APPENDIX

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1 PRISMA checklist

Section and Topic	ltem #	Checklist item	Location where item is reported				
TITLE							
Title	1	Identify the report as a systematic review.	Page 1				
ABSTRACT		T					
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2				
INTRODUCTION	1						
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		T					
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	esent the full search strategies for all databases, registers and websites, including any filters and limits used.					
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.					
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	ltem #	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	T		
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	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 9-12
syntheses	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	ltem #	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.				
	23c	Discuss any limitations of the review processes used.	Page 16			
	23d	Discuss implications of the results for practice, policy, and future research.				
OTHER INFORMA	TION					
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.

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).
 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 (<u>http://cinema.ispm.ch/model/CINeMA paper.pdf</u>). 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

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Type and method of review

Network meta-analysis

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English

Country

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References

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- 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.
- 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 (<u>www.who.int/ictrp</u>);
- 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
Actrn1261800	26	OL-RCT	Schizophrenia	Unsuccessful treatment with 1	Paliperidone	Depot, 4 weeks, n.i. (50- 150)	36	46.4
1115240				oral antipsychotic	Paliperidone	Oral, daily, n.i. (6-12)	36	46.4
Ablfore 10809	26		Schizophrenia (clinical diagnosis)	Unsatisfactory response to	Clopenthixol	Depot, 2 weeks, 280 (50- 280)	87	n.i.
Anifors 1980 ³	20	DB-KC1		present neuroleptic treatment	Perphenazine	Depot, 2 weeks, 141 (20- 600)	85	n.i.
Altamura 2002 ¹⁰	14		Paranoid	partial response to previous	Haloperidol	Oral, daily, 12.3 (5-20)	15	38.3
		DD-INCT	(DSM-IV)	retrospective trials	Olanzapine	Oral, daily, 12.4 (10-20)	13	39.3
Alvarez 2006 ¹¹	52	OL-RCT	Schizophrenia	Prominent negative symptoms and previously treated with	Olanzapine	Oral, daily, 12.2 (10-n.i.)	124	37
				conventional antipsychotics	Risperidone	Oral, daily, 4.9 (3-n.i.)	123	35.5
AstraZanasa			Schizophropia	Historical and prospective	Quetiapine	Oral, daily, 571.2 (n.i750)	130	41
5077IL/0031 ¹²	10	DB-RCT	(DSM-IV)	criteria of treatment-resistance	Chlorpromazine	Oral, daily, 1040.4 (n.i 1500)	130	40.8
AstraZeneca	10		Schizophrenia	Treatment-resistance, at least 2	Quetiapine	Oral, daily, 600 (600-600)	117	39
5077IL/0054 ¹³	10	DB-RCT	(DSM-IV)	retrospective trials	Chlorpromazine	Oral, daily, 900 (900-900)	119	39
Azorin 2001 ¹⁴	12	DB-RCT	Schizophrenia	Poor response to previous treatment, at least 2	Clozapine	Oral, daily, 642 (200-900)	138	38.2
			(DSM-IV)	retrospective trials	Risperidone	Oral, daily, 9 (2-15)	135	39.4
			Schizonbronia	Treatment-resistance or	Clozapine	Oral, daily, 216.2 (100-500)	72	37.4
Bitter 2004 ¹⁵	18	DB-RCT	CT (DSM-IV)	intolerance, at least 1 retrospective trial	Olanzapine	Oral, daily, 17.2 (5-25)	75	37.6
Bondolfi 1009 ¹⁶	Q		Schizophrenia	Treatment-resistance or	Clozapine	Oral, daily, 291.2 (150-400)	43	36.2
B01100111 1998	8	DB-RCT	(DSM-III-R)	intolerance, at least 2	Risperidone	Oral, daily, 6.4 (3-10)	43	38.3

	1				1			
				retrospective trials				
				Partial response to	Clozapine	Oral, daily, 403.6 (200-600)	14	37.7
Breier 1999a ¹⁷	6	DB-RCT	CT Schizophrenia (DSM-IV)	neuroleptics, at least 1 retrospective and 1 prospective trials	Risperidone	Oral, daily, 5.9 (2-9)	15	32.4
Breier 1999b ¹⁸	6	DB-RCT	Schizophrenia, schizophrenifor m disorder, or	Treatment-resistance, at least 1	Olanzapine	Oral, daily, 11.1 (5-20)	352	38.3
			disorder (DSM-III-R)	retrospective trial	Haloperidol	Oral, daily, 10 (5-20)	174	38.2
Browne 1988 ¹⁹	20	DB-RCT	Schizophrenia (Feighner's	Treatment-resistance, at least 1 retrospective trial	Haloperidol	Oral, daily, n.i. (10-160)	6	40.88
	-	_	criteria, 1972)		Placebo	Oral, daily	5	40.88
Buchanan 1998 ²⁰	10	DB-RCT	Schizophrenia or RCT 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	16	5 DB-RCT	-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
2005 ²¹	10				Olanzapine	Oral, daily, 20.3 (10-30)	29	41.9
Chen 2012 ²²	8	SB-BCT	Schizophrenia	Inadequate response to only 1 line of first-generation	Olanzapine	Oral, daily, 17.8 (n.i20)	16	37.9
	5	55 1(01	(DSM-IV)	antipsychotics, 1 retrospective trial	Risperidone	Oral, daily, 4.3 (n.i6)	16	36.7
Chowdhury	16	n.i.	Schizophrenia and it subtypes	Inadequate response, at least 1	Clozapine	Oral, daily, 342.86 (200- 500)	30	30.3
1999			(ICD-10)		Risperidone	Oral, daily, 5.8 (4-8)	30	32.43
Claus 1992 ²⁴	12	DB-RCT	Schizophrenia	Treatment-resistance, at least 1	Haloperidol	Oral, daily, 10.3 (10.3-10.3)	22	39
			(DSM-III-R)	retrospective trial	Risperidone	Oral, daily, 12 (12-12)	22	37.4
Conley 1998 ²⁵	8	DB-RCT	RCT Schizophrenia	Treatment-resistance, at least 2 retrospective and 1 prospective	Chlorpromazine	Oral, daily, 1200 (1200- 1200)	42	42.63
				trials	Olanzapine	Oral, daily, 25 (25-25)	42	42.91

Conley 2003 ²⁶	Q		Schizophrenia	Treatment-resistance, at least 2	Clozapine	Oral, daily, 390 (300-450)	5	40.26
Conney 2003	0	DB-RC1	(DSM-IV)	retrospective trials	Olanzapine	Oral, daily, 50 (30-50)	8	35.91
			Schizonhrenia	Treatment-resistance, at least 2	Fluphenazine	Oral, daily, 13.2 (10-15)	13	44.2
Conley 2005 ²⁷	12	DB-RCT	(DSM-IV)	retrospective and 1 prospective	Quetiapine	Oral, daily, 463.6 (300-500)	12	43.7
				trials	Risperidone	Oral, daily, 4.31 (3-5)	13	46.3
Daniel 1996 ²⁸	6	SB-RCT	Schizophrenia or schizoaffective	Multiple past treatment failures or intolerance of	Clozapine	Oral, daily, n.i. (n.i n.i.)	10	33.8
			disorder (DSM-III-R)	conventional antipsychotic side effects	Risperidone	Oral, daily, n.i. (n.i n.i.)	10	33.8
			Schizophrenia	Fail to respond to previous	Chlorpromazine	Oral, daily, n.i. (2000-3000)	9	37
Dean 1958 ²⁹	15	DB-RCT	(clinical diagnosis)	treatment	Placebo	Oral, daily	9	37
Emsley 2000 ³⁰	8	DB-RCT	Schizophrenia	History of unsuccessful antipsychotic therapy, at least 1	Haloperidol	Oral, daily, 20 (20-20)	145	38.8
			(DSM-IV)	trials	Quetiapine	Oral, daily, 600 (600-600)	143	37.7
Hall 1968 ³¹	12	DB-RCT	Schizophrenia T (clinical diagnosis)	Treatment-resistance, at least 2	Haloperidol	Oral, daily, 6.95 (2-10)	25	45
				retrospective trials	Fluphenazine	Oral, daily, 17.86 (5-25)	25	45
			Schizophrenia (DSM-IV)	Treatment-resistance, at least 2 retrospective and 1 prospective trials	Clozapine	Oral, daily, 543 (100-900)	21	39.7
Hong 1997 ³²	12	DB-RCT			Chlorpromazine	Oral, daily, 1163 (200-1800)	19	37.1
				Poor response to	Clozapine	Oral, daily, 417 (150-900)	75	30
Honigfeld 1984 ³³	4	DB-RCT	Schizophrenia (DSM-II)	previous therapy or sensitivity to extra-pyramidal side effects, at least 2 retrospective trials	Chlorpromazine	Oral, daily, 795 (300-1800)	76	30
407434	10	DDDCT	Chronic psychosis	-	Haloperidol	Oral, daily, 61.57 (10- 133.33)	17	46.6
Howard 1974 ³⁴	12	DB-RC1	(clinical	Treatment-resistance	Placebo	Oral, daily	16	47.8
			diagnosis)		Tiotixene	Oral, daily, 184.7 (30-400)	16	45.3
Kahn 2018 ³⁵	6	DB-RCT	Schizophrenia, schizophrenifor m disorder, or	Not in remission from 1 prospective trial	Amisulpride	Oral, daily, 590.9 (200-800)	47	24.9
			schizoaffective disorder		Olanzapine	Oral, daily, 15.6 (5-20)	46	24.6

