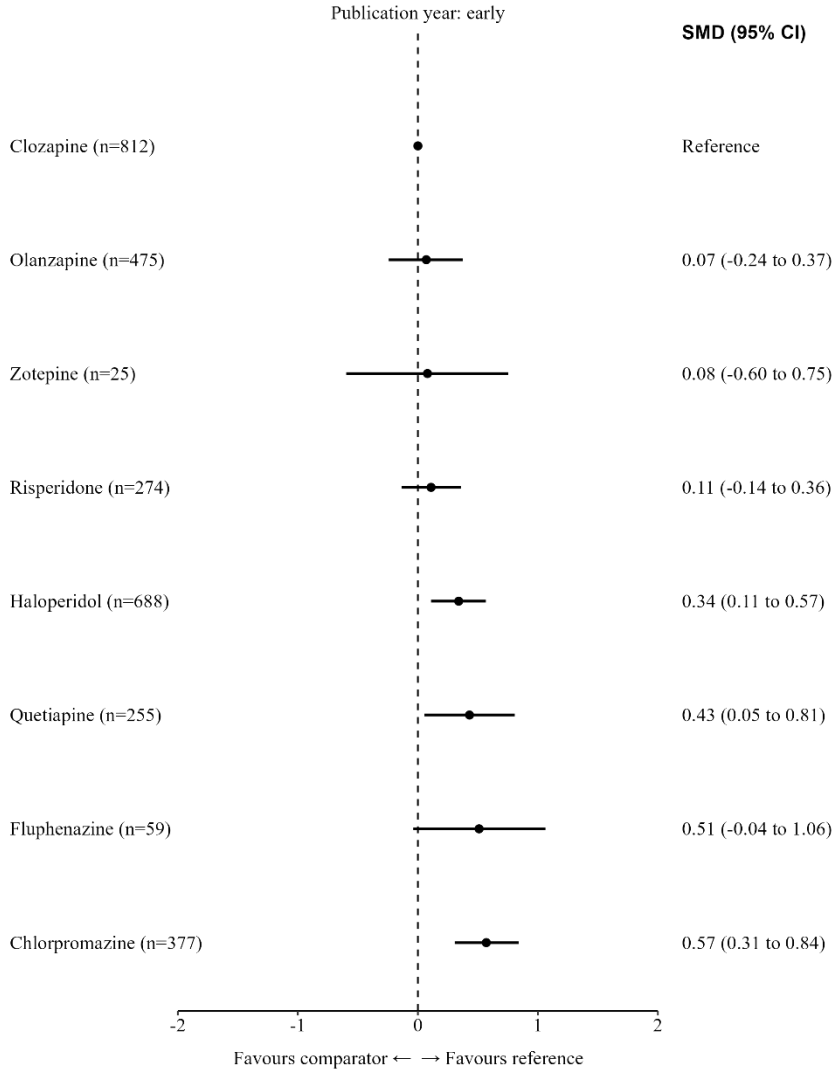
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1966	0.0136	33.33

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	0.14 (-0.34 to 0.63)	-0.08 (-0.37 to 0.20)	-0.08 (-0.75 to 0.60)	-0.26 (-0.57 to 0.04)	NA	NA	**-0.77 (-1.09 to -0.46)**
-0.07 (-0.37 to 0.24)	**Olanzapine**	NA	NA	-0.27 (-0.70 to 0.16)	NA	NA	-0.22 (-0.80 to 0.37)
-0.11 (-0.36 to 0.14)	-0.05 (-0.42 to 0.33)	**Risperidone**	NA	-0.16 (-0.59 to 0.27)	NA	NA	NA
-0.08 (-0.75 to 0.60)	-0.01 (-0.76 to 0.73)	0.03 (-0.69 to 0.75)	**Zotepine**	NA	NA	NA	NA
-0.34 (-0.57 to -0.11)	-0.27 (-0.58 to 0.04)	-0.23 (-0.51 to 0.06)	-0.26 (-0.97 to 0.45)	**Haloperidol**	0.14 (-0.31 to 0.59)	-0.17 (-0.68 to 0.33)	NA
-0.43 (-0.81 to -0.05)	-0.37 (-0.80 to 0.07)	-0.32 (-0.75 to 0.11)	-0.35 (-1.13 to 0.42)	-0.09 (-0.45 to 0.26)	**Quetiapine**	NA	0.11 (-0.36 to 0.57)
-0.51 (-1.06 to 0.04)	-0.45 (-1.04 to 0.14)	-0.40 (-0.98 to 0.18)	-0.43 (-1.31 to 0.44)	-0.17 (-0.68 to 0.33)	-0.08 (-0.70 to 0.53)	**Fluphenazine**	NA
-0.57 (-0.84 to -0.31)	**-0.51 (-0.86 to -0.16)**	**-0.46 (-0.82 to -0.11)**	-0.50 (-1.22 to 0.23)	-0.24 (-0.55 to 0.08)	-0.14 (-0.50 to 0.22)	-0.06 (-0.65 to 0.53)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

b Late

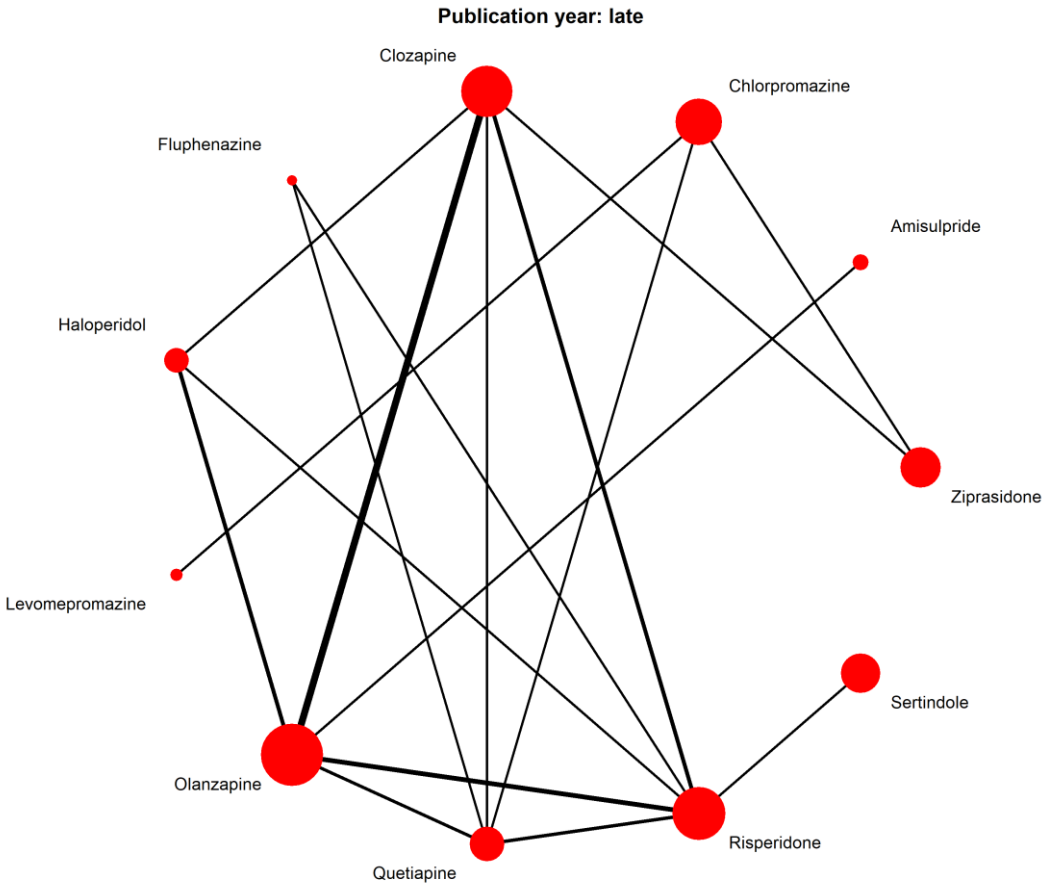
Number of studies: k = 22

Number of pairwise comparisons: m = 34

Number of treatments: n = 11

Number of designs: d = 14

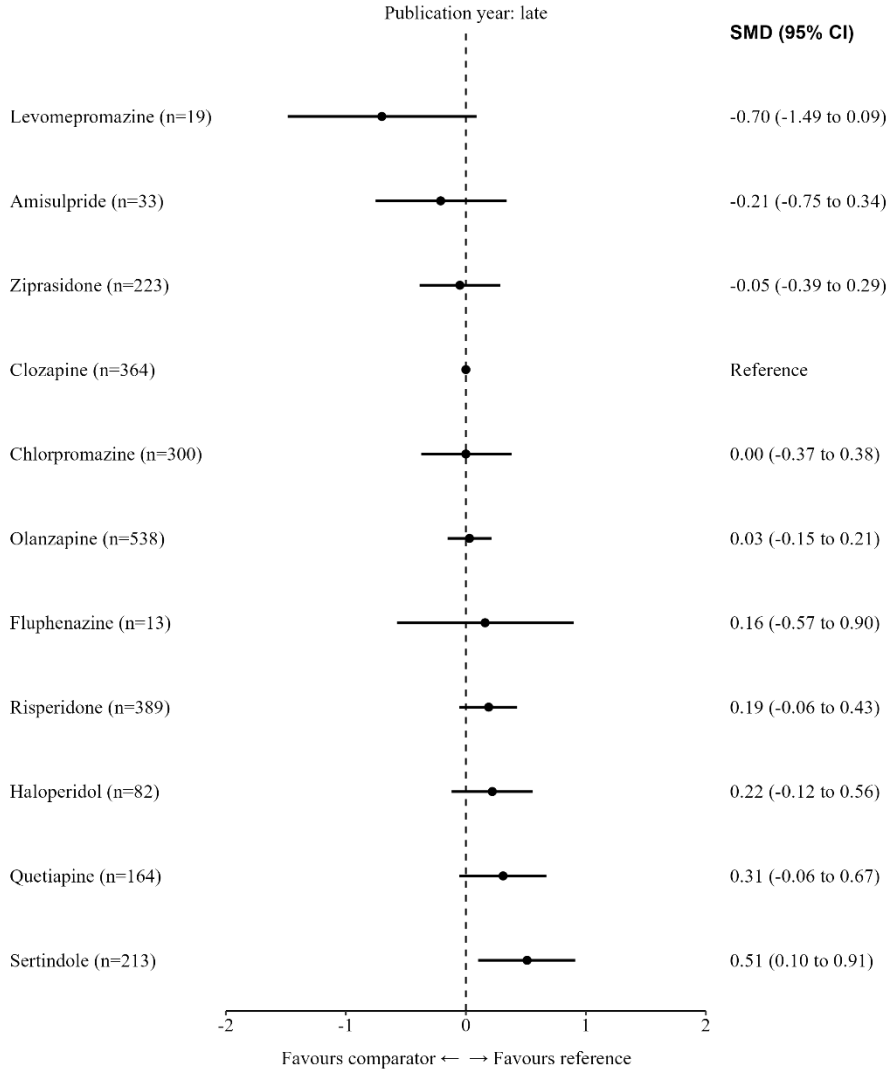
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.1125	0.0935	14.29

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Levomepromazine	NA	NA	NA	**-0.70 (-1.39 to -0.01)**	NA	NA	NA	NA	NA	NA
-0.49 (-1.44 to 0.45)	**Amisulpride**	NA	NA	NA	-0.24 (-0.75 to 0.28)	NA	NA	NA	NA	NA
-0.65 (-1.40 to 0.10)	-0.16 (-0.79 to 0.47)	**Ziprasidone**	-0.02 (-0.42 to 0.37)	-0.07 (-0.39 to 0.24)	NA	NA	NA	NA	NA	NA
-0.70 (-1.49 to 0.09)	-0.21 (-0.75 to 0.34)	-0.05 (-0.39 to 0.29)	**Clozapine**	NA	-0.03 (-0.23 to 0.17)	NA	-0.02 (-0.37 to 0.33)	0.12 (-0.38 to 0.62)	**-1.01 (-1.83 to -0.19)**	NA
-0.70 (-1.39 to -0.01)	-0.21 (-0.86 to 0.44)	-0.05 (-0.34 to 0.23)	-0.00 (-0.38 to 0.37)	**Chlorpromazine**	NA	NA	NA	NA	-0.32 (-0.65 to 0.01)	NA
-0.73 (-1.52 to 0.07)	-0.24 (-0.75 to 0.28)	-0.08 (-0.44 to 0.28)	-0.03 (-0.21 to 0.15)	-0.03 (-0.42 to 0.36)	**Olanzapine**	NA	-0.23 (-0.47 to 0.00)	-0.29 (-0.62 to 0.05)	-0.06 (-0.60 to 0.49)	NA
-0.86 (-1.89 to 0.17)	-0.37 (-1.26 to 0.53)	-0.21 (-0.98 to 0.56)	-0.16 (-0.90 to 0.57)	-0.16 (-0.92 to 0.60)	-0.13 (-0.86 to 0.60)	**Fluphenazine**	-0.02 (-0.82 to 0.78)	NA	-0.15 (-0.96 to 0.67)	NA
-0.88 (-1.69 to -0.08)	-0.39 (-0.95 to 0.16)	-0.24 (-0.63 to 0.16)	-0.19 (-0.43 to 0.06)	-0.18 (-0.60 to 0.23)	-0.16 (-0.37 to 0.05)	-0.02 (-0.75 to 0.70)	**Risperidone**	-0.12 (-0.62 to 0.37)	-0.06 (-0.71 to 0.59)	-0.32 (-0.64 to 0.00)
-0.92 (-1.76 to -0.07)	-0.43 (-1.03 to 0.18)	-0.27 (-0.73 to 0.20)	-0.22 (-0.56 to 0.12)	-0.21 (-0.70 to 0.27)	-0.19 (-0.50 to 0.12)	-0.06 (-0.84 to 0.73)	-0.03 (-0.38 to 0.31)	**Haloperidol**	NA	NA
-1.01 (-1.76 to -0.25)	-0.51 (-1.14 to 0.12)	-0.36 (-0.72 to 0.01)	-0.31 (-0.67 to 0.06)	-0.30 (-0.60 to 0.00)	-0.28 (-0.64 to 0.09)	-0.15 (-0.87 to 0.58)	-0.12 (-0.51 to 0.27)	-0.09 (-0.56 to 0.38)	**Quetiapine**	NA
-1.20 (-2.07 to -0.34)	**-0.71 (-1.36 to -0.07)**	**-0.56 (-1.06 to -0.05)**	**-0.51 (-0.91 to -0.10)**	-0.50 (-1.03 to 0.02)	**-0.48 (-0.86 to -0.09)**	-0.34 (-1.13 to 0.45)	-0.32 (-0.64 to 0.00)	-0.29 (-0.76 to 0.19)	-0.20 (-0.70 to 0.31)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

12.5 Baseline severity

For the purpose of this analysis the median baseline severity of each scale was used.