			(DSM-IV)					
			Schizonhrenia	Treatment-resistance, at least 3	Clozapine	Oral, daily, 600 (500-900)	126	36.2
Kane 1988 ³⁶	6	DB-RCT	(DSM-III)	retrospective and 1 prospective trials	Chlorpromazine	Oral, daily, 1200 (1000- 1800)	142	35.6
Kape 2001 ³⁷	29	DB-RCT	Schizophrenia or schizoaffective	Partial or poor response, at least 3 retrospective trials or 2	Clozapine	Oral, daily, 523 (200-800)	37	41
	25		disorder (DSM-III-R)	retrospective and 1 prospective trials	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	Treatment-resistance, at least 2 retrospective and 1 prospective	Aripiprazole	Oral, daily, 28.8 (15-30)	154	42.6
			(DSM-IV)	trials	Perphenazine	Oral, daily, 39.1 (8-64)	146	41.6
Kane 2011 ⁴⁰	12	DB-RCT	Schizophrenia (DSM-IV)	Treatment-resistance, at least 1	Risperidone	Oral, daily, 9 (6-12)	105	38.8
				trials	Sertindole	Oral, daily, 18.1 (12-24)	216	38.9
			Schizophrenia,		Haloperidol	Oral, daily, 20 (20-20)	13	n.i.
Kinon 1993b ⁴¹	4	DB-RCT	schizoaffective disorder, or schizophrenifor m disorder (DSM-III-R)	Treatment-resistance, non- response to 1 prospective trial	Fluphenazine	Oral, daily, 48.24 (20-80)	34	n.i.
Kinon 2009 ⁴²	12	DB-RCT	Schizophrenia, schizoaffective disorder, or schizophrenifor m disorder (DSM-IV)	Treatment-resistance, non-	Risperidone	Oral, daily, n.i. (2-6)	192	41.87
				response to 1 prospective trial	Olanzapine	Oral, daily, n.i. (10-20)	186	41.84
Kumra 1996 ⁴³	6	DB-RCT	Schizophrenia	Non-response or/and intolerance, at least 2	Clozapine	Oral, daily, 176 (6.25-525)	10	14.4
			(DSM-III-R)	retrospective trials	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
			Schizonhrenia	Treatment-resistance, at least 3	Chlorpromazine	Oral, daily, 762 (600-1000)	19	39.4
Lal 2006 ⁴⁵	15	DB-RCT	(DSM-III-R)	retrospective and 1 prospective trials	Levomepromazine	Oral, daily, 813 (600-1000)	19	38.5
Marjerrison	30	DB-RCT	Chronic psychosis	Treatment resistance	Placebo	Oral, daily	34	47
1964.0			diagnosis)	rreatment-resistance	Trifluoperazine	Oral, daily, 28 (n.i. – n.i.)	16	49
McCreadie	12	DB-RCT	Schizophrenia (clinical	Treatment-resistance	Chlorpromazine	Oral, daily, 350 (100-600)	10	52
197747	12		diagnosis)		Haloperidol	Oral, daily, 57.5 (15-100)	10	52
		DD DCT			Olanzapine	Oral, daily, 23.4 (7.5-30)	19	44.3
McEvoy 2006 ⁴⁸	26	(Clozapi	Schizophrenia	Non-response to prior atypical	Quetiapine	Oral, daily, 642.9 (200-800)	15	37.1
			(DSM-IV)	antipsychotic treatment	Risperidone	Oral, daily, 4.8 (1.5-6)	16	37.7
		ne ol)			Clozapine	Oral, daily, 332.1 (n.i. – n.i.)	49	39.4
Moltzor 200849	26	DB-RCT	Schizophrenia or schizoaffective disorder (DSM-IV) Treatment-resistance, at leas retrospective trials	Treatment-resistance, at least 2	Clozapine	Oral, daily, 564 (300-900)	21	37.2
	20			retrospective trials	Olanzapine	Oral, daily, 33.6 (25-45)	19	36.4
Moreor 1007 ⁵⁰	0		Schizophrenia	Treatment resistance	Chlorpromazine	Oral, daily, 500 (50-850)	12	37.3
Wercer 1997	9	SB-RCI	(DSM-III-R)	freatment-resistance	Risperidone	Oral, daily, 8 (4-16)	15	42.5
Meyer- Lindenberg	6	DB-RCT	Schizophrenia	Treatment-resistance or intolerance, at least 2	Clozapine	Oral, daily, 300 (150-450)	25	33.2
1997 ⁵¹			(DSM-III-R)	retrospective trials	Zotepine	Oral, daily, 300 (150-450)	25	33.7
Maracaa 2004 ⁵²	0		Schizophrenia	Treatment-resistance, at least 2	Clozapine	Oral, daily, 325.4 (300-400)	12	38.3
Woresco 2004	8	DB-RCI	(DSM-IV)	retrospective trials	Olanzapine	Oral, daily, 18.3 (15-20)	11	34.1
Naber 2005 ⁵³	26		Schizophrenia	Non-response or intolerance, at	Clozapine	Oral, daily, 209.4 (100-400)	57	35.2
	20	DB-RCI	(DSM-IV)	least 1 retrospective trial	Olanzapine	Oral, daily, 16.2 (5-25)	57	32.9
Rosenheck	52		Schizophrenia	Treatment-resistance, at least 2	Clozapine	Oral, daily, 552 (100-900)	205	43.2
1997 ⁵⁴	52	DUNCI	(DSM-III-R)	retrospective trials	Haloperidol	Oral, daily, 28 (5-30)	218	43.9
Sacchetti 2009 ⁵⁵	18		Schizophrenia	Treatment-resistance or/and	Clozapine	Oral, daily, 345.7 (250-600)	74	38.3
	10	DD-IICI	(DSM-IV)	intolerance, at least 3	Ziprasidone	Oral, daily, 130.4 (80-160)	73	41.6

				retrospective trials				
					Chlorpromazine	Oral, daily, 894 (200-1000)	20	40.6
C 1 : 1 10C1			Schizophrenia		Placebo	Oral, daily	20	40.6
Schiele 1961,	16	DB-RCT	(clinical diagnosis)	Treatment-resistance	Thioridazine	Oral, daily, 958 (200-1000)	20	40.6
00002**					Trifluoperazine	Oral, daily, 35 (10-50)	20	40.6
Seblesherg			Schizophrenia		Fluphenazine	Depot, 4 weeks, 27.5 (6.25- 50)	30	43
1978 ⁶	52	DB-RCT	(clinical diagnosis)	Treatment-resistance	Pipotiazine	Depot, 4 weeks, 27.5 (6.25- 50)	30	45
					Placebo	Depot	15	39.87
Schooler 2016 ⁵⁷	29	DB-RCT	Schizophrenia		Clozapine	Oral, daily, 456.7 (500-800)	53	42
			or schizoaffective disorder (DSM-IV)	Partial or poor response, at least 2 retrospective trials	Risperidone	Oral, daily, 6.8 (6-16)	54	42
Sec 1000 ⁵⁸	5	DB-RCT	CT Schizophrenia (DSM-IV)	Partial response to typical antipsychotics, at least 1	Haloperidol	Oral, daily, n.i. (15-30)	10	37.7
366 1333	5			retrospective and 1 prospective trials	Risperidone	Oral, daily, n.i. (4-6)	10	33.5
			Cabiasakasais		Haloperidol	Oral, daily, 29.3 (n.i. – n.i.)	18	33
Shalev 1993 ⁵⁹	4	SB-RCT		Treatment-resistance	Perphenazine	Oral, daily, 35.8 (n.i. – n.i.)	21	33
					Levomepromazine	Oral, daily, 379 (n.i. – n.i.)	21	33
Shaw 2006 ⁶⁰	Q		Schizophrenia	Insufficient response, at least 2	Clozapine	Oral, daily, 327 (150-500)	12	11.7
511010 2000	0	DDINCI	(DSM-IV)	retrospective trials	Olanzapine	Oral, daily, 18.1 (5-20)	13	12.8
Sirota 2006 ⁶¹	12	SB-RCT	Schizophrenia	Inadequate response, at least 2	Olanzapine	Oral, daily, 16 (5-20)	21	36.2
			(DSM-IV)	retrospective trials	Quetiapine	Oral, daily, 637.2 (200-800)	19	38.3
Smith 2001 ⁶²	8	DB-RCT	Schizophrenia or CT schizoaffective psychosis (criteria n.i.)	Poor clinical response, at least	Haloperidol	Oral, daily, 37.9 (5-40)	18	43
				2 retrospective trials	Olanzapine	Oral, daily, 19.9 (5-20)	20	43
			Schizonhronia	Non-response to 1 prospective	Olanzapine	Oral, daily, n.i. (n.i 20)	15	44.9
Suzuki 2007 ⁶³	4	OL-RCT	T (DSM-IV)	trial	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	10		Schizophrenia	Treatment-resistance, at least 2	Clozapine	Oral, daily, 303.6 (200-600)	90	38.6
Tollerson 2001	10	DB-RC1	(DSM-IV)	retrospective trials	Olanzapine	Oral, daily, 20.5 (15-25)	90	38.6
Toru 1972 ⁶⁵	8	DB-RCT	Schizophrenia (clinical	Non-response to conventional	Chlorpromazine	Oral, daily, n.i. (150-600)	37	35
	0		diagnosis)	psychotropic	Sulpiride	Oral, daily, n.i. (300-1200)	38	35
			Schizophrenia		Clozapine	Oral, daily, 526.6 (200-800)	40	42.6
			or		Haloperidol	Oral, daily, 25.7 (10-30)	37	37.3
Volavka 2002 ⁶⁶	14	DB-RCT	schizoaffective disorder (DSM-IV)	Suboptimal response, at least 1	Olanzapine	Oral, daily, 30.4 (10-40)	39	41
				retrospective trial	Risperidone	Oral, daily, 11.6 (4-16)	41	42.9
Wahlbeck	10		Schizophrenia	Treatment-resistance, at least 2	Clozapine	Oral, daily, 385 (25-600)	11	35.7
2000 ⁶⁷	10	SB-RCI	(DSM-IV)	trials	Risperidone	Oral, daily, 7.8 (2-10)	9	36.8
Wirching 100068	8		Schizophrenia	Treatment-resistance or	Haloperidol	Oral, daily, 19.4 (5-30)	33	40
with string 1999	0	DB-NCT	(DSM-III-R)	retrospective trials	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	6	DB-RCT	Schizophrenia	Treatment-resistance	Risperidone	Oral, daily, n.i. (6-10)	n.i.	n.i.
1996 ⁶⁹			(DSM-III-R)		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	Clozapine	Oral, daily, 300 (300-300)	n.i.	n.i.
			(000	risperidone	Quetiapine	Oral, daily, 400 (400-400)	n.i.	n.i.
Estrella 1996 ⁷¹	104	OL-RCT	schizophrenic	Treatment-resistance	Clozapine	Oral, n.i., n.i. (n.i n.i.)	n.i.	n.i.
			patients		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	Treatment-resistance to 2 trials of typical neuroleptics or 1 trial	Clozapine	Oral, n.i., n.i. (n.i n.i.)	n.i.	n.i.
			n.i.)	antipsychotic	Olanzapine	Oral, n.i., n.i. (n.i n.i.)	n.i.	n.i.
Hamilton	8	DB-RCT	Schizophrenia	Treatment-resistance	Chlorpromazine	Oral, daily, 300 (300-300)	18	38
1960.5			(clinical diagnosis)		Placebo	Oral, daily	18	38
Heres 2022 ⁷⁴	6	DB-RCT	schizophrenia, schizoaffective	Not in remission from 1 prospective trial	Amisulpride	Oral, daily, n.i. (600-800)	n.i.	n.i.
			disorder or schizophreniform disorder (DSM-IV)		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	Non-response to	Olanzapine	Oral, n.i., n.i. (n.i n.i.)	n.i.	n.i.
			(criteria n.i.)	typical neuroleptics	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	10	DB-RCT	Schizophrenia	Treatment-resistance	Clozapine	Oral, n.i., n.i. (n.i n.i.)	n.i.	66.6
1998 ⁷⁸			(DSM-III-R)		Haloperidol	Oral, n.i., n.i. (n.i n.i.)	n.i.	66.6

Teja 1975 ⁷	20	DB-RCT	Schizophrenia	Non-response to the	Chlorpromazine	Oral, daily, n.i. (100-1080)	14	38.01
			(DSM-II)	various treatments	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 2013⁸⁰. 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