a High

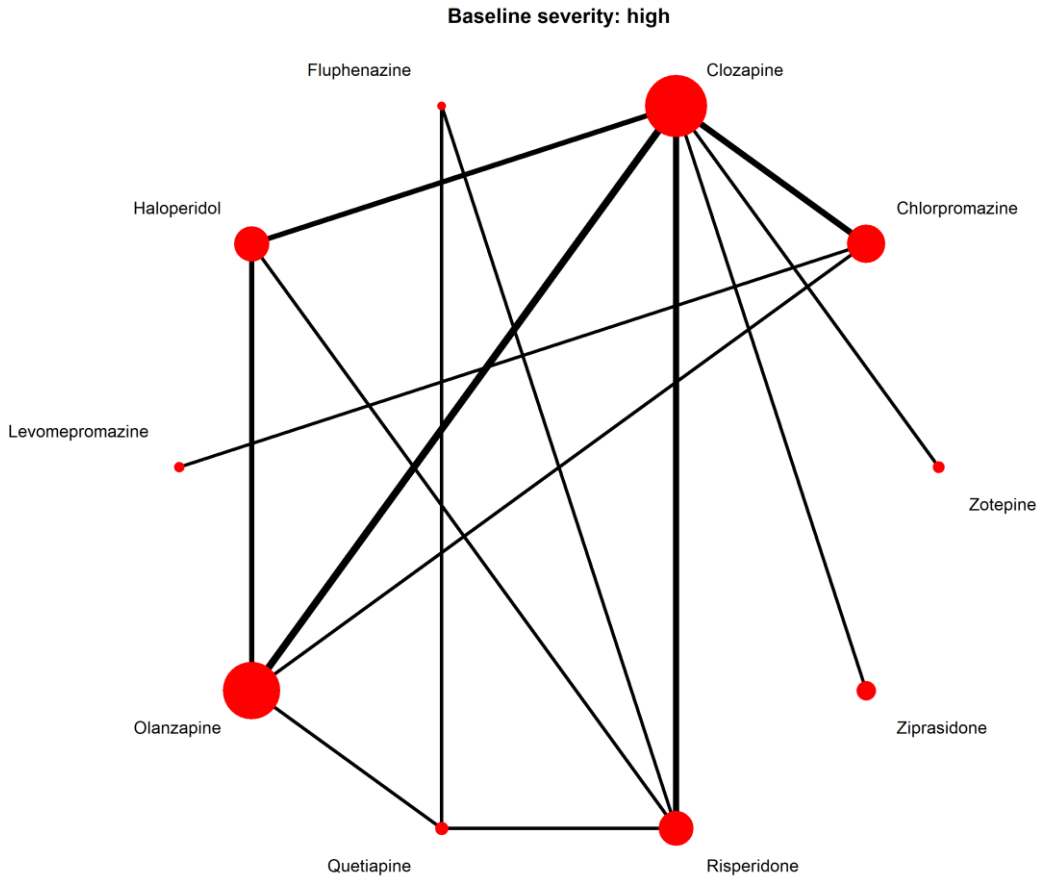
Number of studies: k = 21

Number of pairwise comparisons: m = 23

Number of treatments: n = 10

Number of designs: d = 12

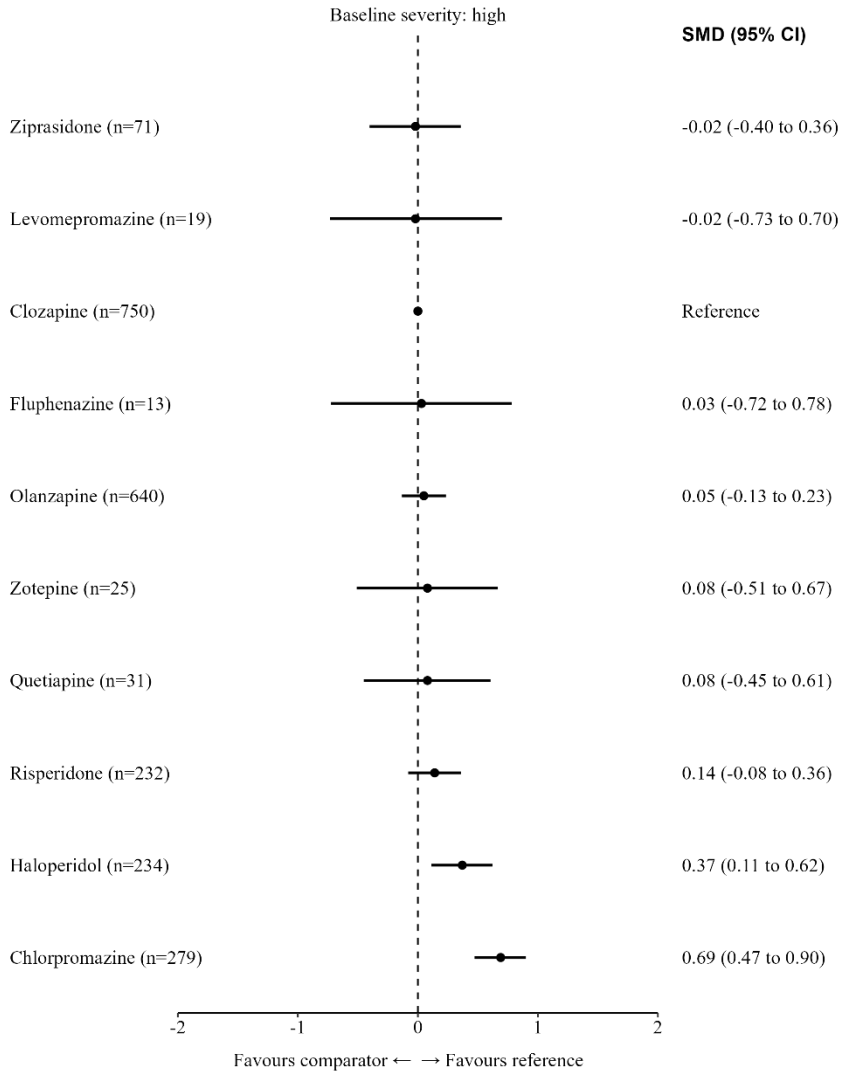
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.0986	0.1524	27.27

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	0.02 (-0.36 to 0.40)	NA	NA	0.05 (-0.16 to 0.27)	NA	-0.08 (-0.67 to 0.51)	-0.14 (-0.38 to 0.10)	-0.47 (-1.05 to 0.10)	**-0.79 (-1.02 to -0.55)**
0.02 (-0.36 to 0.40)	**Ziprasidone**	NA	NA	NA	NA	NA	NA	NA	NA
0.02 (-0.70 to 0.73)	-0.01 (-0.82 to 0.80)	**Levomepromazine**	NA	NA	NA	NA	NA	NA	**-0.70 (-1.39 to -0.02)**
-0.03 (-0.78 to 0.72)	-0.05 (-0.89 to 0.79)	-0.04 (-1.08 to 0.99)	**Fluphenazine**	NA	-0.15 (-0.96 to 0.66)	NA	-0.02 (-0.81 to 0.77)	NA	NA
-0.05 (-0.23 to 0.13)	-0.07 (-0.50 to 0.35)	-0.07 (-0.80 to 0.66)	-0.02 (-0.78 to 0.73)	**Olanzapine**	0.09 (-0.56 to 0.74)	NA	NA	**-0.31 (-0.56 to -0.06)**	-0.22 (-0.69 to 0.26)
-0.08 (-0.61 to 0.45)	-0.10 (-0.75 to 0.55)	-0.09 (-0.98 to 0.79)	-0.05 (-0.79 to 0.69)	-0.03 (-0.54 to 0.49)	**Quetiapine**	NA	0.12 (-0.68 to 0.93)	NA	NA
-0.08 (-0.67 to 0.51)	-0.10 (-0.80 to 0.60)	-0.09 (-1.02 to 0.83)	-0.05 (-1.00 to 0.90)	-0.03 (-0.64 to 0.59)	-0.00 (-0.79 to 0.79)	**Zotepine**	NA	NA	NA
-0.14 (-0.36 to 0.08)	-0.16 (-0.60 to 0.28)	-0.16 (-0.90 to 0.59)	-0.11 (-0.85 to 0.62)	-0.09 (-0.36 to 0.18)	-0.06 (-0.59 to 0.47)	-0.06 (-0.69 to 0.57)	**Risperidone**	-0.16 (-0.71 to 0.39)	NA
-0.37 (-0.62 to -0.11)	-0.39 (-0.85 to 0.07)	-0.38 (-1.14 to 0.37)	-0.34 (-1.11 to 0.44)	**-0.32 (-0.54 to -0.09)**	-0.29 (-0.84 to 0.26)	-0.29 (-0.93 to 0.35)	-0.23 (-0.53 to 0.07)	**Haloperidol**	NA
-0.69 (-0.90 to -0.47)	**-0.71 (-1.14 to -0.27)**	**-0.70 (-1.39 to -0.02)**	-0.66 (-1.44 to 0.12)	**-0.63 (-0.89 to -0.38)**	**-0.61 (-1.17 to -0.05)**	-0.61 (-1.23 to 0.02)	**-0.55 (-0.85 to -0.24)**	-0.32 (-0.64 to 0.00)	**Chlorpromazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

b Low

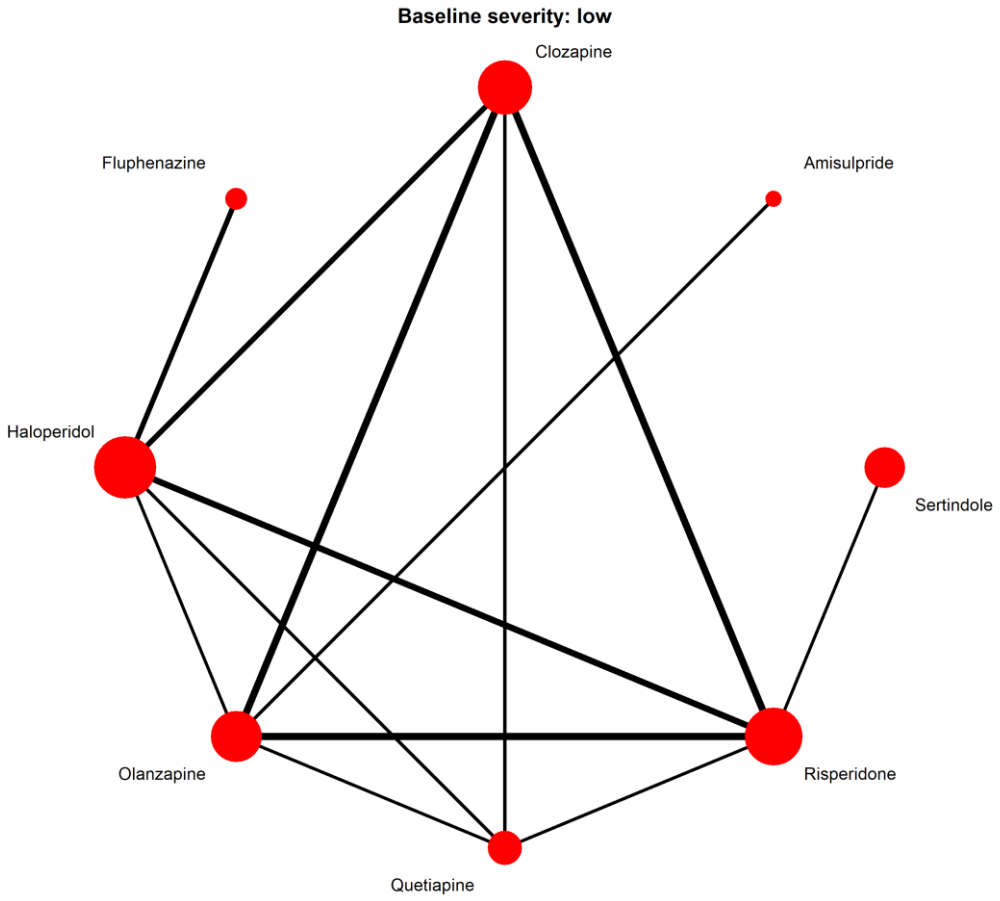
Number of studies: k = 19

Number of pairwise comparisons: m = 26

Number of treatments: n = 8

Number of designs: d = 11

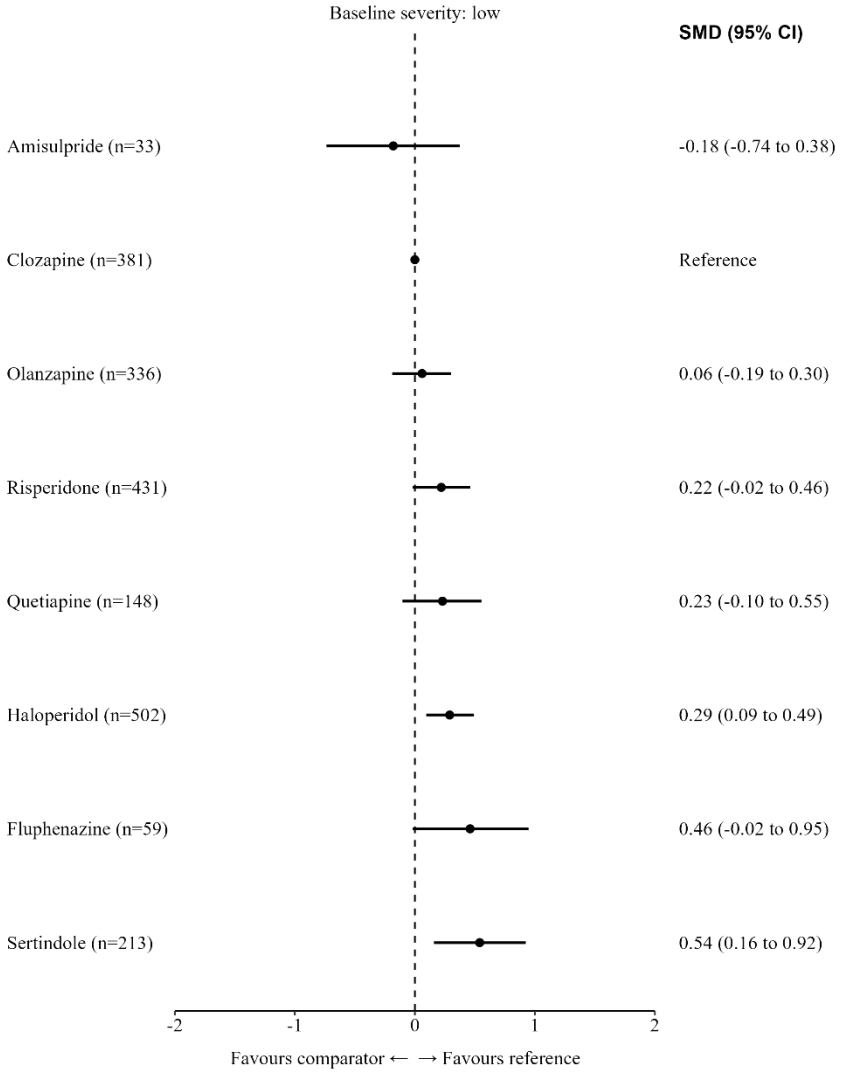
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.0925	0.1893	20.0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Amisulpride	NA	-0.24 (-0.74 to 0.26)	NA	NA	NA	NA	NA
-0.18 (-0.74 to 0.38)	**Clozapine**	-0.28 (-0.63 to 0.07)	**-1.01 (-1.82 to -0.20)**	-0.18 (-0.55 to 0.20)	-0.21 (-0.44 to 0.02)	NA	NA
-0.24 (-0.74 to 0.26)	-0.06 (-0.30 to 0.19)	**Olanzapine**	-0.38 (-1.33 to 0.57)	**-0.23 (-0.45 to -0.01)**	-0.36 (-0.85 to 0.12)	NA	NA
-0.41 (-1.03 to 0.21)	-0.23 (-0.55 to 0.10)	-0.17 (-0.54 to 0.20)	**Quetiapine**	-0.06 (-1.13 to 1.01)	-0.14 (-0.44 to 0.15)	NA	NA
-0.40 (-0.94 to 0.14)	-0.22 (-0.46 to 0.02)	-0.17 (-0.37 to 0.04)	0.00 (-0.36 to 0.37)	**Risperidone**	-0.13 (-0.48 to 0.22)	NA	**-0.32 (-0.62 to -0.02)**
-0.47 (-1.04 to 0.09)	**-0.29 (-0.49 to -0.09)**	-0.24 (-0.50 to 0.03)	-0.07 (-0.35 to 0.21)	-0.07 (-0.32 to 0.18)	**Haloperidol**	-0.17 (-0.61 to 0.27)	NA
-0.65 (-1.36 to 0.07)	-0.46 (-0.95 to 0.02)	-0.41 (-0.92 to 0.10)	-0.24 (-0.76 to 0.28)	-0.24 (-0.75 to 0.26)	-0.17 (-0.61 to 0.27)	**Fluphenazine**	NA
-0.72 (-1.34 to -0.11)	**-0.54 (-0.92 to -0.16)**	**-0.49 (-0.85 to -0.13)**	-0.32 (-0.78 to 0.15)	**-0.32 (-0.62 to -0.02)**	-0.25 (-0.64 to 0.14)	-0.08 (-0.66 to 0.51)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

12.6 Study duration

For the purpose of this analysis the median number of study duration was used.

a Short

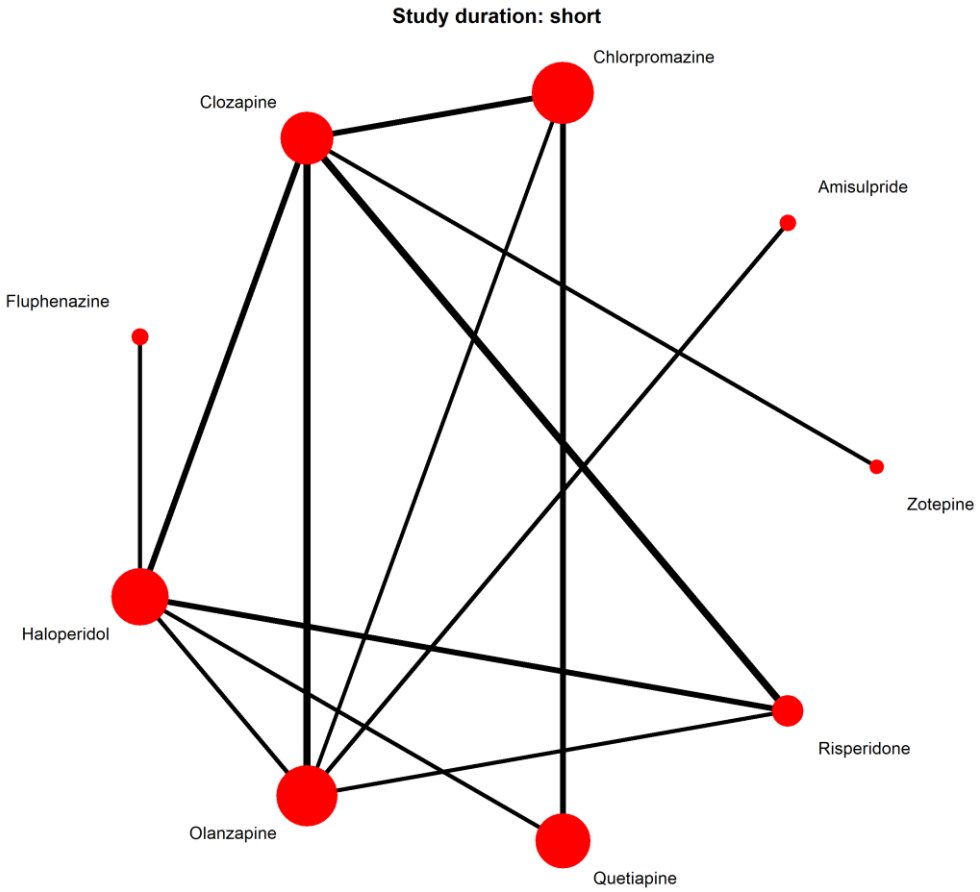
Number of studies: k = 21

Number of pairwise comparisons: m = 21

Number of treatments: n = 9

Number of designs: d = 13

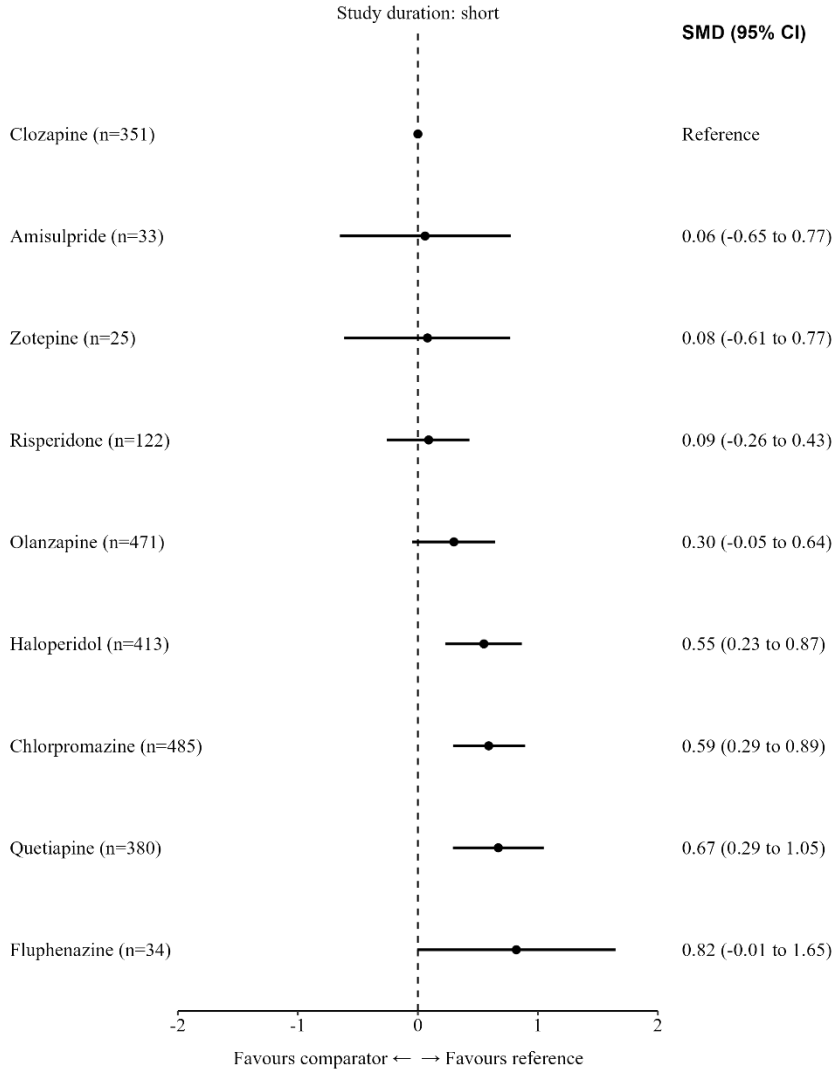
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.2106	0.0370	30.0

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

League table

Clozapine	0.10 (-0.33 to 0.54)	NA	-0.08 (-0.77 to 0.61)	-0.46 (-1.06 to 0.15)	-0.32 (-0.84 to 0.20)	**-0.78 (-1.14 to -0.41)**	NA	NA
-0.09 (-0.43 to 0.26)	**Risperidone**	NA	NA	0.15 (-0.66 to 0.96)	-0.33 (-0.88 to 0.22)	NA	NA	NA
-0.06 (-0.77 to 0.65)	0.02 (-0.72 to 0.77)	**Amisulpride**	NA	-0.24 (-0.86 to 0.39)	NA	NA	NA	NA
-0.08 (-0.77 to 0.61)	0.01 (-0.77 to 0.78)	-0.02 (-1.01 to 0.98)	**Zotepine**	NA	NA	NA	NA	NA
-0.30 (-0.64 to 0.05)	-0.21 (-0.62 to 0.19)	-0.24 (-0.86 to 0.39)	-0.22 (-0.99 to 0.55)	**Olanzapine**	-0.27 (-0.72 to 0.18)	-0.22 (-0.82 to 0.39)	NA	NA
-0.55 (-0.87 to -0.23)	**-0.46 (-0.83 to -0.09)**	-0.49 (-1.19 to 0.22)	-0.47 (-1.23 to 0.29)	-0.25 (-0.58 to 0.08)	**Haloperidol**	NA	0.14 (-0.33 to 0.62)	-0.27 (-1.04 to 0.49)
-0.59 (-0.89 to -0.29)	**-0.51 (-0.93 to -0.09)**	-0.53 (-1.25 to 0.19)	-0.52 (-1.27 to 0.24)	-0.30 (-0.66 to 0.07)	-0.05 (-0.40 to 0.31)	**Chlorpromazine**	-0.22 (-0.56 to 0.13)	NA
-0.67 (-1.05 to -0.29)	**-0.58 (-1.04 to -0.13)**	-0.61 (-1.36 to 0.14)	-0.59 (-1.38 to 0.20)	-0.37 (-0.79 to 0.05)	-0.12 (-0.48 to 0.24)	-0.08 (-0.38 to 0.23)	**Quetiapine**	NA
-0.82 (-1.65 to 0.01)	-0.74 (-1.58 to 0.11)	-0.76 (-1.80 to 0.28)	-0.74 (-1.82 to 0.34)	-0.52 (-1.36 to 0.31)	-0.27 (-1.04 to 0.49)	-0.23 (-1.07 to 0.61)	-0.15 (-0.99 to 0.69)	**Fluphenazine**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

b Long

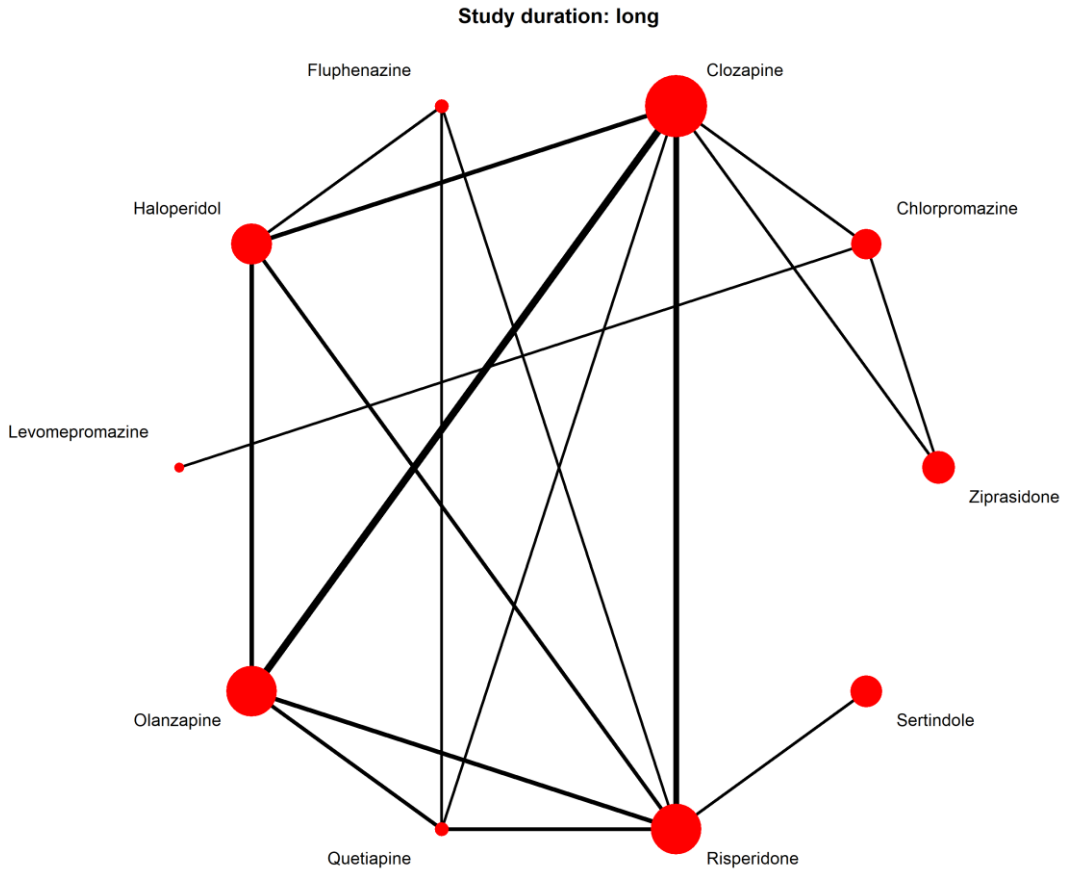
Number of studies: k = 24

Number of pairwise comparisons: m = 36

Number of treatments: n = 10

Number of designs: d = 16

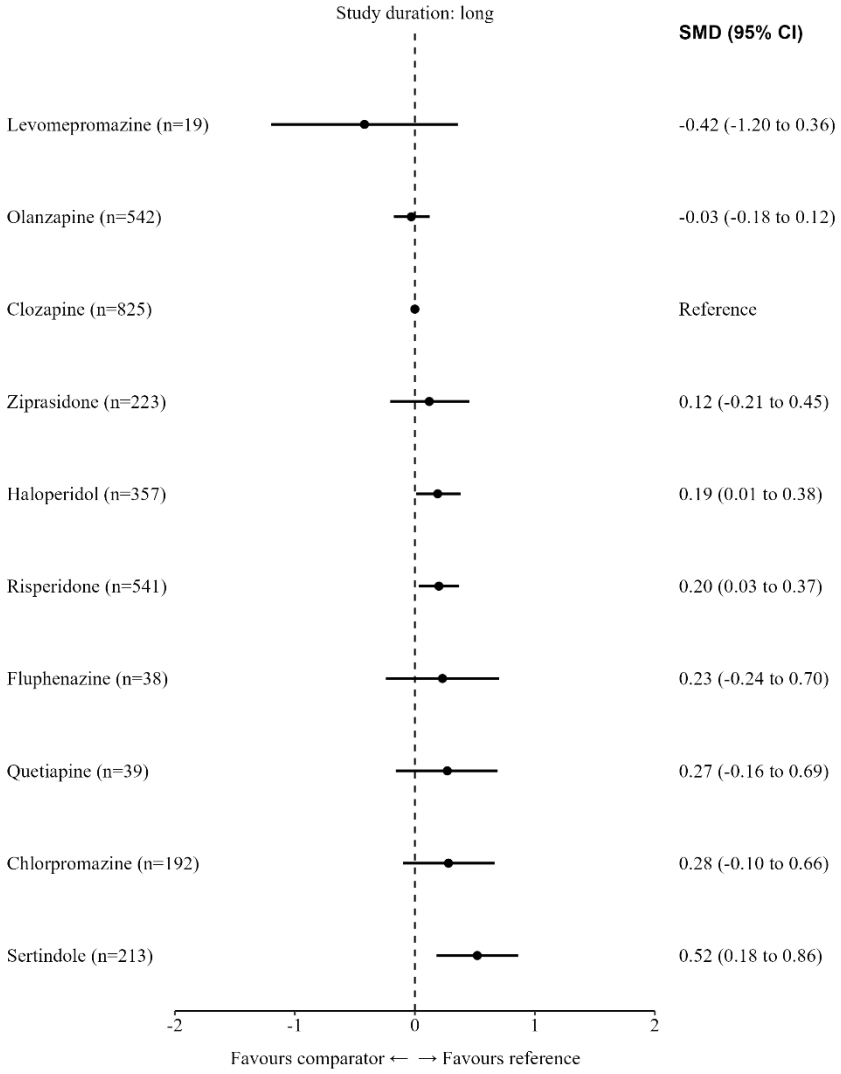
Network plot



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.

τ	P-value	Inconsistency loop (%)
0.0893	**0.1223**	**26.67**

Forest-plot of results of network meta-analysis for antipsychotic drugs versus clozapine



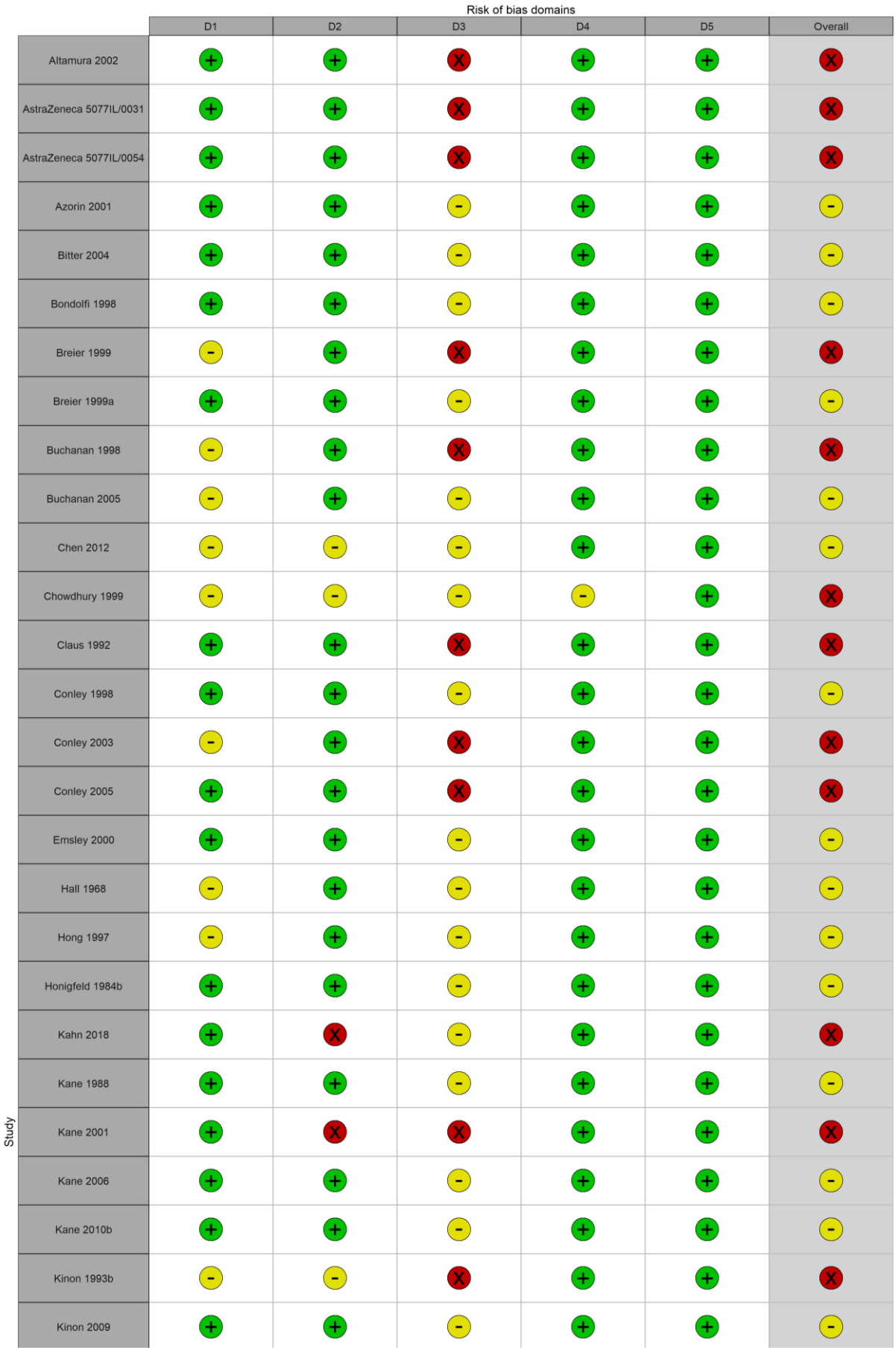
Effect sizes, measured as standardized mean difference (SMD), are from the network meta-analysis. Order of treatments is according to the mean effect size. Reference is clozapine. The direction of the effect is indicated below the x-axis.