Study	Total	Experimental Mean SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (common)	Weight (random)
comparison = Haloperidol_Olanzapine Altamura 2002 Haloperidol Olanzapine Buchanan 2005 Haloperidol Olanzapine Volavka 2002 Haloperidol Olanzapine Breier 1999a Haloperidol Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.54$	11 34 37 172 254	42.39 12.3266 33.60 10.6000 88.70 18.7651 -13.40 20.9000	13 29 39 344 425	33.44 33.40 81.90 -19.40	12.3266 9.9000 18.7651 23.0000		0.70 0.02 0.36 0.27 0.27 0.27	[-0.13; 1.53] [-0.48; 0.51] [-0.09; 0.81] [0.08; 0.45] [0.11; 0.43] [0.11; 0.43]	0.4% 1.1% 1.3% 7.8% 10.5%	0.9% 1.7% 1.9% 3.1%
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Breier 1999 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Wahlbeck 2000 Clozapine Risperidone Chowdhury 1999 Clozapine Risperidone Schooler 2016 Clozapine Risperidone Common effect model Random effects model Heterogenelity: I ² = 53%, x ² = 0.0556, p = 0.04	124 43 14 33 40 10 24 30 318	-37.50 22.5000 -23.20 21.5000 32.00 6.3700 -18.40 16.9303 90.90 18.7651 76.00 22.0000 50.00 17.0800 31.50 7.9000	125 43 15 6 41 9 22 22 283	-29.90 -27.40 35.80 -0.30 86.40 63.00 50.45 31.30	23.9000 23.6000 9.8900 16.9303 18.7651 17.0000 20.7400 6.5000		-0.33 0.18 -0.44 -1.05 0.24 0.63 -0.02 0.03 -0.12 -0.07	$\begin{matrix} [-0.58; -0.08] \\ [-0.24; 0.61] \\ [-1.18; 0.30] \\ [-1.95; -0.14] \\ [-0.20; 0.67] \\ [-0.30; 1.55] \\ [-0.60; 0.56] \\ [-0.52; 0.58] \\ [-0.28; 0.05] \\ [-0.33; 0.18] \end{matrix}$	4.2% 1.5% 0.5% 0.3% 1.4% 0.3% 0.8% 0.9% 9.8%	2.8% 2.0% 1.1% 0.8% 2.0% 0.8% 1.5% 1.6%
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Conley 2003 Clozapine Olanzapine McEvoy 2006 Clozapine Olanzapine Metzy 2008 Clozapine Olanzapine Meltzer 2008 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Heterogeneity: $I^2 = 18\%$, $x^2 = 0.0039$, $p = 0.27$	70 12 5 18 33 21 6 56 87 40 348	-37.90 23.4000 -20.00 18.3300 -5.80 7.3600 31.40 9.3000 -18.40 16.9303 72.10 15.6000 55.80 18.9000 -30.20 29.6000 -22.10 23.1000 90.90 18.7651	70 13 8 21 10 19 9 52 89 39 330	-37.70 -13.00 -0.88 34.30 -7.70 71.70 65.00 -32.60 -25.60 81.90	23.1000 18.3300 8.7300 13.6000 16.9303 12.2000 20.9000 25.5000 18.7651	++++++++++++++++++++++++++++++++++++++	-0.01 -0.37 -0.55 -0.24 -0.62 0.03 -0.43 0.08 0.14 0.47 0.03 0.03	$ \begin{bmatrix} -0.34; & 0.32 \\ [-1.16; & 0.42] \\ [-1.70; & 0.59] \\ [-0.87; & 0.39] \\ [-1.34; & 0.10] \\ [-1.34; & 0.12] \\ [-0.59; & 0.65] \\ [-1.48; & 0.65] \\ [-0.43; & 0.46] \\ [-0.15; & 0.44] \\ [0.03; & 0.92] \\ [-0.12; & 0.18] \\ [-0.13; & 0.19] \\ \end{bmatrix} $	2.4% 0.4% 0.7% 0.5% 0.7% 0.2% 1.8% 3.0% 1.3% 1.3%	2.4% 1.0% 0.5% 1.3% 1.3% 0.6% 2.2% 2.6% 1.9% 15.1%
comparison = Clozapine_Haloperidol Buchanan 1998 Clozapine Haloperidol Kumra 1996 Clozapine Haloperidol Kane 2001 Clozapine Haloperidol Rosenheck 1997 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.48$	38 10 23 205 40 316	35.60 10.6000 52.50 12.6000 37.50 9.0000 79.10 19.8100 90.90 18.7651	37 11 11 218 37 314	37.00 64.70 40.20 83.60 88.70	9.4000 18.1000 12.2000 19.8100 18.7651	*	-0.14 -0.74 -0.26 -0.23 0.12 -0.19 -0.19	$\begin{matrix} [-0.59; \ 0.32] \\ [-1.64; \ 0.15] \\ [-0.98; \ 0.46] \\ [-0.42; \ -0.04] \\ [-0.33; \ 0.56] \\ [-0.35; \ -0.03] \\ [-0.35; \ -0.03] \end{matrix}$	1.3% 0.3% 0.5% 7.2% 1.3% 10.6%	1.9% 0.8% 1.1% 3.1% 1.9% 8.8%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone See 1999 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Wirshing 1999 Haloperidol Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%, \tau^2 = < 0.0001, p = 0.54$	21 10 37 29 97	74.30 20.1600 67.55 11.4500 88.70 18.7651 59.30 12.3500	21 10 41 29 101	76.90 59.95 86.40 57.30	20.1600 9.6400 18.7651 12.3500	++++	-0.13 0.69 0.12 0.16 0.13 0.13	[-0.73; 0.48] [-0.22; 1.60] [-0.32; 0.57] [-0.36; 0.68] [-0.15; 0.41] [-0.15; 0.41]	0.7% 0.3% 1.3% 1.0% 3.3%	1.4% 0.8% 1.9% 1.7% 5.8%
comparison = Chlorpromazine_Olanzapine Conley 1998 Chlorpromazine Olanzapine	39	56.90 11.7000	42	54.10	14.1000		0.21	[-0.22; 0.65]	1.4%	2.0%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	141	-8.87 18.4800	140	-11.50	18.4800	-	0.14	[-0.09; 0.38]	4.8%	2.9%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	102	-19.00 21.3000	213	-12.00	22.1000		-0.32	[-0.56; -0.08]	4.7%	2.9%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	33	-18.40 16.9303	8	-1.30	16.9303		-0.99	[-1.79; -0.19]	0.4%	0.9%
comparison = Olanzapine_Quetiapine McEvoy 2006 Olanzapine Quetiapine Sirota 2006 Olanzapine Quetiapine Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.43$	10 21 31	-7.70 16.9303 -11.00 21.2004	8 19 27	-1.30 -13.00	16.9303 21.2004		-0.36 0.09 -0.05 -0.05	[-1.30; 0.58] [-0.53; 0.71] [-0.56; 0.47] [-0.56; 0.47]	0.3% 0.7% 1.0%	0.7% 1.3% 2.1%
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Volavka 2002 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Kinon 2009 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.98$	10 39 16 179 244	-7.70 16.9303 81.90 18.7651 -14.80 13.7000 -17.02 15.5200	6 41 16 189 252	-0.30 86.40 -12.70 -13.53	16.9303 18.7651 14.3000 15.5300		-0.41 -0.24 -0.15 -0.22 -0.23 -0.23	[-1.44; 0.61] [-0.68; 0.20] [-0.84; 0.55] [-0.43; -0.02] [-0.40; -0.05] [-0.40; -0.05]	0.2% 1.4% 0.5% 6.2% 8.4%	0.6% 2.0% 1.2% 3.0% 6.8%
comparison = Quetiapine_Risperidone McEvoy 2006 Quetiapine Risperidone Conley 2005 Quetiapine Risperidone Common effect model Random effects model Heterogeneity: $t^2 = 0\%$, $t^2 = 0$, $p = 0.79$	8 12 20	-1.30 16.9303 53.83 13.5013	6 13 19	-0.30 52.15	16.9303 13.5013		-0.06 0.12 0.06 0.06	[-1.11; 1.00] [-0.67; 0.91] [-0.57; 0.69] [-0.57; 0.69]	0.2% 0.4% 0.7%	0.6% 1.0% 1.6%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	150	-9.80 21.5600	144	-10.50	21.4300	÷	0.03	[-0.20; 0.26]	5.0%	2.9%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	13	51.85 13.5013	12	53.83	13.5013	<u> </u>	-0.14	[-0.93; 0.64]	0.4%	1.0%