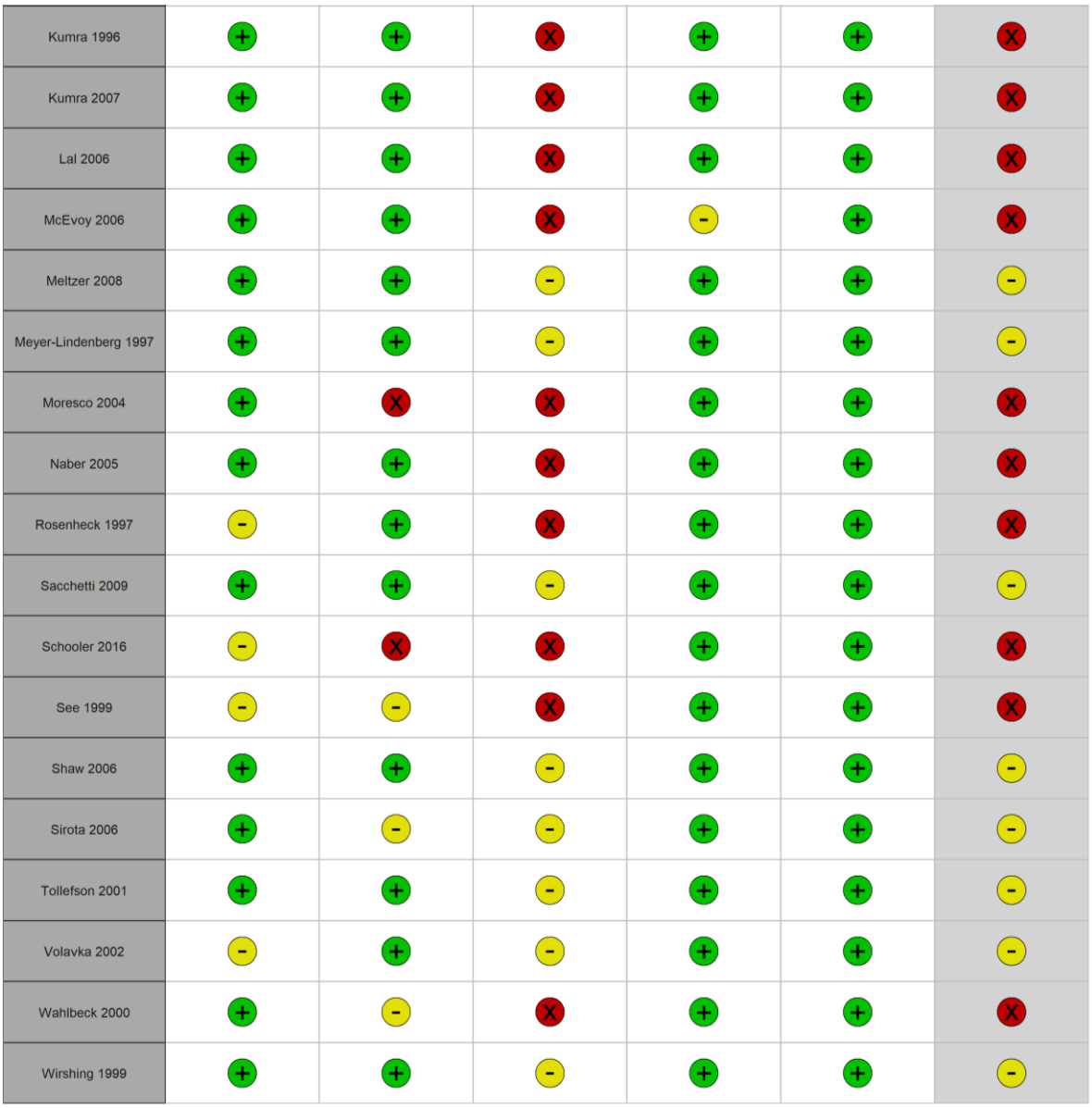
League table

Levomepromazine	NA	NA	NA	NA	NA	NA	NA	**-0.70 (-1.38 to -0.02)**	NA
-0.39 (-1.19 to 0.40)	**Olanzapine**	-0.06 (-0.24 to 0.11)	NA	-0.28 (-0.61 to 0.05)	**-0.24 (-0.47 to -0.01)**	NA	-0.06 (-0.59 to 0.48)	NA	NA
-0.42 (-1.20 to 0.36)	-0.03 (-0.18 to 0.12)	**Clozapine**	0.02 (-0.35 to 0.39)	-0.16 (-0.38 to 0.06)	-0.17 (-0.38 to 0.05)	NA	**-1.01 (-1.82 to -0.20)**	**-0.76 (-1.42 to -0.09)**	NA
-0.54 (-1.27 to 0.18)	-0.15 (-0.51 to 0.21)	-0.12 (-0.45 to 0.21)	**Ziprasidone**	NA	NA	NA	NA	-0.07 (-0.36 to 0.21)	NA
-0.62 (-1.42 to 0.19)	**-0.22 (-0.43 to -0.01)**	**-0.19 (-0.38 to -0.01)**	-0.07 (-0.45 to 0.31)	**Haloperidol**	0.03 (-0.35 to 0.41)	-0.09 (-0.67 to 0.49)	NA	NA	NA
-0.62 (-1.42 to 0.18)	**-0.23 (-0.40 to -0.05)**	**-0.20 (-0.37 to -0.03)**	-0.07 (-0.45 to 0.30)	-0.00 (-0.22 to 0.22)	**Risperidone**	0.02 (-0.77 to 0.81)	-0.06 (-0.70 to 0.59)	NA	**-0.32 (-0.62 to -0.03)**
-0.65 (-1.56 to 0.26)	-0.26 (-0.73 to 0.22)	-0.23 (-0.70 to 0.24)	-0.11 (-0.68 to 0.47)	-0.04 (-0.49 to 0.42)	-0.03 (-0.50 to 0.44)	**Fluphenazine**	-0.15 (-0.95 to 0.66)	NA	NA
-0.69 (-1.57 to 0.20)	-0.29 (-0.71 to 0.13)	-0.27 (-0.69 to 0.16)	-0.14 (-0.68 to 0.40)	-0.07 (-0.51 to 0.37)	-0.07 (-0.49 to 0.36)	-0.04 (-0.60 to 0.53)	**Quetiapine**	NA	NA
-0.70 (-1.38 to -0.02)	-0.31 (-0.72 to 0.10)	-0.28 (-0.66 to 0.10)	-0.16 (-0.42 to 0.11)	-0.09 (-0.51 to 0.34)	-0.08 (-0.50 to 0.34)	-0.05 (-0.66 to 0.56)	-0.02 (-0.59 to 0.55)	**Chlorpromazine**	NA
-0.94 (-1.79 to -0.09)	**-0.55 (-0.89 to -0.20)**	**-0.52 (-0.86 to -0.18)**	-0.40 (-0.87 to 0.08)	-0.33 (-0.69 to 0.04)	**-0.32 (-0.62 to -0.03)**	-0.29 (-0.85 to 0.27)	-0.25 (-0.77 to 0.26)	-0.24 (-0.75 to 0.27)	**Sertindole**

Treatments are presented in order of efficacy ranking. Results of the network meta-analysis are reported in the left lower half and results of pairwise meta-analyses in the right upper half. Each cell provides the effect estimate and the corresponding 95% credible interval (95% CI) of a comparison (left lower half: treatment in column versus treatment in row; right upper half: treatment in row versus treatment in column). The type of effect size measure is standardized mean difference (SMD). Bold results indicate 95% CI excluding no effect. NA=not available.

13 Risk of bias Assessment





Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

14 Investigation of the small-study effect and publication bias

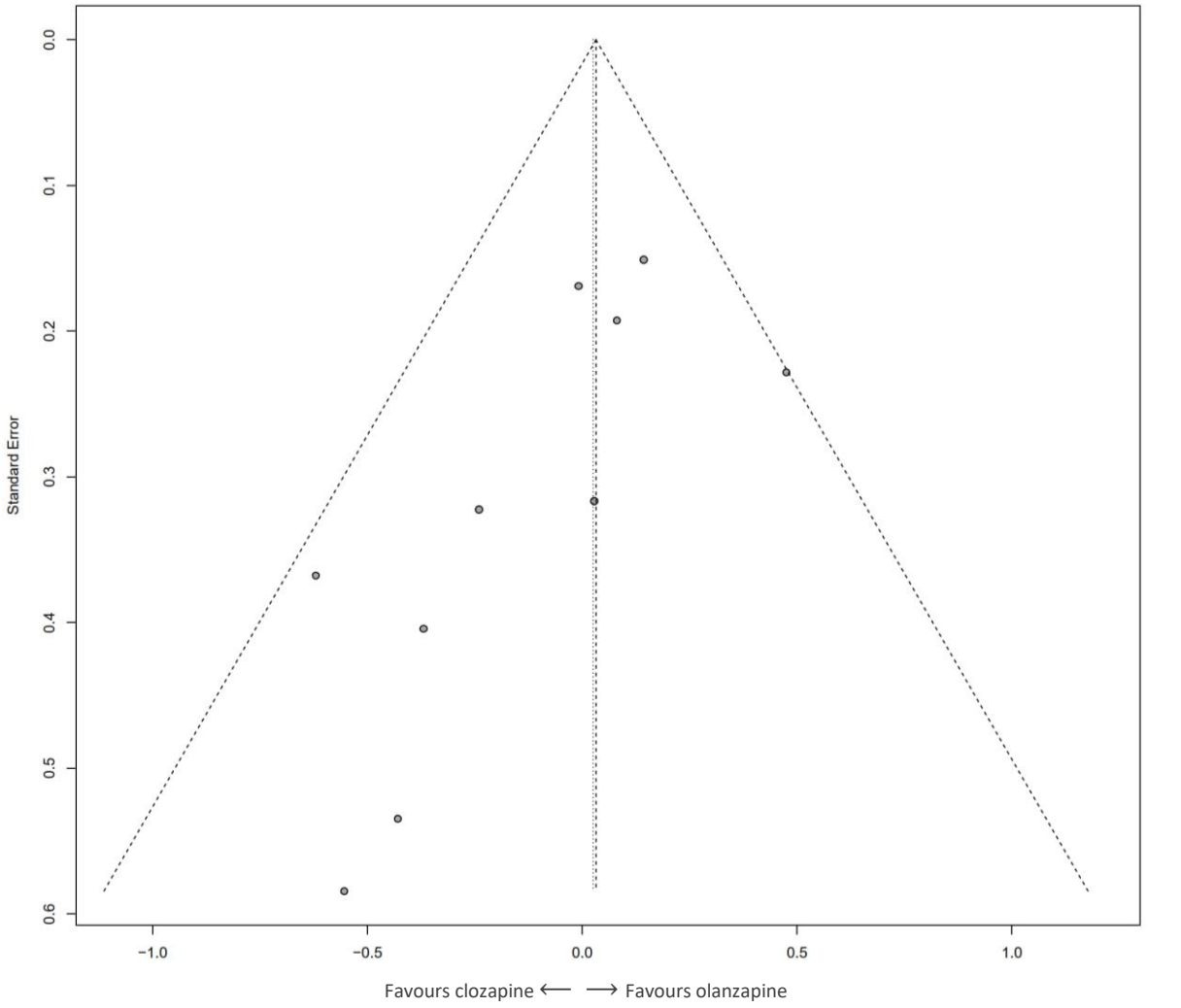
We investigated the presence of the small-study effect for the primary outcome of overall symptoms of schizophrenia. We used funnel plots for pairwise meta-analysis including 10 or more studies and comparison-adjusted funnel plots for network meta-analysis. In our study only one comparison, clozapine versus olanzapine, included 10 studies.

In comparison-adjusted funnel plots, comparisons have been directed according to the oldness and the effectiveness of the treatments: namely, all comparisons are “older interventions versus newer interventions” and “more efficacious interventions versus less efficacious interventions,” respectively. Each comparison is represented by a different colored symbol in the graph. The x-axis shows the difference between the study effect and the summary effect for each comparison, while the y-axis depicts the standard error of the observed effect size. Potential asymmetry would indicate a form of small-study effects depending on the defined direction, while symmetry in the funnel plot suggests lack of evidence of small-study effects. Egger’s tests for funnel plot asymmetry results are also presented.

Comparison-adjusted funnel plots suggest no clear indication of small-study effects in general. However, small-study effects could be suspected of clozapine-olanzapine studies according to the funnel plot for pairwise meta-analysis.

Funnel plot of pairwise meta-analysis for clozapine and olanzapine

Potential missing studies on the right side of the figure would indicate that small studies are likely to provide larger effects in clozapine. The Egger's test shows the asymmetry is significant ($p < 0.05$).

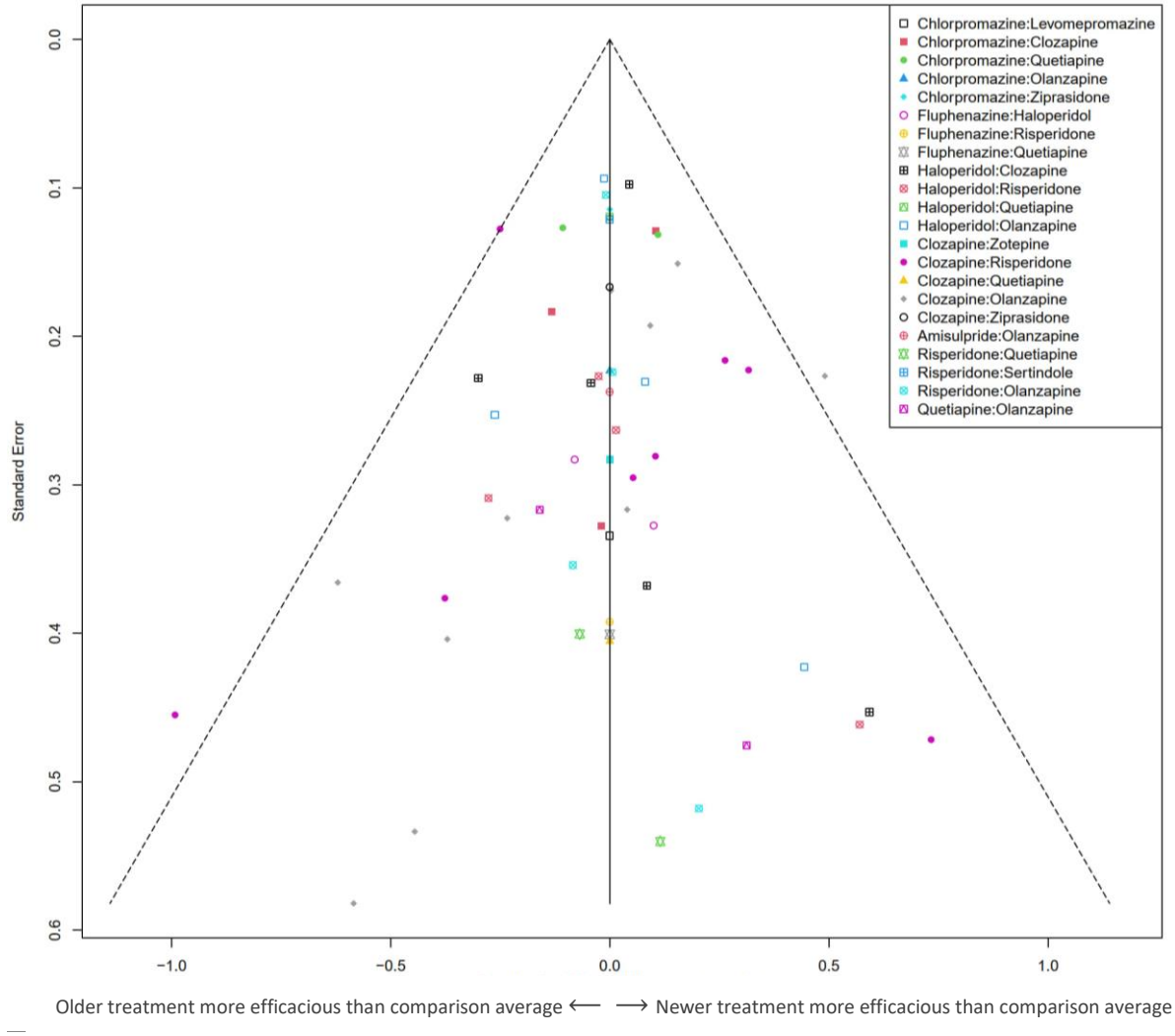


Egger's test for funnel plot asymmetry

t	df	p-value
-2.51	8	0.0364

Comparison-adjusted funnel plot for the primary outcome according to oldness of the treatment

Potential missing studies on the left side of the figure would indicate that small studies are likely to provide larger effects for the newer interventions. However, the Egger's test shows the asymmetry is not significant.

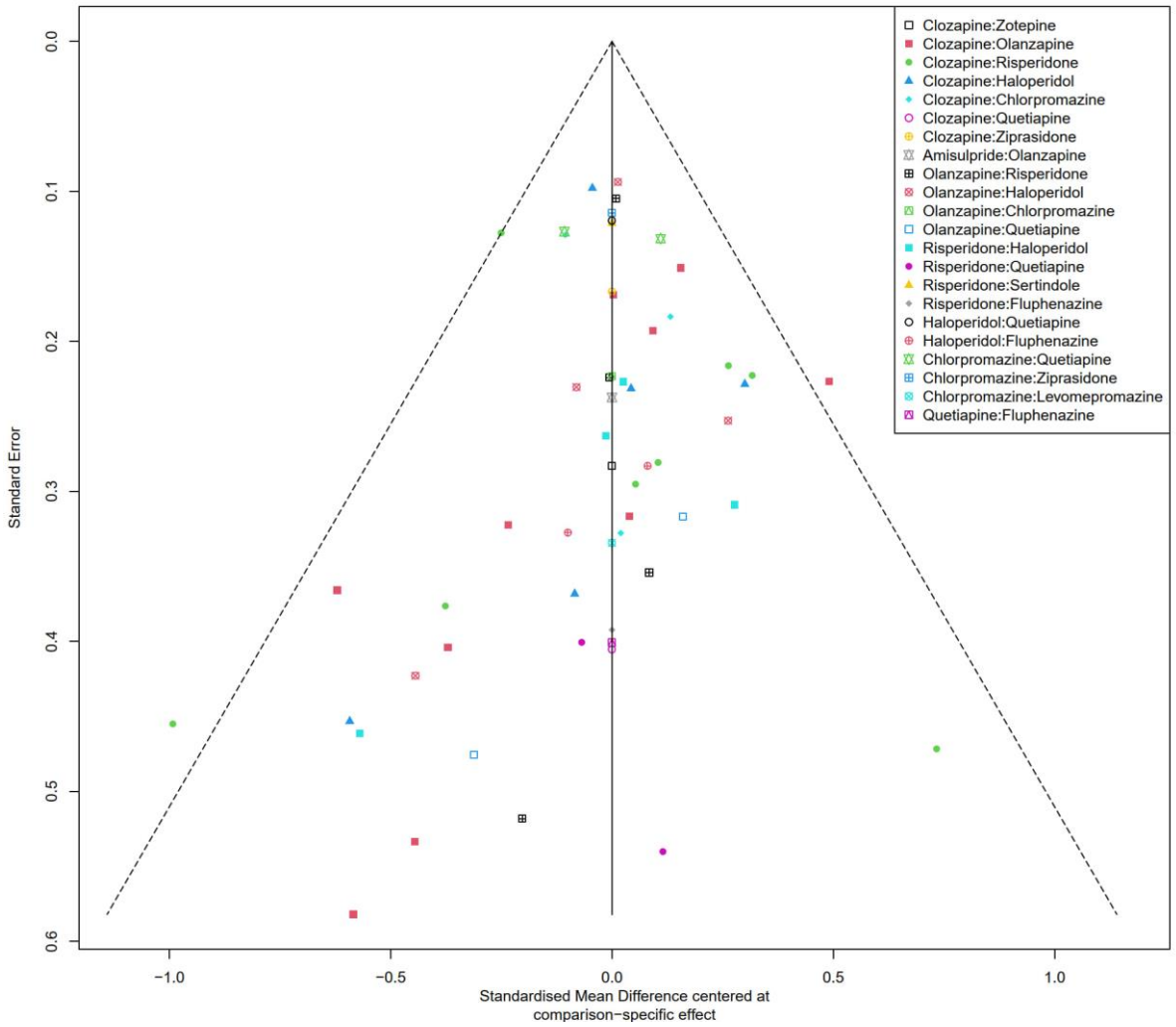


Egger's test for funnel plot asymmetry

t	df	p-value
-0.25	55	0.8049

Comparison-adjusted funnel plot for the primary outcome according to effectiveness of the treatment

Potential missing studies on the right side of the figure would indicate that small studies are likely to provide larger effects for the more efficacious interventions. However, the Egger's test shows the asymmetry is not significant.



Treatment higher in the total ranking appears more efficacious than comparison average ⟵ ⟶ Treatment lower in the total ranking appears more efficacious than comparison average

Egger's test for funnel plot asymmetry

t	df	p-value
-1.02	55	0.3120

15 Evaluating the confidence in NMA: CINeMA

We evaluated the confidence in evidence of network meta-analytic estimates for the primary outcome with Confidence in Network Meta-Analysis (CINeMA) framework[81] and the official online tool (https://cinema.ispm.unibe.ch/). The CINeMA framework considers six domains that affect the level of confidence in the NMA results: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. These domains are evaluated for each comparison, which subsequently determine an overall confidence in evidence for a comparison. The tool estimates the contribution of each study to the effect size of a comparison using original data and then calculates a contribution matrix. Therefore, some settings and judgements need to be given, which we report in the following.

Domain 1: Within-study bias

We assessed within-study bias using the overall risk of bias rating from the Cochrane's RoB 2.0. Within-study bias for each comparison was classified into "no concerns," "some concerns," and "major concerns" based on the average overall risk of bias according to the contribution matrix.

Domain 2: Reporting bias

We accessed reporting bias using ROB-MEN (Risk of Bias due to Missing Evidence in Network meta-analysis).[83] ROB-MEN, as part of the CINeMA framework, is a web application (https://cinema.ispm.unibe.ch/rob-men/) that simplifies the evaluation of risk of bias due to missing evidence in the estimates from network meta-analysis. The tool has two core parts: the Pairwise Comparisons table and the ROB-MEN table. After the assessment within both tables, a level of "low risk," "some concerns," or "high risk" for the bias due to missing evidence is assigned to each comparison as the final output. Judgements were given based on the recommendations in the guideline[83] and were reported in Appendix 16 ROB-MEN.

Domain 3: Indirectness

For indirectness, it should be judged whether study populations, interventions, outcomes, and study settings are representative of the ones relevant for the research questions. In the cases of the studies included in the present review, the inclusion criteria led to a selection of studies in which these characteristics are directly relevant for the research question, so no indirectness is identified. Details are provided below.

Population: We included only studies in participants with a treatment-resistant form of schizophrenia, schizoaffective disorder, or schizophreniform disorder. Therefore, we consider the study populations as directly relevant for the research question.

Intervention: All investigated interventions were licensed antipsychotics or placebo and thus directly relevant for the research question.

Outcome: Only validated scales, measuring overall symptom of schizophrenia, were used for the primary outcome and are thus relevant for the research question.

Setting: We included studies conducted with out-patients, in-patients, or both. The baseline severity of patients with treatment-resistant schizophrenia is varied. In some studies, patients had symptoms and required rehospitalizations, but in other studies patients were not so symptomatic and were treated as outpatients. Therefore, all these settings can be relevant to the research question.

Domain 4: Imprecision

This domain requires setting thresholds for clinically important differences between the interventions. We considered standardized mean differences (SMDs) outside the range -0.1 to +0.1 as clinically important.

Domain 5: Heterogeneity

We considered standardized mean differences (SMDs) outside the range -0.1 to +0.1 as clinically important. Heterogeneity was evaluated based on the relation of both the 95% confidence intervals and the 95% prediction intervals, with the clinically meaningful threshold defined above in the domain of imprecision according to CINeMA documentation.[82] Comparisons could be classified according to heterogeneity evaluation as “no concerns,” “some concerns,” and “major concerns.”

Domain 6: Incoherence

We considered standardized mean differences (SMDs) outside the range -0.1 to +0.1 as clinically important. Incoherence was evaluated using a design-by-treatment test (for comparisons with only direct or indirect evidence) and the SIDE approach (when both direct and indirect evidence was available) according to CINeMA documentation.[82] Comparisons could be classified according to incoherence evaluation as “no concerns,” “some concerns,” and “major concerns.”

Overall confidence

In CINeMA, judgments for each domain can be summarized in an overall judgment on the confidence in the NMA estimate for each comparison. The level of confidence in the estimate can be classified as “very low,” “low,” “moderate,” “and “high.” The meaning of these four levels can be interpreted as follows:

- High quality: Further research is very unlikely to change our confidence in the estimate of effect.

- Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

- Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

- Very low quality: We are very uncertain about the estimate.

The CINeMA-guidance document[82] suggests starting at the first level (i.e., high) for each comparison and to downgrade for one level for a rating of “some concerns,” and by two levels for a rating of “major concerns.” In the case that several domains are at the level of some concerns or major concerns, it is recommended to consider judgements on different domains jointly rather than in isolation. The reason is that domains are interconnected and downgrading more than once for related concerns should be avoided. The following examples are given in the guidance document: Indirectness includes considerations on intransitivity, which manifests itself in the data as statistical incoherence. Heterogeneity will increase imprecision in treatment effects and may be related to variability in within-study bias or the presence of reporting bias.) Based on these recommendations, we used the following approach that was reported in two previous network meta-analysis studies[84,85] to reach an overall level of confidence for each comparison:

- One judgement of “some concerns” leads to downgrading by one level.

- One judgement of “major concerns” leads to downgrading by two levels.

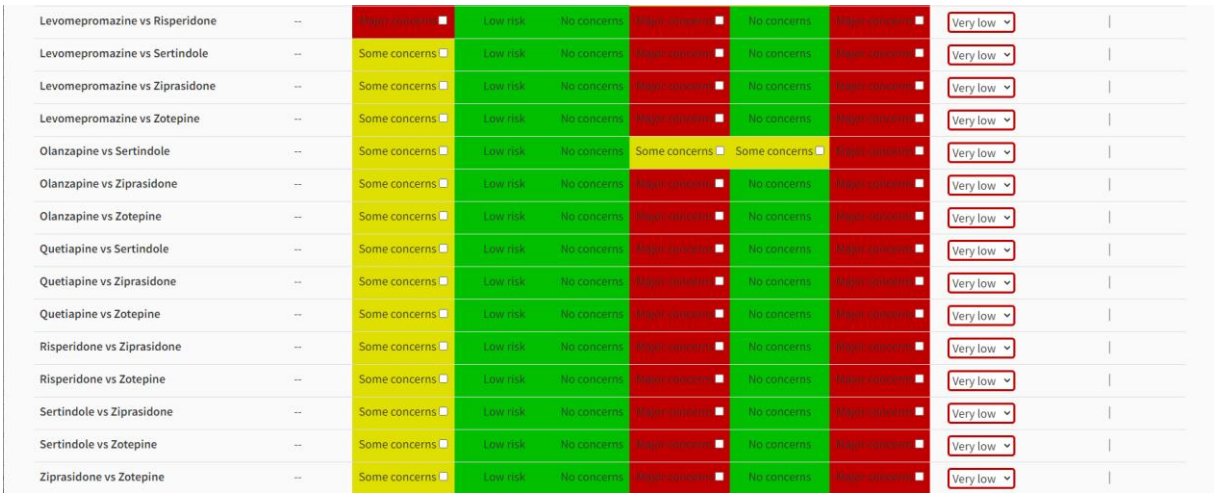
- Two judgements of “some concerns” could be interconnected and do not justify downgrading more than by one level.

- One judgement of “major concerns” and up to two judgements of “some concerns” or one additional judgement of “major concerns” could be interconnected and do not justify downgrading by more than two levels.

- Two judgements of “major concerns” and any additional judgements of “some concerns” or “major concerns” (or more than four judgements of some concerns) lead to downgrading by three levels.

Confidence in the estimates for the primary outcomes

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
				Mixed evidence					
Amisulpride vs Olanzapine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Chlorpromazine vs Clozapine	3	Some concerns	Low risk	No concerns	No concerns	No concerns	Major concerns	Low	
Chlorpromazine vs Levomepromazine	1	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	
Chlorpromazine vs Olanzapine	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	
Chlorpromazine vs Quetiapine	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Chlorpromazine vs Ziprasidone	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	
Clozapine vs Haloperidol	5	Major concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Low	
Clozapine vs Olanzapine	10	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	
Clozapine vs Quetiapine	1	Some concerns	Low risk	No concerns	No concerns	No concerns	No concerns	Moderate	
Clozapine vs Risperidone	8	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	
Clozapine vs Ziprasidone	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	
Clozapine vs Zotepine	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Fluphenazine vs Haloperidol	2	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	
Fluphenazine vs Quetiapine	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	
Fluphenazine vs Risperidone	1	Major concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Low	
Haloperidol vs Olanzapine	4	Some concerns	Low risk	No concerns	No concerns	Major concerns	No concerns	Low	
Haloperidol vs Quetiapine	1	Some concerns	Low risk	No concerns	Major concerns	No concerns	Some concerns	Low	
Haloperidol vs Risperidone	4	Some concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low	
Olanzapine vs Quetiapine	2	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	
Olanzapine vs Risperidone	4	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	
Quetiapine vs Risperidone	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low	
Risperidone vs Sertindole	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	
				Indirect evidence					
Amisulpride vs Chlorpromazine	--	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	
Amisulpride vs Clozapine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Amisulpride vs Fluphenazine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Amisulpride vs Haloperidol	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Amisulpride vs Levomepromazine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Amisulpride vs Quetiapine	--	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	
Amisulpride vs Risperidone	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Amisulpride vs Sertindole	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	
Amisulpride vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Amisulpride vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Chlorpromazine vs Fluphenazine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Chlorpromazine vs Haloperidol	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Chlorpromazine vs Risperidone	--	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low	
Chlorpromazine vs Sertindole	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Chlorpromazine vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Clozapine vs Fluphenazine	--	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	
Clozapine vs Levomepromazine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Clozapine vs Sertindole	--	Some concerns	Low risk	No concerns	No concerns	Major concerns	Major concerns	Very low	
Fluphenazine vs Levomepromazine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Fluphenazine vs Olanzapine	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	
Fluphenazine vs Sertindole	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Fluphenazine vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Fluphenazine vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Haloperidol vs Levomepromazine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Haloperidol vs Sertindole	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Haloperidol vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Haloperidol vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Levomepromazine vs Olanzapine	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low	
Levomepromazine vs Quetiapine	--	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low	



Levomepromazine vs Risperidone	--	Major concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Levomepromazine vs Sertindole	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Levomepromazine vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Levomepromazine vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Olanzapine vs Sertindole	--	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low
Olanzapine vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Olanzapine vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Quetiapine vs Sertindole	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Quetiapine vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Quetiapine vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Risperidone vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Risperidone vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Sertindole vs Ziprasidone	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Sertindole vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low
Ziprasidone vs Zotepine	--	Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low

16 ROB-MEN

In the Pairwise Comparisons table, judgements need to be given in two columns: within-study assessment of bias and across-study assessment of bias. Then the overall bias of this table is given automatically. For the ROB-MEN Table, evaluation of contribution from evidence with suspected bias and evaluation of small-study effects require judgements, and overall risk of bias is also automatically given. We report the details in the following.

Within-study assessment of bias

No bias detected was given if no study was suspected of selective non-reporting or under-reporting of results for a specific comparison. Otherwise, we assessed each study for the presence of selective non-reporting of results. Then, we assessed the potential impact of the missing results across all studies using two signaling questions[83] to reach an overall judgement of *no bias detected* or *suspected bias favoring X* for each comparison.

We found three comparisons to be potentially biased because the extra studies did not report the full results and were sponsored by the company manufacturing the drug favored by the bias. For the rest comparisons, the extra studies were either small-studies that were not sufficient to have a notable effect on the overall result or studies that used other primary outcomes instead of overall symptoms.

Across-study assessment of bias

For this situation, it should be evaluated whether there are studies undertaken but not published (publication bias) for each comparison. We assigned *no bias detected* for risk of publication bias to all comparisons because (i) we hypothesized that studies for patients with treatment-resistant schizophrenia are hard to conduct; therefore, there should not be more studies that are not published, especially after the comprehensive search for both published and unpublished studies; (ii) two comparison-adjusted funnel plots and their Egger's test results did not indicate clear evidence for missing small-studies.