comparison = Fluphenazine Risperidone					1					
Conley 2005 Fluphenazine Risperidone	13 51.85 13	.5013	13 52	.15 13.5013		-0.02	[-0.79;	0.75]	0.4%	1.0%
comparison = Chlorpromazine_Clozapine Hong 1997 Chlorpromazine Clozapine Honigfeld 1984b Chlorpromazine Clozapine Kane 1988 Chlorpromazine Clozapine Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.56$	19 -2.00 3 63 -13.94 14 139 56.00 12 221	.0000 .2400 .0000	21 -12 62 -23 126 45 209	.00 18.0000 .24 14.6400 .00 13.0000	+++ \$	0.74 0.64 0.88 0.79 0.79	[0.10; [0.28; [0.63; [0.60; [0.60;	1.38] 1.00] 1.13] 0.99] 0.99]	0.6% 2.0% 4.1% 6.8%	1.3% 2.3% 2.8% 6.4%
comparison = Chlorpromazine_Ziprasidone Kane 2006 Chlorpromazine Ziprasidone	154 -13.00 21	.2004	152 -14	.50 21.2004	+	0.07	[-0.15;	0.29]	5.2%	2.9%
comparison = Clozapine_Zotepine Meyer-Lindenberg 1997 Clozapine Zotepine	25 36.10 15	.3000	25 37	.40 17.9000	_	-0.08	[-0.63;	0.48]	0.9%	1.5%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	73 -24.50 22	.5000	71 -25	.00 22.0000	+	0.02	[-0.30;	0.35]	2.5%	2.4%
comparison = Chlorpromazine_Levomepromazine Lal 2006 Chlorpromazine Levomepromazine	19 97.00 24	.0000	19 81	.10 21.2000		0.69	[0.03;	1.34]	0.6%	1.3%
comparison = Fluphenazine_Haloperidol Hall 1968 Fluphenazine Haloperidol Kinon 1993b Fluphenazine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.68$	25 45.30 16 34 41.02 9 59	.0904 .5719	25 43 13 38 38	.80 16.0904 .60 6.5300	40	0.09 0.27 0.17 0.17	[-0.46; [-0.37; [-0.25; [-0.25;	0.65] 0.91] 0.59] 0.59]	0.9% 0.6% 1.5%	1.5% 1.3% 2.8%
comparison = Amisulpride_Olanzapine Kahn 2018 Amisulpride Olanzapine	33 -10.10 19	.9000	39 -6	.10 13.9000		-0.23	[-0.70;	0.23]	1.2%	1.9%
$\label{eq:comparison} = Chlorpromazine_Quetiapine\\ AstraZeneca 50771L/0031 Chlorpromazine Quetiapine\\ AstraZeneca 50771L/0054 Chlorpromazine Quetiapine\\ Common effect model\\ Random effects model\\ Heterogeneity: I^2 = 29\%, \tau^2 = 0.0068, p = 0.24 \\ \end{tabular}$	127 -7.22 12 117 -18.85 20 244	.7300	125 -3 115 -16 240	.11 12.7500 .72 20.2200	**	-0.32 -0.10 -0.22 -0.22	[-0.57; [-0.36; [-0.40; [-0.43;	-0.07] 0.15] -0.04] 0.00]	4.2% 4.0% 8.2%	2.8% 2.8% 5.6%
comparison = Fluphenazine_LAI_Pipotiazine_LAI Schlosberg 1978 Fluphenazine_LAI Pipotiazine_LAI	9 -22.07 14	.0353	9 -27	.01 14.0353		0.34	[-0.60;	1.27]	0.3%	0.8%
comparison = Fluphenazine_LAI_Placebo Schlosberg 1978 Fluphenazine_LAI Placebo	9 -22.07 14	.0353	2 -17	.50 14.0353		-0.30	[-1.84;	1.24]	0.1%	0.3%
comparison = Pipotiazine_LAI_Placebo Schlosberg 1978 Pipotiazine_LAI Placebo	9 -27.01 14	.0353	2 -17	.50 14.0353		-0.62	[-2.18;	0.95]	0.1%	0.3%
Common effect model Random effects model Heterogeneity: $l^2 = 61\%$, $r^2 = 0.0611$, $p < 0.01$ Test for subgroup differences (fixed effect): $\chi^2_{2n} = 116.61$, df Test for subgroup differences (random effects): $\chi^2_{2n} = 112.11$	2974 = 25 (p < 0.01) I, df = 25 (p < 0.01)	:	3129		-2 -1 0 1 Experimental Control	0.02 0.02 2	[-0.03; [-0.07;	0.07] 0.11]	100.0%	100.0%

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.

			FGAs		C	lozapine				Weight	Weight
Study	Total	Mean	SD	Total	Mean	SD	Overall symptoms	SMD	95%-CI	(common)	(random)
comparison = Chlorpro	mazin	e vs. C	lozapine								
Hong 1997	19	-2.00	3.0000	21	-12.00	18.0000		0.74	[0.10; 1.38]	3.6%	9.3%
Honigfeld 1984b	63	-13.94	14.2400	62	-23.24	14.6400		0.64	[0.28; 1.00]	11.7%	14.8%
Kane 1988	139	56.00	12.0000	126	45.00	13.0000		0.88	[0.63; 1.13]	23.7%	17.2%
Common effect model	221			209			•	0.79	[0.60: 0.99]	39.0%	
Random effects model							\diamond	0.79	[0.60: 0.99]		41.4%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p =	= 0.56									
comparison = Haloperi	dol vs	. Clozaj	pine								
Buchanan 1998	37	37.00	9.4000	38	35.60	10.6000		0.14	[-0.32; 0.59]	7.4%	12.8%
Kumra 1996	11	64.70	18.1000	10	52.50	12.6000		0.74	[-0.15; 1.64]	1.9%	6.3%
Kane 2001	11	40.20	12.2000	23	37.50	9.0000		0.26	[-0.46; 0.98]	2.9%	8.2%
Rosenheck 1997	218	83.60	19.8100	205	79.10	19.8100		0.23	[0.04; 0.42]	41.3%	18.4%
Volavka 2002	37	88.70	18.7651	40	90.90	18.7651		-0.12	[-0.56; 0.33]	7.5%	13.0%
Common effect model	314			316				0.19	[0.03; 0.35]	61.0%	
Random effects model							\diamond	0.19	[0.03; 0.35]		58.6%
Heterogeneity: $I^2 = 0\%$, τ^2	= < 0.0	001 <i>. p</i> =	0.48						•		
Common effect model	535			525			\$	0.43	[0.30; 0.55]	100.0%	
Random effects model								0.43	[0.16; 0.70]		100.0%
							-1.5 -1 -0.5 0 0.5 1 1.5				
Heterogeneity: $I^2 = 74\%$, τ^2	2 = 0.09)24, <i>p</i> <	0.01	21 99 7	f = 1 (n)	F	GAs Cloza	apine			

Test for subgroup differences (common effect): $\chi_2^2 = 21.99$, df = 1 (p < 0.01) Test for subgroup differences (random effects): $\chi_2^2 = 21.99$, df = 1 (p < 0.01)

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.

Chudu	Tetal	Maan	SGAS	Tatal	C	lozapine	0	lloumenterno	CMD	05% 01	Weight	Weight
Study	Total	Mean	50	Total	Mean	50	Overa	an symptoms	SMD	95%-01	(common)	(random)
comparison = Olanzapi	ne vs.	Clozap	ine					i i				
Bitter 2004	70	-37.70	23.1000	70	-37.90	23.4000		<u>_</u>	0.01	[-0.32; 0.34]	9.7%	8.3%
Shaw 2006	13	-13.00	18.3300	12	-20.00	18.3300		<u>i</u>	0.37	[-0.42; 1.16]	1.7%	2.5%
Conley 2003	8	-0.88	8.7300	5	-5.80	7.3600	2.5	<u>i</u> ,	- 0.55	[-0.59; 1.70]	0.8%	1.3%
Kumra 2007	21	34.30	13.6000	18	31.40	9.3000			0.24	[-0.39; 0.87]	2.7%	3.6%
McEvoy 2006	10	-7.70	16.9303	33	-18.40	16.9303			0.62	[-0.10; 1.34]	2.0%	2.9%
Meltzer 2008	19	71.70	12.2000	21	72.10	15.6000	80		-0.03	[-0.65; 0.59]	2.8%	3.7%
Moresco 2004	9	65.00	20.9000	6	55.80	18.9000			- 0.43	[-0.62; 1.48]	1.0%	1.5%
Naber 2005	52	-32.60	29.6000	56	-30.20	29.6000	24		-0.08	[-0.46; 0.30]	7.4%	7.3%
Tollefson 2001	89	-25.60	25.5000	87	-22.10	23.1000			-0.14	[-0.44; 0.15]	12.1%	9.2%
Volavka 2002	39	81.90	18.7651	40	90.90	18.7651	_		-0.47	[-0.92; -0.03]	5.3%	5.9%
Common effect model	330			348				4	-0.03	[-0.18; 0.12]	45.4%	
Random effects model								\$	-0.03	[-0.19; 0.13]		46.4%
Heterogeneity: $I^2 = 18\%$, τ^2	= 0.00	(39, p = (0.27					í.				
comparison = Quetiapi	ne vs.	Clozapi	ine					6				
McEvoy 2006	8	-1.30	16.9303	33	-18.40	16.9303		i — •	- 0.99	[0.19; 1.79]	1.6%	2.4%
comparison = Risperid	one vs	. Cloza	pine									
Azorin 2001	125	-29.90	23.9000	124	-37.50	22.5000		i	0.33	[0.08; 0.58]	17.0%	10.5%
Bondolfi 1998	43	-27.40	23.6000	43	-23.20	21.5000	-		-0.18	[-0.61; 0.24]	5.9%	6.3%
Breier 1999	15	35.80	9.8900	14	32.00	6.3700			0.44	[-0.30; 1.18]	1.9%	2.8%
McEvoy 2006	6	-0.30	16.9303	33	-18.40	16.9303		i	1.05	[0.14; 1.95]	1.3%	2.0%
Volavka 2002	41	86.40	18.7651	40	90.90	18.7651			-0.24	[-0.67; 0.20]	5.5%	6.1%
Wahlbeck 2000	9	63.00	17.0000	10	76.00	22.0000			-0.63	[-1.55; 0.30]	1.2%	1.9%
Chowdhury 1999	22	50.45	20.7400	24	50.00	17.0800	-	`	0.02	[-0.56; 0.60]	3.2%	4.1%
Schooler 2016	22	31.30	6.5000	30	31.50	7.9000	-		-0.03	[-0.58; 0.52]	3.5%	4.5%
Common effect model	283			318				•	0.12	[-0.05; 0.28]	39.6%	
Random effects model								\Leftrightarrow	0.07	[-0.18; 0.33]		38.3%
Heterogeneity: $I^2 = 53\%$, τ^2	2 = 0.05	i56, p = (0.04									
comparison = Ziprasido	one vs	. Clozaj	pine					6 6				
Sacchetti 2009	71	-25.00	22.0000	73	-24.50	22.5000			-0.02	[-0.35; 0.30]	9.9%	8.4%
comparison = Zotepine	vs. Cl	ozapine	e									
Meyer-Lindenberg 1997	25	37.40	17.9000	25	36.10	15.3000	1		0.08	[-0.48; 0.63]	3.4%	4.4%
Common effect model	717			797				\$	0.05	[-0.06; 0.15]	100.0%	
Random effects model								\diamond	0.06	[-0.08; 0.19]		100.0%
Heterogeneity: $I^2 = 39\% \tau^2$	2 = 0.02	97 n = (0.03				-1 SGAs	U 1 Clozan	ine			
	0.02											