Overall bias of Pairwise Comparisons Table

	Pairwise comparison	Number of studies in each comparison		Within-study assessment of bias	Across-study assessment of bias	Overall judgement
		Reporting this outcome (sample size)	Total identified in the SR (total sample size)	set all to "No bias"	set all to "No bias"	calculate overall judgement
Group A: observed for this outcome						
1	Amisulpride:Olanzapine	1 (72)	1 (72)	No bias detected	No bias detected	No bias detected
2	Chlorpromazine:Clozapine	3 (430)	3 (430)	No bias detected	No bias detected	No bias detected
3	Chlorpromazine:Levomepromazine	1 (38)	1 (38)	No bias detected	No bias detected	No bias detected
4	Chlorpromazine:Olanzapine	1 (81)	1 (81)	No bias detected	No bias detected	No bias detected
5	Chlorpromazine:Placebo	1 (40)	4 (108)	No bias detected	No bias detected	No bias detected
6	Chlorpromazine:Quetiapine	2 (484)	2 (484)	No bias detected	No bias detected	No bias detected
7	Chlorpromazine:Sulpiride	1 (75)	1 (75)	No bias detected	No bias detected	No bias detected
8	Chlorpromazine:Thioridazine	1 (40)	1 (40)	No bias detected	No bias detected	No bias detected
9	Chlorpromazine:Trifluoperazine	1 (40)	1 (40)	No bias detected	No bias detected	No bias detected
10	Chlorpromazine:Ziprasidone	1 (306)	1 (306)	No bias detected	No bias detected	No bias detected
11	Clozapine:Haloperidol	5 (630)	6 (630)	No bias detected	No bias detected	No bias detected
12	Clozapine:Olanzapine	10 (678)	13 (678)	No bias detected	No bias detected	No bias detected
13	Clozapine:Quetiapine	1 (41)	2 (41)	Suspected bias favouring Clozapine	No bias detected	Suspected bias favouring Clozapine
14	Clozapine:Risperidone	8 (601)	10 (621)	No bias detected	No bias detected	No bias detected

15	Clozapine:Ziprasidone	1 (144)	1 (144)	No bias detected	No bias detected	No bias detected
16	Clozapine:Zotepine	1 (50)	1 (50)	No bias detected	No bias detected	No bias detected
17	Fluphenazine:Haloperidol	2 (97)	2 (97)	No bias detected	No bias detected	No bias detected
18	Fluphenazine:Quetiapine	1 (25)	1 (25)	No bias detected	No bias detected	No bias detected
19	Fluphenazine:Risperidone	1 (26)	1 (26)	No bias detected	No bias detected	No bias detected
20	Haloperidol:Olanzapine	4 (679)	5 (717)	No bias detected	No bias detected	No bias detected
21	Haloperidol:Quetiapine	1 (281)	1 (281)	No bias detected	No bias detected	No bias detected
22	Haloperidol:Risperidone	4 (198)	6 (198)	Suspected bias favouring Risperidone	No bias detected	Suspected bias favouring Risperidone
23	Olanzapine:Quetiapine	2 (58)	3 (83)	No bias detected	No bias detected	No bias detected
24	Olanzapine:Risperidone	4 (496)	6 (770)	No bias detected	No bias detected	No bias detected
25	Placebo:Thioridazine	1 (40)	1 (40)	No bias detected	No bias detected	No bias detected
26	Placebo:Trifluoperazine	1 (40)	2 (90)	No bias detected	No bias detected	No bias detected
27	Quetiapine:Risperidone	2 (39)	3 (61)	No bias detected	No bias detected	No bias detected
28	Risperidone:Sertindole	1 (315)	1 (315)	No bias detected	No bias detected	No bias detected
29	Thioridazine:Trifluoperazine	1 (40)	1 (40)	No bias detected	No bias detected	No bias detected
Group B: observed for other outcomes						
30	Chlorpromazine:Haloperidol	NA (NA)	2 (47)	No bias detected	No bias detected	No bias detected
31	Chlorpromazine:Risperidone	NA (NA)	1 (27)	No bias detected	No bias detected	No bias detected
32	Haloperidol:Levomepromazine	NA (NA)	1 (39)	No bias detected	No bias detected	No bias detected
33	Haloperidol:Placebo	NA (NA)	3 (57)	Suspected bias favouring Haloperidol	No bias detected	Suspected bias favouring Haloperidol
Group C: unobserved						
34	Amisulpride:Chlorpromazine	NA (NA)	NA (NA)		No bias detected	No bias detected
35	Amisulpride:Clozapine	NA (NA)	NA (NA)		No bias detected	No bias detected
36	Amisulpride:Fluphenazine	NA (NA)	NA (NA)		No bias detected	No bias detected
37	Amisulpride:Haloperidol	NA (NA)	NA (NA)		No bias detected	No bias detected
38	Amisulpride:Levomepromazine	NA (NA)	NA (NA)		No bias detected	No bias detected
39	Amisulpride:Placebo	NA (NA)	NA (NA)		No bias detected	No bias detected
40	Amisulpride:Quetiapine	NA (NA)	NA (NA)		No bias detected	No bias detected
41	Amisulpride:Risperidone	NA (NA)	NA (NA)		No bias detected	No bias detected
42	Amisulpride:Sertindole	NA (NA)	NA (NA)		No bias detected	No bias detected
43	Amisulpride:Sulpiride	NA (NA)	NA (NA)		No bias detected	No bias detected
44	Amisulpride:Thioridazine	NA (NA)	NA (NA)		No bias detected	No bias detected
45	Amisulpride:Trifluoperazine	NA (NA)	NA (NA)		No bias detected	No bias detected
46	Amisulpride:Ziprasidone	NA (NA)	NA (NA)		No bias detected	No bias detected
47	Amisulpride:Zotepine	NA (NA)	NA (NA)		No bias detected	No bias detected
48	Chlorpromazine:Fluphenazine	NA (NA)	NA (NA)		No bias detected	No bias detected
49	Chlorpromazine:Sertindole	NA (NA)	NA (NA)		No bias detected	No bias detected
50	Chlorpromazine:Zotepine	NA (NA)	NA (NA)		No bias detected	No bias detected
51	Clozapine:Fluphenazine	NA (NA)	NA (NA)		No bias detected	No bias detected
52	Clozapine:Levomepromazine	NA (NA)	NA (NA)		No bias detected	No bias detected
53	Clozapine:Placebo	NA (NA)	NA (NA)		No bias detected	No bias detected
54	Clozapine:Sertindole	NA (NA)	NA (NA)		No bias detected	No bias detected
55	Clozapine:Sulpiride	NA (NA)	NA (NA)		No bias detected	No bias detected
56	Clozapine:Thioridazine	NA (NA)	NA (NA)		No bias detected	No bias detected
57	Clozapine:Trifluoperazine	NA (NA)	NA (NA)		No bias detected	No bias detected
58	Fluphenazine:Levomepromazine	NA (NA)	NA (NA)		No bias detected	No bias detected
59	Fluphenazine:Olanzapine	NA (NA)	NA (NA)		No bias detected	No bias detected
60	Fluphenazine:Placebo	NA (NA)	NA (NA)		No bias detected	No bias detected
61	Fluphenazine:Sertindole	NA (NA)	NA (NA)		No bias detected	No bias detected
62	Fluphenazine:Sulpiride	NA (NA)	NA (NA)		No bias detected	No bias detected
63	Fluphenazine:Thioridazine	NA (NA)	NA (NA)		No bias detected	No bias detected

64	Fluphenazine:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
65	Fluphenazine:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
66	Fluphenazine:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
67	Haloperidol:Sertindole	NA (NA)	NA (NA)	No bias detected	No bias detected
68	Haloperidol:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected
69	Haloperidol:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected
70	Haloperidol:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
71	Haloperidol:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
72	Haloperidol:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
73	Levomepromazine:Olanzapine	NA (NA)	NA (NA)	No bias detected	No bias detected
74	Levomepromazine:Placebo	NA (NA)	NA (NA)	No bias detected	No bias detected
75	Levomepromazine:Quetiapine	NA (NA)	NA (NA)	No bias detected	No bias detected
76	Levomepromazine:Risperidone	NA (NA)	NA (NA)	No bias detected	No bias detected
77	Levomepromazine:Sertindole	NA (NA)	NA (NA)	No bias detected	No bias detected
78	Levomepromazine:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected
79	Levomepromazine:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected
80	Levomepromazine:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
81	Levomepromazine:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
82	Levomepromazine:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
83	Olanzapine:Placebo	NA (NA)	NA (NA)	No bias detected	No bias detected
84	Olanzapine:Sertindole	NA (NA)	NA (NA)	No bias detected	No bias detected
85	Olanzapine:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected
86	Olanzapine:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected
87	Olanzapine:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
88	Olanzapine:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
89	Olanzapine:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
90	Placebo:Quetiapine	NA (NA)	NA (NA)	No bias detected	No bias detected
91	Placebo:Risperidone	NA (NA)	NA (NA)	No bias detected	No bias detected
92	Placebo:Sertindole	NA (NA)	NA (NA)	No bias detected	No bias detected
93	Placebo:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected
94	Placebo:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
95	Placebo:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
96	Quetiapine:Sertindole	NA (NA)	NA (NA)	No bias detected	No bias detected
97	Quetiapine:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected
98	Quetiapine:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected
99	Quetiapine:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
100	Quetiapine:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
101	Quetiapine:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
102	Risperidone:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected
103	Risperidone:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected
104	Risperidone:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
105	Risperidone:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
106	Risperidone:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
107	Sertindole:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected
108	Sertindole:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected
109	Sertindole:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
110	Sertindole:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
111	Sertindole:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
112	Sulpiride:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected
113	Sulpiride:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected
114	Sulpiride:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected

115	Sulpiride:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
116	Thioridazine:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
117	Thioridazine:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
118	Trifluoperazine:Ziprasidone	NA (NA)	NA (NA)	No bias detected	No bias detected
119	Trifluoperazine:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected
120	Ziprasidone:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected

Showing 1 to 120 of 120 entries

Evaluation of contribution from evidence with suspected bias

The possible levels for contribution are *no substantial contribution from bias*, *substantial contribution from bias balanced*, and *substantial contribution from bias favoring X*. We considered the contribution from biased evidence as substantially in favor of one treatment if the relative difference between treatments was at least 15%.

Evaluation of small-study effects

To assess the presence of small-study effects, we compared the obtained adjusted-estimates (column 6 of the ROB-MAN table: NMR treatment effect at the smallest observed variance) with the original estimates (column 5 of the ROB-MAN table: NMA treatment effect) by looking at the overlap of their corresponding confidence intervals. A lack of overlap between the two intervals indicates that effect estimates differ between smaller and larger studies. No small-study effect was identified among all comparisons.

Overall risk of bias

	NMA estimate	% contribution of evidence from pairwise comparisons with suspected bias: Favouring first treatment	% contribution of evidence from pairwise comparisons with suspected bias: Favouring second treatment	Evaluation of contribution from evidence with suspected bias (set all to "No substantial contribution")	Bias assessment for indirect evidence	NMA treatment effect	NMR treatment effect at the smallest observed variance	Evaluation of small-study effects (set all to "No evidence")	Overall risk of bias (calculate overall RoB)
mixed/only direct									
1	Amisulpride:Olanzapine	0	0	No substantial contribution from bias	No bias detected	0.23 (-0.42,0.86)	0.3 (-11.2,12.53)	No evidence of small-study effects	Low risk
2	Chlorpromazine:Clozapine	0	1	No substantial contribution from bias	No bias detected	-0.44 (-0.68,-0.19)	-0.52 (-0.91,-0.13)	No evidence of small-study effects	Low risk
3	Chlorpromazine:Levomepromazine	0	0	No substantial contribution from bias	No bias detected	-0.69 (-1.45,0.07)	2.14 (-30.61,18.33)	No evidence of small-study effects	Low risk
4	Chlorpromazine:Olanzapine	0	0	No substantial contribution from bias	No bias detected	-0.38 (-0.64,-0.1)	-0.5 (-0.93,-0.08)	No evidence of small-study effects	Low risk
5	Chlorpromazine:Placebo	0	0	No substantial contribution from bias	No bias detected	0.52 (-0.18,1.22)	2.75 (-12.97,16.74)	No evidence of small-study effects	Low risk
6	Chlorpromazine:Quetiapine	0	0	No substantial contribution from bias	No bias detected	-0.01 (-0.29,0.26)	0.06 (-0.32,0.44)	No evidence of small-study effects	Low risk
7	Chlorpromazine:Sulpiride	0	0	No substantial contribution from bias	No bias detected	-0.44 (-1.07,0.18)	4.84 (-20.02,20.36)	No evidence of small-study effects	Low risk
8	Chlorpromazine:Thioridazine	0	0	No substantial contribution from bias	No bias detected	-0.09 (-0.79,0.62)	-7.49 (-33.25,6.5)	No evidence of small-study effects	Low risk
9	Chlorpromazine:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.21 (-0.96,0.53)	-0.56 (-12.07,16.99)	No evidence of small-study effects	Low risk
10	Chlorpromazine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.24 (-0.62,0.15)	0.14 (-0.63,0.97)	No evidence of small-study effects	Low risk
11	Clozapine:Haloperidol	1	0	No substantial contribution from bias	No bias detected	0.32 (0.12,0.52)	0.3 (0,0.57)	No evidence of small-study effects	Low risk
12	Clozapine:Olanzapine	0	0	No substantial contribution from bias	No bias detected	0.06 (-0.11,0.24)	0.02 (-0.23,0.26)	No evidence of small-study effects	Low risk
13	Clozapine:Quetiapine	6	0	No substantial contribution from bias	Suspected bias favouring Clozapine	0.42 (0.14,0.71)	0.58 (0.17,0.98)	No evidence of small-study effects	Low risk
14	Clozapine:Risperidone	0	8	No substantial contribution from bias	No bias detected	0.19 (0,0.38)	0.27 (-0.01,0.55)	No evidence of small-study effects	Low risk
15	Clozapine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	0.2 (-0.2,0.59)	0.67 (-0.18,1.53)	No evidence of small-study effects	Low risk
16	Clozapine:Zotepine	0	0	No substantial contribution from bias	No bias detected	0.07 (-0.63,0.76)	19.23 (2.56,38.72)	No evidence of small-study effects	Low risk