Test for subgroup differences (common effect): $\chi_4^2 = 7.16$, df = 4 (p = 0.13) Test for subgroup differences (random effects): $\chi_4^2 = 6.16$, df = 4 (p = 0.19)

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)	Levomeproma zine	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)	Chlorpromazi ne	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

Study	Total	Expe Mean	rimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (common)	Weight (random)
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Breier 1999 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Vahlbeck 2000 Clozapine Risperidone Chowdhury 1999 Clozapine Risperidone Schooler 2016 Clozapine Risperidone Common effect model Random effect model Heterogeneity: I ² = 43%, x ² = 0.0431, p = 0.09	126 43 14 33 40 10 24 30 320	-10.40 -6.70 7.43 -4.90 23.40 17.00 10.08 2.50	6.6100 7.1000 2.2100 5.6498 7.1257 6.0000 3.0600 0.9000	130 43 15 6 41 9 22 22 288	-8.30 9.53 -0.50 21.20 15.00 10.04 2.40	7.3900 10.7000 4.7300 5.6498 7.1257 7.0000 3.2600 1.0000	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	-0.30 0.17 -0.55 -0.76 0.31 0.29 0.01 0.10 -0.09 -0.05	[-0.54; -0.05] [-0.25; 0.60] [-1.29; 0.20] [-1.65; 0.13] [-0.13; 0.74] [-0.61; 1.20] [-0.57; 0.59] [-0.45; 0.65] [-0.26; 0.07] [-0.29; 0.18]	4.8% 1.6% 0.5% 1.5% 0.4% 0.9% 1.0% 11.1%	3.2% 2.3% 1.2% 0.9% 2.2% 0.9% 1.6% 1.6%
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Conley 2003 Clozapine Olanzapine McEvoy 2006 Clozapine Olanzapine McEvoy 2006 Clozapine Olanzapine Meltzer 2008 Clozapine Olanzapine Moresco 2004 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 21\%$, $\tau^2 = 0.0158$, $p = 0.25$	70 12 5 18 33 21 6 56 87 40 348	-11.80 -22.00 -0.80 6.30 -4.90 15.10 9.50 -7.60 -6.40 23.40	7.9000 16.5739 2.8707 2.6000 5.6498 5.0400 3.3000 8.0000 7.2000 7.1257	70 13 8 21 10 19 9 52 89 39 330	-11.70 -13.00 0.31 8.10 -2.90 17.80 11.20 -9.00 -6.80 21.60	7.3000 16.5739 2.8707 4.5000 5.6498 3.9200 1.8000 8.5000 7.6000 7.1257	++++++++++++++++++++++++++++++++++++++	-0.01 -0.53 -0.36 -0.47 -0.35 -0.58 -0.58 -0.64 0.17 0.05 0.25 -0.05 -0.05	[-0.34; 0.32] [-1.33; 0.28] [-1.49; 0.77] [-1.11; 0.17] [-1.06; 0.76] [-1.22; 0.05] [-1.71; 0.42] [-0.21; 0.55] [-0.24; 0.35] [-0.29; 0.69] [-0.20; 0.11] [-0.26; 0.10]	2.7% 0.5% 0.2% 0.7% 0.6% 0.3% 2.0% 3.4% 1.5%	2.7% 1.1% 0.6% 1.5% 1.3% 0.7% 2.5% 2.9% 2.2%
comparison = Clozapine_Haloperidol Buchanan 1998 Clozapine Haloperidol Kumra 1996 Clozapine Haloperidol Kane 2001 Clozapine Haloperidol Rosenheck 1997 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 41\%$, $\tau^2 = < 0.0001$, $p = 0.15$	38 10 23 205 40 316	11.00 19.10 12.10 19.50 23.40	5.2000 11.7000 3.5000 8.4800 7.1257	37 11 11 218 37 314	11.80 35.90 14.80 21.20 22.80	4.8000 15.6000 5.7000 8.4800 7.1257	*	-0.16 -1.16 -0.61 -0.20 0.08 -0.21 -0.21	[-0.61; 0.30] [-2.10; -0.22] [-1.35; 0.12] [-0.39; -0.01] [-0.36; 0.53] [-0.36; -0.05] [-0.36; -0.05]	1.4% 0.3% 0.5% 8.0% 1.5% 11.8%	2.1% 0.8% 1.2% 3.4% 2.1% 9.7%
comparison = Haloperidol_Olanzapine Buchanan 2005 Haloperidol Olanzapine Volavka 2002 Haloperidol Olanzapine Breier 1999a Haloperidol Olanzapine Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.93$	34 37 172 243	10.10 22.80 -4.00	5.3000 7.1257 6.2000	29 39 344 412	9.80 21.60 -5.10	5.3000 7.1257 7.3000		0.06 0.17 0.16 0.15 0.15	[-0.44; 0.55] [-0.28; 0.62] [-0.03; 0.34] [-0.01; 0.31] [-0.01; 0.31]	1.2% 1.4% 8.7% 11.3%	1.9% 2.1% 3.5% 7.5%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone See 1999 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Wirshing 1999 Haloperidol Risperidone Common effect model Random effects model Helerogeneity: $l^2 = 0\%$, $\tau^2 = < 0.0001$, $p = 0.51$	21 10 37 29 97	15.40 13.05 22.80 14.40	5.9600 2.9400 7.1257 4.6300	21 10 41 29 101	15.90 10.90 21.20 13.10	6.4200 2.5000 7.1257 4.6300		-0.08 0.75 0.22 0.28 0.22 0.22	[-0.68; 0.53] [-0.16; 1.67] [-0.22; 0.67] [-0.24; 0.79] [-0.06; 0.50] [-0.06; 0.50]	0.8% 0.4% 1.5% 1.1% 3.7%	1.6% 0.9% 2.2% 1.9% 6.4%
comparison = Chlorpromazine_Olanzapine Conley 1998 Chlorpromazine Olanzapine	39	19.40	3.1000	42	18.10	4.2000		0.35	[-0.09; 0.79]	1.5%	2.2%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	<mark>140</mark>	-2.85	6.1800	140	-3.43	6.1800	+	0.09	[-0.14; 0.33]	5.3%	3.2%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	102	-5.80	6.3000	213	-3.30	6.9000	-	-0.37	[-0.61; -0.13]	5.2%	3.2%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	33	-4.90	5.6498	8	0.60	5.6498		-0.95	[-1.76; -0.15]	0.5%	1.1%
comparison = Olanzapine_Quetiapine McEvoy 2006 Olanzapine Quetiapine Sirota 2006 Olanzapine Quetiapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.87$	10 21 31	-2.90 -4.00	5.6498 5.9421	8 19 27	0.60 -1.00	5.6498 5.9421		-0.59 -0.49 -0.52 -0.52	[-1.54; 0.36] [-1.13; 0.14] [-1.05; 0.00] [-1.05; 0.00]	0.3% 0.7% 1.1%	0.8% 1.5% 2.3%
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Volavka 2002 Olanzapine Risperidone Alvarez 2006 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: I^2 = 48%, τ^2 = 0.0600, p = 0.12	10 39 120 16 185	-2.90 21.60 -18.98 -3.50	5.6498 7.1257 16.4317 3.3000	6 41 115 16 178	-0.50 21.20 -13.64 -5.80	5.6498 7.1257 17.1581 5.7000	+++++++++++++++++++++++++++++++++++++++	-0.40 0.06 -0.32 0.48 -0.17 -0.07	[-1.43; 0.62] [-0.38; 0.49] [-0.57; -0.06] [-0.22; 1.19] [-0.38; 0.04] [-0.43; 0.28]	0.3% 1.5% 4.4% 0.6% 6.8%	0.7% 2.2% 3.1% 1.3% 7.3%
comparison = Quetiapine_Risperidone McEvoy 2006 Quetiapine Risperidone Conley 2005 Quetiapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 23\%$, $\tau^2 = 0.0696$, $p = 0.26$	8 12 20	0.60 -0.67	5.6498 1.1009	6 13 19	-0.50 -1.77	5.6498 1.1009		0.18 0.97 0.67 0.65	[-0.88; 1.24] [0.13; 1.80] [0.01; 1.32] [-0.11; 1.40]	0.3% 0.4% 0.7%	0.7% 1.0% 1.7%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	150	-2.70	6.4000	144	-2.65	6.4900	÷	-0.01	[-0.24; 0.22]	5.6%	3.2%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	13	-0.92	1.1009	12	-0.67	1.1009		-0.22	[-1.01; 0.57]	0.5%	1.1%
comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	13	-0.92	1.1009	13	-1.77	1.1009	· · · · · · · · · · · · · · · · · · ·	0.75	[-0.05; 1.55]	0.5%	1.1%