17	Fluphenazine:Haloperidol	0	0	No substantial contribution from bias	No bias detected	-0.1 (-0.52,0.32)	-0.3 (-1.2,0.48)	No evidence of small-study effects	Low risk
18	Fluphenazine:Quetiapine	0	0	No substantial contribution from bias	No bias detected	0.01 (-0.48,0.49)	-0.01 (-0.98,0.85)	No evidence of small-study effects	Low risk
19	Fluphenazine:Risperidone	0	12	No substantial contribution from bias	No bias detected	-0.22 (-0.67,0.23)	-0.32 (-1.3,0.53)	No evidence of small-study effects	Low risk
20	Haloperidol:Olanzapine	0	0	No substantial contribution from bias	No bias detected	-0.26 (-0.46,-0.05)	-0.28 (-0.57,0.01)	No evidence of small-study effects	Low risk
21	Haloperidol:Quetiapine	0	0	No substantial contribution from bias	No bias detected	0.11 (-0.2,0.4)	0.29 (-0.12,0.69)	No evidence of small-study effects	Low risk
22	Haloperidol:Risperidone	0	33	Substantial contribution from bias favouring Risperidon	Suspected bias favouring Risperidone	-0.13 (-0.36,0.1)	-0.03 (-0.37,0.33)	No evidence of small-study effects	Some concerns
23	Olanzapine:Quetiapine	0	0	No substantial contribution from bias	No bias detected	0.37 (0.06,0.65)	0.56 (0.13,0.99)	No evidence of small-study effects	Low risk
24	Olanzapine:Risperidone	0	8	No substantial contribution from bias	No bias detected	0.13 (-0.08,0.33)	0.25 (-0.05,0.56)	No evidence of small-study effects	Low risk
25	Placebo:Thioridazine	0	0	No substantial contribution from bias	No bias detected	-0.61 (-1.35,0.15)	-10.53 (-35.1,3.13)	No evidence of small-study effects	Low risk
26	Placebo:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.73 (-1.51,0.07)	-1.89 (-19.76,14.98)	No evidence of small-study effects	Low risk
27	Quetiapine:Risperidone	0	9	No substantial contribution from bias	No bias detected	-0.23 (-0.54,0.09)	-0.31 (-0.77,0.16)	No evidence of small-study effects	Low risk
28	Risperidone:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.32 (-0.18,0.82)	-0.11 (-13.58,16.37)	No evidence of small-study effects	Low risk
29	Thioridazine:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.12 (-0.89,0.65)	9.3 (-10.26,43.24)	No evidence of small-study effects	Low risk
indirect									
30	Chlorpromazine:Haloperidol	0	0	No substantial contribution from bias	No bias detected	-0.12 (-0.4,0.18)	-0.22 (-0.66,0.19)	No evidence of small-study effects	Low risk
31	Chlorpromazine:Risperidone	0	5	No substantial contribution from bias	No bias detected	-0.25 (-0.54,0.05)	-0.25 (-0.72,0.21)	No evidence of small-study effects	Low risk
32	Haloperidol:Levomepromazine	0	0	No substantial contribution from bias	No bias detected	-0.57 (-1.39,0.25)	2.34 (-30.34,18.53)	No evidence of small-study effects	Low risk
33	Haloperidol:Placebo	0	0	No substantial contribution from bias	Suspected bias favouring Haloperidol	0.64 (-0.14,1.4)	3.04 (-12.76,16.94)	No evidence of small-study effects	Low risk
34	Amisulpride:Chlorpromazine	0	0	No substantial contribution from bias	No bias detected	0.61 (-0.11,1.3)	0.8 (-10.78,13.15)	No evidence of small-study effects	Low risk
35	Amisulpride:Clozapine	0	0	No substantial contribution from bias	No bias detected	0.17 (-0.51,0.83)	0.28 (-11.21,12.52)	No evidence of small-study effects	Low risk
36	Amisulpride:Fluphenazine	0	0	No substantial contribution from bias	No bias detected	0.59 (-0.22,1.36)	0.87 (-10.6,13.16)	No evidence of small-study effects	Low risk
37	Amisulpride:Haloperidol	0	0	No substantial contribution from bias	No bias detected	0.49 (-0.2,1.16)	0.59 (-10.93,12.81)	No evidence of small-study effects	Low risk
38	Amisulpride:Levomepromazine	0	0	No substantial contribution from bias	No bias detected	-0.09 (-1.12,0.97)	0.12 (-17.17,20.63)	No evidence of small-study effects	Low risk
39	Amisulpride:Placebo	0	0	No substantial contribution from bias	No bias detected	1.13 (0.13,2.13)	2.17 (-17.17,21.78)	No evidence of small-study effects	Low risk
40	Amisulpride:Quetiapine	0	0	No substantial contribution from bias	No bias detected	0.6 (-0.13,1.3)	0.86 (-10.66,13.21)	No evidence of small-study effects	Low risk
41	Amisulpride:Risperidone	0	6	No substantial contribution from bias	No bias detected	0.36 (-0.33,1.04)	0.53 (-10.96,12.78)	No evidence of small-study effects	Low risk
42	Amisulpride:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.68 (-0.18,1.52)	-1.92 (-16.62,29.98)	No evidence of small-study effects	Low risk
43	Amisulpride:Sulpiride	0	0	No substantial contribution from bias	No bias detected	0.17 (-0.81,1.08)	8.34 (-27.19,22.88)	No evidence of small-study effects	Low risk
44	Amisulpride:Thioridazine	0	0	No substantial contribution from bias	No bias detected	0.52 (-0.48,1.49)	-10.29 (-32.01,14.26)	No evidence of small-study effects	Low risk
45	Amisulpride:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	0.4 (-0.63,1.41)	-1.69 (-17.79,28.55)	No evidence of small-study effects	Low risk
46	Amisulpride:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	0.37 (-0.42,1.14)	0.92 (-10.64,13.24)	No evidence of small-study effects	Low risk
47	Amisulpride:Zotepine	0	0	No substantial contribution from bias	No bias detected	0.24 (-0.74,1.18)	16.09 (-6.22,50.2)	No evidence of small-study effects	Low risk
48	Chlorpromazine:Fluphenazine	0	0	No substantial contribution from bias	No bias detected	-0.02 (-0.51,0.47)	0.07 (-0.8,1.06)	No evidence of small-study effects	Low risk
49	Chlorpromazine:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.07 (-0.5,0.66)	-0.33 (-13.85,16.16)	No evidence of small-study effects	Low risk
50	Chlorpromazine:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.37 (-1.1,0.37)	18.7 (2.02,38.31)	No evidence of small-study effects	Low risk
51	Clozapine:Fluphenazine	1	0	No substantial contribution from bias	No bias detected	0.41 (-0.03,0.86)	0.59 (-0.24,1.55)	No evidence of small-study effects	Low risk
52	Clozapine:Levomepromazine	1	0	No substantial contribution from bias	No bias detected	-0.25 (-1.04,0.54)	2.59 (-30.05,18.85)	No evidence of small-study effects	Low risk
53	Clozapine:Placebo	1	0	No substantial contribution from bias	No bias detected	0.96 (0.2,1.7)	3.32 (-12.44,17.2)	No evidence of small-study effects	Low risk
54	Clozapine:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.51 (-0.02,1.05)	0.3 (-13.31,16.66)	No evidence of small-study effects	Low risk
55	Clozapine:Sulpiride	1	0	No substantial contribution from bias	No bias detected	0 (-0.68,0.66)	5.35 (-19.55,20.88)	No evidence of small-study effects	Low risk
56	Clozapine:Thioridazine	1	0	No substantial contribution from bias	No bias detected	0.35 (-0.4,1.09)	-6.98 (-32.74,6.98)	No evidence of small-study effects	Low risk
57	Clozapine:Trifluoperazine	1	0	No substantial contribution from bias	No bias detected	0.23 (-0.56,1)	-0.04 (-11.59,17.5)	No evidence of small-study effects	Low risk
58	Fluphenazine:Levomepromazine	0	0	No substantial contribution from bias	No bias detected	-0.66 (-1.58,0.24)	2.11 (-30.78,18.3)	No evidence of small-study effects	Low risk
59	Fluphenazine:Olanzapine	0	0	No substantial contribution from bias	No bias detected	-0.36 (-0.8,0.1)	-0.58 (-1.52,0.23)	No evidence of small-study effects	Low risk
60	Fluphenazine:Placebo	0	0	No substantial contribution from bias	No bias detected	0.54 (-0.32,1.39)	2.8 (-13.06,16.64)	No evidence of small-study effects	Low risk
61	Fluphenazine:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.09 (-0.57,0.78)	-0.93 (-14.02,16.02)	No evidence of small-study effects	Low risk
62	Fluphenazine:Sulpiride	0	0	No substantial contribution from bias	No bias detected	-0.42 (-1.22,0.36)	4.73 (-20.04,20.11)	No evidence of small-study effects	Low risk
63	Fluphenazine:Thioridazine	0	0	No substantial contribution from bias	No bias detected	-0.07 (-0.92,0.81)	-7.68 (-33.21,6.42)	No evidence of small-study effects	Low risk
64	Fluphenazine:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.17 (-1.09,0.69)	-0.71 (-12.18,16.87)	No evidence of small-study effects	Low risk
65	Fluphenazine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.21 (-0.81,0.37)	0.07 (-1.13,1.2)	No evidence of small-study effects	Low risk
66	Fluphenazine:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.35 (-1.16,0.47)	18.7 (1.93,38.13)	No evidence of small-study effects	Low risk
67	Haloperidol:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.19 (-0.35,0.74)	-0.11 (-13.58,16.37)	No evidence of small-study effects	Low risk
68	Haloperidol:Sulpiride	0	0	No substantial contribution from bias	No bias detected	-0.32 (-1.02,0.36)	5.07 (-19.88,20.55)	No evidence of small-study effects	Low risk
69	Haloperidol:Thioridazine	0	0	No substantial contribution from bias	No bias detected	0.03 (-0.74,0.79)	-7.27 (-33.01,6.69)	No evidence of small-study effects	Low risk
70	Haloperidol:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.08 (-0.89,0.7)	-0.33 (-11.87,17.17)	No evidence of small-study effects	Low risk
71	Haloperidol:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.11 (-0.96,0.3)	0.37 (-0.47,1.25)	No evidence of small-study effects	Low risk
72	Haloperidol:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.25 (-0.97,0.48)	18.9 (2.27,38.42)	No evidence of small-study effects	Low risk

73	Levomepromazine:Olanzapine	0	0	No substantial contribution from bias	No bias detected	0.31 (-0.5,1.12)	-2.63 (-18.83,30.07)	No evidence of small-study effects	Low risk
74	Levomepromazine:Placebo	0	0	No substantial contribution from bias	No bias detected	1.21 (0.18,2.24)	3.11 (-29.49,38.91)	No evidence of small-study effects	Low risk
75	Levomepromazine:Quetiapine	0	0	No substantial contribution from bias	No bias detected	0.67 (-0.14,1.49)	-2.02 (-18.23,30.62)	No evidence of small-study effects	Low risk
76	Levomepromazine:Risperidone	0	4	No substantial contribution from bias	No bias detected	0.44 (-0.38,1.26)	-2.33 (-18.52,30.33)	No evidence of small-study effects	Low risk
77	Levomepromazine:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.76 (-0.19,1.71)	-1.48 (-27.81,47.5)	No evidence of small-study effects	Low risk
78	Levomepromazine:Sulpiride	0	0	No substantial contribution from bias	No bias detected	0.26 (-0.75,1.22)	2.49 (-28.06,35.97)	No evidence of small-study effects	Low risk
79	Levomepromazine:Thioridazine	0	0	No substantial contribution from bias	No bias detected	0.6 (-0.43,1.63)	-11.66 (-44.06,31.09)	No evidence of small-study effects	Low risk
80	Levomepromazine:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	0.49 (-0.61,1.54)	-2.32 (-29.18,46.82)	No evidence of small-study effects	Low risk
81	Levomepromazine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	0.45 (-0.4,1.29)	-1.82 (-18.2,30.58)	No evidence of small-study effects	Low risk
82	Levomepromazine:Zotepine	0	0	No substantial contribution from bias	No bias detected	0.32 (-0.74,1.36)	15.02 (-0.76,68.05)	No evidence of small-study effects	Low risk
83	Olanzapine:Placebo	0	0	No substantial contribution from bias	No bias detected	0.9 (0.13,1.65)	3.3 (-12.47,17.17)	No evidence of small-study effects	Low risk
84	Olanzapine:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.45 (-0.1,0.98)	0.27 (-13.31,16.64)	No evidence of small-study effects	Low risk
85	Olanzapine:Sulpiride	0	0	No substantial contribution from bias	No bias detected	-0.06 (-0.76,0.6)	5.34 (-19.58,20.82)	No evidence of small-study effects	Low risk
86	Olanzapine:Thioridazine	0	0	No substantial contribution from bias	No bias detected	0.29 (-0.47,1.04)	-7 (-32.74,6.96)	No evidence of small-study effects	Low risk
87	Olanzapine:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	0.17 (-0.63,0.95)	-0.06 (-11.61,17.46)	No evidence of small-study effects	Low risk
88	Olanzapine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	0.14 (-0.29,0.55)	0.65 (-0.21,1.52)	No evidence of small-study effects	Low risk
89	Olanzapine:Zotepine	0	0	No substantial contribution from bias	No bias detected	0.01 (-0.71,0.71)	19.2 (2.55,38.66)	No evidence of small-study effects	Low risk
90	Placebo:Quetiapine	0	0	No substantial contribution from bias	No bias detected	-0.54 (-1.29,0.22)	-2.66 (-16.66,13.01)	No evidence of small-study effects	Low risk
91	Placebo:Risperidone	0	3	No substantial contribution from bias	No bias detected	-0.77 (-1.53,0.01)	-3.07 (-16.93,12.68)	No evidence of small-study effects	Low risk
92	Placebo:Sertindole	0	0	No substantial contribution from bias	No bias detected	-0.45 (-1.35,0.48)	-3.11 (-11.77,9.66)	No evidence of small-study effects	Low risk
93	Placebo:Sulpiride	0	0	No substantial contribution from bias	No bias detected	-0.96 (-1.89,-0.02)	3.06 (-33.35,28.42)	No evidence of small-study effects	Low risk
94	Placebo:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.75 (-1.56,0.03)	-2.47 (-16.59,13.15)	No evidence of small-study effects	Low risk
95	Placebo:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.88 (-1.91,0.13)	16.29 (-4.89,42.48)	No evidence of small-study effects	Low risk
96	Quetiapine:Sertindole	0	0	No substantial contribution from bias	No bias detected	0.08 (-0.5,0.68)	-0.44 (-13.91,16.13)	No evidence of small-study effects	Low risk
97	Quetiapine:Sulpiride	0	0	No substantial contribution from bias	No bias detected	-0.42 (-1.12,0.24)	4.79 (-20.11,20.23)	No evidence of small-study effects	Low risk
98	Quetiapine:Thioridazine	0	0	No substantial contribution from bias	No bias detected	-0.07 (-0.82,0.68)	-7.55 (-33.35,6.44)	No evidence of small-study effects	Low risk
99	Quetiapine:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.19 (-0.99,0.59)	-0.64 (-12.15,16.91)	No evidence of small-study effects	Low risk
100	Quetiapine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.22 (-0.67,0.22)	0.08 (-0.75,0.93)	No evidence of small-study effects	Low risk
101	Quetiapine:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.36 (-1.11,0.4)	18.63 (1.96,38.21)	No evidence of small-study effects	Low risk
102	Risperidone:Sulpiride	4	0	No substantial contribution from bias	No bias detected	-0.19 (-0.88,0.48)	5.12 (-19.85,20.55)	No evidence of small-study effects	Low risk
103	Risperidone:Thioridazine	3	0	No substantial contribution from bias	No bias detected	0.16 (-0.61,0.93)	-7.26 (-33.02,6.66)	No evidence of small-study effects	Low risk
104	Risperidone:Trifluoperazine	3	0	No substantial contribution from bias	No bias detected	0.04 (-0.76,0.83)	-0.33 (-11.85,17.24)	No evidence of small-study effects	Low risk
105	Risperidone:Ziprasidone	4	0	No substantial contribution from bias	No bias detected	0.01 (-0.42,0.44)	0.4 (-0.47,1.28)	No evidence of small-study effects	Low risk
106	Risperidone:Zotepine	5	0	No substantial contribution from bias	No bias detected	-0.12 (-0.84,0.6)	18.94 (2.28,38.44)	No evidence of small-study effects	Low risk
107	Sertindole:Sulpiride	0	0	No substantial contribution from bias	No bias detected	-0.51 (-1.37,0.34)	2.42 (-27.3,28.68)	No evidence of small-study effects	Low risk
108	Sertindole:Thioridazine	0	0	No substantial contribution from bias	No bias detected	-0.16 (-1.07,0.74)	-10.47 (-27.35,6.25)	No evidence of small-study effects	Low risk
109	Sertindole:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.27 (-1.23,0.65)	-2.42 (-17.33,20.82)	No evidence of small-study effects	Low risk
110	Sertindole:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.31 (-0.97,0.34)	0.44 (-16.1,14.03)	No evidence of small-study effects	Low risk
111	Sertindole:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.44 (-1.31,0.44)	16.69 (0.81,44.14)	No evidence of small-study effects	Low risk
112	Sulpiride:Thioridazine	0	0	No substantial contribution from bias	No bias detected	0.35 (-0.59,1.28)	-4.08 (-51.87,16.98)	No evidence of small-study effects	Low risk
113	Sulpiride:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	0.23 (-0.73,1.21)	-3.22 (-27.25,21.37)	No evidence of small-study effects	Low risk
114	Sulpiride:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	0.2 (-0.52,0.95)	-4.77 (-20.06,20.08)	No evidence of small-study effects	Low risk
115	Sulpiride:Zotepine	0	0	No substantial contribution from bias	No bias detected	0.07 (-0.88,1.03)	17.35 (-4.05,38.2)	No evidence of small-study effects	Low risk
116	Thioridazine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.15 (-0.95,0.65)	7.59 (-6.32,33.5)	No evidence of small-study effects	Low risk
117	Thioridazine:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.28 (-1.29,0.73)	23.59 (0.77,69.11)	No evidence of small-study effects	Low risk
118	Trifluoperazine:Ziprasidone	0	0	No substantial contribution from bias	No bias detected	-0.03 (-0.84,0.81)	0.7 (-16.84,12.34)	No evidence of small-study effects	Low risk
119	Trifluoperazine:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.16 (-1.2,0.88)	19.45 (-6.43,77)	No evidence of small-study effects	Low risk
120	Ziprasidone:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.13 (-0.92,0.66)	18.43 (1.83,38.15)	No evidence of small-study effects	Low risk

Showing 1 to 120 of 120 entries

17 References

1 Lefebvre C, Glanville J, Briscoe S, et al. Searching for and selecting studies, 2019.

2 Shokraneh F, Adams CE. Study-based registers reduce waste in systematic reviewing: discussion and case report. *Syst Rev* 2019; **8:** 129. https://doi.org/10.1186/s13643-019-1035-3.

3 Shokraneh F, Adams CE. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. *Bioimpacts* 2017; **7:** 209–17. https://doi.org/10.15171/bi.2017.25.

4 Shokraneh F, Adams CE. Cochrane Schizophrenia Group's Study-Based Register of Randomized Controlled Trials: Development and Content Analysis. *Schizophr Bull Open* 2020; **1:** sgaa061. https://doi.org/10.1093/schizbullopen/sgaa061.

5 Shokraneh F, Adams CE. Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis. *Health Info Libr J* 2021. https://doi.org/10.1111/hir.12366.

6 Schlosberg A, Shadmi M. A comparative controlled study of two long-acting phenothiazines. pipotiazine palmitate and fluphenazine decanoate. *Current Therapeutic Research, Clinical and Experimental* 1978; **23:** 642–54.

7 Teja JS, Grey WH, Clums JM, Warren C. Tranquilizers or anti-depressants for chronic schizophrenics: a long term study. *Aust N Z J Psychiatry* 1975; **9:** 241–47.

8 Bozzatello P, Bellino S, Mancini I, Sandei L, Zanalda E, Rocca P. Effects on Satisfaction and Service Engagement of Paliperidone Palmitate Compared with Oral Paliperidone in Patients with Schizophrenia. An Open Label Randomized Controlled Trial. *Clinical drug investigation* 2019; **39:** 169–78.

9 Ahlfors UG, Dencker SJ, Gravem A, Remvig J. Clopenthixol decanoate and perphenazine enanthate in schizophrenic patients. A double-blind Nordic multicentre trial. *Acta Psychiatrica Scandinavica Supplementum* 1980; **279:** 77–91.

10 Altamura AC, Velona I, Curreli R, Mundo E, Bravi D. Is olanzapine better than haloperidol in resistant schizophrenia? A double-blind study in partial responders. *International Journal of Psychiatry in Clinical Practice* 2002; **6:** 107–11.

11 Alvarez E, Ciudad A, Olivares JM, Bousono M, Gomez JC. A randomized, 1-year follow-up study of olanzapine and risperidone in the treatment of negative symptoms in outpatients with schizophrenia. *Journal of Clinical Psychopharmacology* 2006; **26:** 238–49.

12 AstraZeneca. A multicenter, double-blind, randomized, comparison of quetiapine (seroquel) and chlorpromazine in the treatment of subjects with treatment-resistant schizophrenia. *http://www.Clinicalstudyresults.org/* 2005.

13 AstraZeneca. A multicenter, double-blind, randomized, comparison of quetiapine (seroquel) and chlorpromazine in the treatment of subjects with treatment-resistant schizophrenia. *http://www.Clinicalstudyresults.org/* 2005.

14 Azorin JM, Spiegel R, Remington G, et al. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. *The American Journal of Psychiatry* 2001; **158:** 1305–13.

15 Bitter I, Dossenbach MRK, Brook S, et al. Olanzapine versus clozapine in treatment-resistant or treatment-intolerant schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2004; **28:** 173–80.

16 Bondolfi G, Dufour H, Patris M, et al. Risperidone versus clozapine in treatment-resistant chronic schizophrenia. a randomized double-blind study. *American Journal of Psychiatry* 1998; **155:** 499–504.

17 Breier AF, Malhotra AK, Su TP, et al. Clozapine and risperidone in chronic schizophrenia. effects on symptoms, parkinsonian side effects, and neuroendocrine response. *American Journal of Psychiatry* 1999; **156:** 294–98.
18 Breier A, Hamilton SH, David S. Comparative efficacy of olanzapine and haloperidol for patients with treatment resistant schizophrenia. *Schizophrenia Research* 1999; **36:** 271.
19 Browne FW, Cooper SJ, Wilson R, King DJ. Serum haloperidol levels and clinical response in chronic, treatment resistant schizophrenic patients. *Journal of Psychopharmacology* 1988; **2:** 94–103.
20 Buchanan RW, Breier A, Kirkpatrick B, Ball P, Carpenter, W. T., Jr. Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. *American Journal of Psychiatry* 1998; **155:** 751–60.
21 Buchanan RW, Ball MP, Weiner E, et al. Olanzapine treatment of residual positive and negative symptoms. *American Journal of Psychiatry* 2005; **162:** 124–29.
22 Chen JJ, Chan HY, Chen CH, Gau SSF, Hwu HG. Risperidone and olanzapine versus another first generation antipsychotic in patients with schizophrenia inadequately responsive to first generation antipsychotics. *PharmacoPsychiatry* 2012; **45:** 64–71.
23 Chowdhury AN, Mukherjee A, Ghosh K, Chowdhury S, Das SK. Horizon of a new hope. recovery of schizophrenia in India. *International Medical Journal* 1999; **6:** 181–85.
24 Claus A, Bollen J, De CH, et al. Risperidone versus haloperidol in the treatment of chronic schizophrenic inpatients. a multicentre double-blind comparative study. *Acta Psychiatrica Scandinavica* 1992; **85:** 295–305.
25 Conley RR, Tamminga CA, Bartko JJ, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. *American Journal of Psychiatry* 1998; **155:** 914–20.
26 Conley RR, Kelly DL, Richardson CM, Tamminga CA, Carpenter, W. T., Jr. The efficacy of high-dose olanzapine versus clozapine in treatment-resistant schizophrenia. a double-blind, crossover study. *Journal of Clinical Psychopharmacology* 2003; **23:** 668–71.
27 Conley RR, Kelly DL, Nelson MW, et al. Risperidone, quetiapine, and fluphenazine in the treatment of patients with therapy-refractory schizophrenia. *Clinical Neuropharmacology* 2005; **28:** 163–68.
28 Daniel DG, Goldberg TE, Weinberger DR, et al. Different side effect profiles of risperidone and clozapine in 20 outpatients with schizophrenia or schizoaffective disorder. a pilot study. *American Journal of Psychiatry* 1996; **153:** 417–19.
29 Dean EF, Buker S. Schizophrenia treated with and without chlorpromazine. *Rocky Mountain Medical Journal* 1958; **55:** 47–50.
30 Emsley RA, Raniwalla J, Bailey PJ, Jones-Am. A comparison of the effects of quetiapine ('seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. *International Clinical Psychopharmacology* 2000; **15:** 121–31.
31 Hall WB, Vestre ND, Schiele BC, Zimmermann R. A controlled comparison of haloperidol and fluphenazine in chronic treatment-resistant schizophrenics. *Diseases of the Nervous System* 1968; **29:** 405–08.
32 Hong CJ, Chen JY, Chiu HJ, Sim CB. A double-blind comparative study of clozapine versus chlorpromazine on Chinese patients with treatment-refractory schizophrenia. *International Clinical Psychopharmacology* 1997; **12:** 123–30.
33 Honigfeld G, Patin J, Singer J. Clozapine. antipsychotic activity in treatment-resistant schizophrenics. *Advances in Therapy* 1984; **1:** 77–97.
34 Howard JS. Haloperidol for chronically hospitalized psychotics. a double blind comparison with thiothixene and placebo: a follow up open evaluation. *Diseases of the Nervous System* 1974; **35:** 458–63.

35 Kahn RS, van Winter RI, Leucht S, et al. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE). a three-phase switching study. *Lancet Psychiatry* 2018; **5:** 797–807.
36 Kane JM, Honigfeld G, Singer J, Meltzer H. Clozapine in treatment-resistant schizophrenics. *Psychopharmacology Bulletin* 1988; **24:** 62–67.
37 Kane JM, Marder SR, Schooler NR, et al. Clozapine and haloperidol in moderately refractory schizophrenia. a 6-month randomized double-blind comparison. *Archives of General Psychiatry* 2001; **58:** 965–72.
38 Kane JM, Khanna S, Rajadhyaksha S, Giller E. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. *International Clinical Psychopharmacology* 2006; **21:** 21–28.
39 Kane JM, Meltzer HY, Carson, W. H., Jr., McQuade RD, Marcus RN, Sanchez R. Aripiprazole for treatment-resistant schizophrenia. results of a multicenter, randomized, double-blind, comparison study versus perphenazine. *Journal of Clinical Psychiatry* 2007; **68:** 213–23.
40 Kane JM, Potkin SG, Daniel DG, Buckley PF. A double-blind, randomized study comparing the efficacy and safety of sertindole and risperidone in patients with treatment-resistant schizophrenia. *Journal of Clinical Psychiatry* 2011; **72:** 194–204.
41 Kane JM, Kinon B, Johns C. Alternative strategies for treating neuroleptic non responsive patients. *Schizophrenia Research* 1993; **9:** 240.
42 Kinon BJ, Chen L, Ascher-Svanum H, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. *Neuropsychopharmacology* 2010; **35:** 581–90.
43 Kumra S, Frazier JA, Jacobsen LK, et al. Childhood-onset schizophrenia. A double-blind clozapine-haloperidol comparison. *Archives of General Psychiatry* 1996; **53:** 1090–97.
44 Kumra S, Kranzler H, Gerbino-Rosen G, et al. Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia. a 12-week randomized and double-blind comparison. *Biological Psychiatry* 2008; **63:** 524–29.
45 Lal S, Thavundayil JX, Nair NPV, et al. Levomepromazine versus chlorpromazine in treatment-resistant schizophrenia. a double-blind randomized trial. *Journal of Psychiatry and Neuroscience* 2006; **31:** 271–79.
46 Marjerrison G, Irvine D, Stewart CN, Williams R, Matheu H, Demay M. Withdrawal of long term phenothiazines from chronically hospitalized psychiatric patients. *Canadian Psychiatric Association Journal* 1964; **60:** 290–98.
47 McCreadie RG, MacDonald IM. High dosage haloperidol in chronic schizophrenia. *British Journal of Psychiatry* 1977; **131:** 310–16.
48 McEvoy JP, Lieberman JA, Stroup TS, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *American Journal of Psychiatry* 2006; **163:** 600–10.
49 Meltzer HY, Bobo WV, Roy A, et al. A randomized, double-blind comparison of clozapine and high-dose olanzapine in treatment-resistant patients with schizophrenia. *Journal of Clinical Psychiatry* 2008; **69:** 274–85.
50 Mercer G, Finlayson A, Johnstone EC, Murray C, Owens DGC. A study of enhanced management in patients with treatment-resistant schizophrenia. *Journal of Psychopharmacology* 1997; **11:** 349–56.
51 Meyer-Lindenberg A, Gruppe, H., Bauer U, Lis S, Krieger S, Gallhofer B. Improvement of cognitive function in schizophrenic patients receiving clozapine or zotepine. results from a double-blind study. *PharmacoPsychiatry* 1997; **30:** 35–42.

52 Moresco RM, Cavallaro R, Messa C, et al. Cerebral D2 and 5-HT2 receptor occupancy in schizophrenic patients treated with olanzapine or clozapine. *Journal of Psychopharmacology* 2004; **18:** 355–65.
53 Naber D, Riedel M, Klimke A, et al. Randomized double blind comparison of olanzapine vs clozapine on subjective well-being and clinical outcome in patients with schizophrenia. *Acta Psychiatrica Scandinavica* 2005; **111:** 106–15.
54 Rosenheck R, Cramer J, Xu W, et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. *New England Journal of Medicine* 1997; **337:** 809–15.
55 Sacchetti E, Galluzzo A, Valsecchi P, Romeo F, Gorini B, Warrington L. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments. the MOZART study. *Schizophrenia Research* 2009; **113:** 112–21.
56 Schiele BC, Vestre ND, Stein KE. A comparison of thioridazine, trifluoperazine, chlorpromazine, and placebo. a double-blind controlled study on the treatment of chronic hospitalized, schizophrenic patients. *Journal of Clinical and Experimental Psychopathology* 1961; **22:** 151–62.
57 Schooler NR, Marder SR, Chengappa KN, et al. Clozapine and risperidone in moderately refractory schizophrenia. a 6-month randomized double-blind comparison. *Journal of Clinical Psychiatry* 2016; **77:** 628–34.
58 See RE, Fido AA, Maurice M, Ibrahim MM, Salama GM. Risperidone induced increase of plasma norepinephrine is not correlated with symptom improvement in chronic schizophrenia. *Biological Psychiatry* 1999; **45:** 1653–56.
59 Shalev A, Hermesh H, Rothberg J, Munitz H. Poor neuroleptic response in acutely exacerbated schizophrenic patients. *Acta Psychiatrica Scandinavica* 1993; **87:** 86–91.
60 Shaw P, Sporn A, Gogtay N, et al. Childhood-onset schizophrenia. a double-blind, randomized clozapine-olanzapine comparison. *Archives of General Psychiatry* 2006; **63:** 721–30.
61 Sirota P, Pannet I, Koren a, Tchernichovsky E. Quetiapine versus olanzapine for the treatment of negative symptoms in patients with schizophrenia. *Human Psychopharmacology* 2006; **21:** 227–34.
62 Smith RC, Infante M, Singh A, Khandat A. The effects of olanzapine on neurocognitive functioning in medication-refractory schizophrenia. *International Journal of Neuropsychopharmacology* 2001; **4:** 239–50.
63 Suzuki T, Uchida H, Watanabe K, et al. How effective is it to sequentially switch among olanzapine, quetiapine and risperidone? - A randomized, open-label study of algorithm-based antipsychotic treatment to patients with symptomatic schizophrenia in the real-world clinical setting. *Psychopharmacology* 2007; **195:** 285–95.
64 Tollefson GD, Birkett MA, Kiesler GM, Wood AJ, Lilly, Resistant Schizophrenia Study Group. Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine. *Biological Psychiatry* 2001; **49:** 52–63.
65 Toru M, Shimazono Y, Miyasaka M, Kokubo T, Mori Y, Nasu T. A double-blind comparison of sulpiride with chlorpromazine in chronic schizophrenia. *Journal of Clinical Pharmacology and New Drugs* 1972; **12:** 221–29.
66 Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. *American Journal of Psychiatry* 2002; **159:** 255–62.
67 Wahlbeck K, Cheine M, Tuisku K, Ahokas A, Joffe G, Rimon R. Risperidone versus clozapine in treatment-resistant schizophrenia. a randomized pilot study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2000; **24:** 911–22.
68 Wirshing DA, Marshall, B. D., Jr., Green MF, Mintz J, Marder SR, Wirshing WC. Risperidone in treatment-refractory schizophrenia. *American Journal of Psychiatry* 1999; **156:** 1374–79.

69 Addington J, Addington D. Neurocognitive functioning in schizophrenia. a trial of risperidone versus haloperidol. *Canadian Journal of Psychiatry [Revue Canadienne de Psychiatrie]* 1997; **42:** 983.
70 Byerly M, Weber M. Clozapine versus quetiapine for schizophrenia. *Stanley Foundation Research Programs* 1999.
71 Estrella MH, Soria FL, Gonzalez CJC, Butron MAL, Torres JA, Escareño RR. Cost-effectiveness of clozapine vs respiridone for treatment-resistant schizophrenic patients. *Proceedings of the 10th World Congress of Psychiatry; 1996 Aug 23-28; Madrid, Spain* 1996.
72 Nct. Clozapine vs olanzapine. an effectiveness study. *https://ClinicalTrials.gov/* 2005.
73 Hamilton M, Smith ALG, Lapidus HR, Cadogan EP. A controlled trial of thiopropazate dihydrochloride (dartalan), chlorpromazine and occupational therapy in chronic schizophrenics. *Journal of Mental Science* 1960; **106:** 40–55.
74 Heres S, Cordes J, Feyerabend S, et al. Changing the Antipsychotic in Early Nonimprovers to Amisulpride or Olanzapine: Randomized, Double-Blind Trial in Patients With Schizophrenia. *Schizophrenia Bulletin* 2022; **48:** 1273–83. https://doi.org/10.1093/schbul/sbac068.
75 Heylen S, Gelders Y, Bussche GV. Risperidone versus haloperidol in chronic psychotic patients. an 8 week multicenter double-blind comparative trial. *Psychopharmacology* 1988; **96:** 238.
76 Mergl RP, Gallinat J, Riedel M, Schröter A, Tigges P, Hegerl U. Digitised hand movement analysis of EPMS. *Proceedings of the 11th World Congress of Psychiatry; 1999 Aug 6-11; Hamburg, Germany* 1999; **2:** 164.
77 Oliemeulen EAP, Jogems-Kosterman BJM, Van, Hoof J. J. M. Is olanzapine a substitute for clozapine? *Schizophrenia Research* 1999; **36:** 146–47.
78 Salganik I, Modai I, Bercovici BR, Kutzuk D, Weizman A. Clozapine vs haloperidol therapy in elderly chronic schizophrenic inpatients. preliminary results. A double blind, cross over randomized study. *International Journal of Geriatric Psychopharmacology* 1998; **1:** 185–87.
79 Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Undertaking network meta-analyses, 2019.
80 Leucht S, Rothe P, Davis JM, Engel RR. Equipercentile linking of the BPRS and the PANSS. *Eur Neuropsychopharmacol* 2013; **23:** 956–59. https://doi.org/10.1016/j.euroneuro.2012.11.004.
81 Samara MT, Dold M, Gianatsi M, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. *JAMA psychiatry* 2016; **73:** 199–210. https://doi.org/10.1001/jamapsychiatry.2015.2955.
82 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020; **17:** e1003082. https://doi.org/10.1371/journal.pmed.1003082.
83 Chiocchia V, Nikolakopoulou A, Higgins JPT, et al. ROB-MEN: a tool to assess risk of bias due to missing evidence in network meta-analysis. *BMC Medicine* 2021; **19:** 304. https://doi.org/10.1186/s12916-021-02166-3.
84 Schneider-Thoma J, Chalkou K, Dörries C, et al. Comparative efficacy and tolerability of 32 oral and long-acting injectable antipsychotics for the maintenance treatment of adults with schizophrenia: a systematic review and network meta-analysis. *Lancet* 2022; **399:** 824–36. https://doi.org/10.1016/S0140-6736(21)01997-8.
85 Bighelli I, Rodolico A, García-Mieres H, et al. Psychosocial and psychological interventions for relapse prevention in schizophrenia: a systematic review and network meta-analysis. *Lancet Psychiatry* 2021; **8:** 969–80. https://doi.org/10.1016/S2215-0366(21)00243-1.