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comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	150	-2.70	6.4000	144	-2.65	6.4900	+	-0.01	[-0.24; 0.22]	5.6%	3.2%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	13	-0.92	1.1009	12	-0.67	1.1009		-0.22	[-1.01; 0.57]	0.5%	1.1%
comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	13	-0.92	1.1009	13	-1.77	1.1009	Tana	0.75	[-0.05; 1.55]	0.5%	1.1%
comparison = Chlorpromazine_Clozapine Hong 1997 Chlorpromazine Clozapine Kane 1988 Chlorpromazine Clozapine Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.58$	19 139 158	-1.00 17.00	5.0000 4.0000	21 126 147	-16.00 14.00	23.0000 5.0000	\$ \$ \$	0.86 0.66 0.69 0.69	[0.21; 1.51] [0.42; 0.91] [0.46; 0.92] [0.46; 0.92]	0.7% 4.8% 5.5%	1.4% 3.1% 4.6%
comparison = Chlorpromazine_Ziprasidone Kane 2006 Chlorpromazine Ziprasidone	154	-3.25	2.8707	152	-3.50	2.8707	0.005	0.09	[-0.14; 0.31]	5.8%	3.3%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	73	-7.00	7.2000	71	-6.00	7.8000		-0.13	[-0.46; 0.19]	2.7%	2.7%
comparison = Chlorpromazine_Levomepromazine Lal 2006 Chlorpromazine Levomepromazine	19	26.80	7.7000	19	21.90	6.6000	1.1%	0.67	[0.01; 1.32]	0.7%	1.4%
comparison = Amisulpride_Olanzapine Kahn 2018 Amisulpride Olanzapine	33	-2.80	6.0000	39	-1.10	4.2000	2.1%	-0.33	[-0.80; 0.14]	1.3%	2.1%
comparison = Chlorpromazine_Quetiapine AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine	128	-2.45	4.3000	125	-1.11	4.3600	-	-0.31	[-0.56; -0.06]	4.8%	3.1%
comparison = Paliperidone_Paliperidone_LAI Actm12618001113246 Paliperidone Paliperidone_LAI	32	3.30	1.2900	33	3.45	1.0100	22,096	-0.13	[-0.61; 0.36]	1.2%	2.0%
Common effect model Random effects model Heterogeneity. $l^2 = 61\%, r^2 = 0.0616, p < 0.01$ Test for subgroup differences (fixed effect): $\chi^2_{21} = 92.71$, df = Test for subgroup differences (random effects): $\chi^2_{3.} = 88.80$.	2647 21 (p < df = 21	: 0.01) (p < 0.0	1)	2827		-2 E	-1 0 1 (xperimental Control	-0.02 -0.02	[-0.07; 0.04] [-0.12; 0.08]	100.0%	 100.0%

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)	Levomeproma zine	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	-0.88 (-1.36 to	-1.02 (-2.25 to	-0.81 (-1.32 to	-0.76 (-1.70 to	-0.77 (-1.95 to	-0.67 (-1.42 to	-0.66 (-1.28 to	-0.68 (-1.23 to	-0.67 (-1.23 to	-0.49 (-1.64 to	Chlorpromazi

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

Study	Total	Exper Mean	rimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-C	Weight (common)	Weight (random)
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Breier 1999 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Valvka 2002 Clozapine Risperidone Chowdhury 1999 Clozapine Risperidone Schooler 2016 Clozapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 34\%$, $r^2 = 0.0092$, $p = 0.16$	124 43 14 33 40 10 24 30 318	-8.80 -6.10 48.93 -5.30 23.50 21.00 14.08 1.80	6.7500 6.1000 8.4300 5.6292 5.9836 4.0000 6.6600 0.7000	128 43 15 6 41 9 22 22 286	-7.10 -6.00 47.60 0.00 22.90 17.00 14.55 1.80	7.2400 6.5000 9.4200 5.6292 5.9836 4.0000 8.3300 0.6000	*** ***	-0.24 -0.02 0.14 -0.92 0.10 0.96 -0.06 0.00 -0.09 -0.07	[-0.49; 0.01] [-0.59; 0.87 [-1.82; -0.03] [-0.34; 0.54] [-0.01; 1.92] [-0.64; 0.52] [-0.55; 0.55] [-0.26; 0.07] [-0.26; 0.11]	4.7% 1.6% 0.5% 0.4% 1.5% 0.3% 0.9% 1.0% 10.9%	2.2% 2.0% 1.6% 1.3% 2.0% 1.2% 1.8% 1.8% 1.8%
Comparison Coloraphie Coloraphie Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Kumra 2003 Clozapine Olanzapine Kumra 2003 Clozapine Olanzapine Metter 2006 Clozapine Olanzapine Metter 2008 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 55\%$, $r^2 = 0.095$, $p = 0.02$	70 12 5 18 33 21 6 56 87 40 348	-7.70 -25.00 0.30 6.60 -5.30 20.90 18.90 -8.00 -5.60 23.50	6.1000 12.7426 0.9008 4.4000 5.6292 5.5000 5.6000 8.5000 6.9000 5.9836	70 13 8 21 10 19 9 52 89 39 330	-7.60 -14.00 1.08 7.60 -0.70 19.10 17.30 -8.50 -7.10 20.10	6.0000 12.7426 0.9008 3.8000 5.6292 4.3600 3.4000 8.6000 7.4000 5.9836	* + + + + + + + + + + + + + + + + + + +	-0.02 -0.83 -0.81 -0.24 -0.80 0.35 0.34 0.06 0.21 0.56 0.06 -0.02	$ \begin{bmatrix} -0.35; \ 0.31\\ [-1.66; -0.01]\\ [-1.98; \ 0.37\\ [-0.87; \ 0.39]\\ [-1.53; -0.07]\\ [-0.27; \ 0.98\\ [-0.70; \ 1.39]\\ [-0.22; \ 0.44\\ [-0.09; \ 0.50]\\ [0.11; \ 1.01]\\ [-0.99; \ 0.22]\\ [-0.29; \ 0.25] \end{bmatrix} $	2.6% 0.4% 0.2% 0.5% 0.5% 0.3% 2.0% 3.3% 1.4%	2.1% 1.4% 1.0% 1.7% 1.6% 1.7% 2.1% 2.2% 2.0%
comparison = Clozapine_Haloperidol Buchanan 1998 Clozapine Haloperidol Kumra 1996 Clozapine Haloperidol Kane 2001 Clozapine Haloperidol Rosenheck 1997 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 20\%$, $r^2 = < 0.0001$, $p = 0.29$	38 10 23 205 40 316	27.00 46.00 9.70 20.90 23.50	11.5000 30.3000 15.5955 1.3200 5.9836	37 11 218 37 314	28.40 72.20 10.40 21.20 22.60	11.1000 24.7000 15.5955 1.3200 5.9836	++ ++ **	-0.12 -0.91 -0.04 -0.23 0.15 -0.18 -0.18	[-0.58; 0.33 [-1.82; -0.01 [-0.76; 0.67 [-0.42; -0.04 [-0.30; 0.60 [-0.34; -0.02] [-0.34; -0.02]	1.4% 0.3% 0.6% 7.9% 1.4% 11.6%	2.0% 1.3% 1.6% 2.3% 2.0% 9.1%
comparison = Haloperidol_Olanzapine Buchanan 2005 Haloperidol Olanzapine Volavka 2002 Haloperidol Olanzapine Breier 1999a Haloperidol Olanzapine Common effect model Random effects model Heterogeneity: $f^2 = 0\%$, $\tau^2 = 0$, $p = 0.56$	34 37 172 243	30.20 22.60 -2.90	11.6000 5.9836 6.4000	29 39 344 412	29.60 20.10 -4.70	12.4000 5.9836 6.6000	+ • • •	0.05 0.41 0.28 0.27 0.27	[-0.45; 0.54] [-0.04; 0.87] [0.09; 0.46] [0.11; 0.43] [0.11; 0.43]	1.2% 1.4% 8.5% 11.1%	1.9% 2.0% 2.3% 6.1%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone See 1999 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Wirshing 1999 Haloperidol Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = <0.0001$, $p = 0.44$	21 10 37 29 97	22.00 21.90 22.60 8.70	7.7900 5.8500 5.9836 3.2800	21 10 41 29 101	25.20 19.20 22.90 9.40	8.2500 4.9600 5.9836 3.2800	****	-0.39 0.48 -0.05 -0.21 -0.12 -0.12	[-1.00; 0.22] [-0.41; 1.37] [-0.49; 0.39] [-0.73; 0.31] [-0.40; 0.16] [-0.40; 0.16]	0.8% 0.4% 1.5% 1.1% 3.7%	1.7% 1.3% 2.0% 1.9% 6.9%
comparison = Chlorpromazine_Olanzapine Conley 1998 Chlorpromazine Olanzapine	39	14.00	9.5000	42	<mark>13.10</mark>	8.2000		0.10	[-0.34; 0.54]	1.5%	2.0%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	140	-2.39	4.9900	139	-3.00	4.9900		0.12	[-0.11; 0.36]	5.2%	2.2%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	102	-3.70	5.9000	213	-2.50	6.5000	-	-0.19	[-0.43; 0.05]	5.2%	2.2%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	33	-5.30	5.6292	8	-1.10	5.6292		-0.73	[-1.52; 0.06]	0.5%	1.5%
comparison = Olanzapine_Quetiapine McEvoy 2006 Olanzapine Quetiapine Sirota 2006 Olanzapine Quetiapine Common effect model Random effects model Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$	10 21 31	-0.70 -5.00	5.6292 9.6957	8 19 27	-1.10 -5.00	5.6292 9.6957		0.07 0.00 0.02 0.02	[-0.86; 1.00] [-0.62; 0.62] [-0.50; 0.54] [-0.50; 0.54]	0.3% 0.7% 1.1%	1.3% 1.7% 3.0%
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Volavka 2002 Olanzapine Risperidone Alvarez 2006 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.87$	10 39 120 16 185	-0.70 20.10 -32.59 -4.10	5.6292 5.9836 25.1952 6.3000	6 41 115 16 178	0.00 22.90 -24.97 -1.20	5.6292 5.9836 25.7371 6.0000		-0.12 -0.46 -0.30 -0.46 -0.34 -0.34	[-1.13; 0.90] [-0.91; -0.02] [-0.56; -0.04 [-1.16; 0.24] [-0.55; -0.13] [-0.55; -0.13]	0.3% 1.5% 4.4% 0.6% 6.7%	1.2% 2.0% 2.2% 1.6%
comparison = Quetiapine_Risperidone McEvoy 2006 Quetiapine Risperidone Conley 2005 Quetiapine Risperidone Common effect model Random effects model Heterogeneity: $J^2 = 0\%$, $\pi^2 = 0$, $p = 0.69$	8 12 20	-1.10 6.42	5.6292 3.0428	6 13 19	0.00 7.85	5.6292 3.0428		-0.18 -0.45 -0.36	[-1.24; 0.88] [-1.25; 0.34] [-0.99; 0.28] [-0.99; 0.28]	0.3% 0.5% 0.7%	1.1% 1.5% 2.6%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	150	-2.35	5.9400	144	-2.59	6.0000	E F	0.04	[-0.19; 0.27]	5.5%	2.2%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	13	6.31	3.0428	12	6.42	3.0428		-0.03	[-0.82; 0.75]	0.5%	1.5%
comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	13	6.31	3.0428	13	7.85	3.0428		-0.49	[-1.27; 0.29]	0.5%	1.5%

comparison = Chlorpromazine_Clozapine Hong 1997 Chlorpromazine Clozapine Honigfeld 1984b Chlorpromazine Clozapine Kane 1988 Chlorpromazine Clozapine Common effect model Random effects model Heterogeneity: I^2 = 98%, τ^2 = 1.8242, $p < 0.01$	19 63 139 221	-2.00 -0.69 0.10	4.0000 0.8200 0.8498	21 60 125 206	-9.00 -1.18 -2.40	16.0000 0.8800 0.8498	*	0.58 0.57 2.93 1.63 1.37	[-0.06; [0.21; [2.58; [1.39; [-0.18;]	1.21] 0.93] 3.28] 1.86] 2.92]	0.7% 2.2% 2.4% 5.3%	1.7% 2.1% 2.1% 5.9%
comparison = Chlorpromazine_Ziprasidone Kane 2006 Chlorpromazine Ziprasidone	154	-2.13	4.7900	152	- <mark>3.37</mark>	5.3300		0.24	[0.02;	0.47]	5.7%	2.2%
comparison = Clozapine_Zotepine Meyer-Lindenberg 1997 Clozapine Zotepine	25	35.40	26.6000	25	31.80	25.4000		0.14	[-0.42;	0.69]	0.9%	1.8%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	73	-6.10	6.5000	71	-7.60	6.7000	-	0.23	[-0.10;	0.55]	2.7%	2.1%
comparison = Chlorpromazine_Levomepromazine Lal 2006 Chlorpromazine Levomepromazine	19	23.70	5.2000	19	<mark>19.70</mark>	5.2000	*	0.75	[0.09;	1.41]	0.7%	1.7%
comparison = Fluphenazine_Haloperidol Kinon 1993b Fluphenazine Haloperidol	34	54.74	22.7531	13	52.27	17.4500		0.11	[-0.53;	0.75]	0.7%	1.7%
comparison = Amisulpride_Olanzapine Kahn 2018 Amisulpride Olanzapine	33	-3.70	6.8000	39	-1.80	5.1000		-0.32	[-0.78;	0.15]	1.3%	1.9%
comparison = Chlorpromazine_Quetiapine AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine	128	-0.04	2.7200	125	-0.79	2.6800	-	0.28	[0.03;	0.52]	4.7%	2.2%
comparison = Paliperidone_Paliperidone_LAI Actrn12618001113246 Paliperidone Paliperidone_LAI	32	3.86	1.4500	33	2.89	1.0400		0.76	[0.26;	1.27]	1.1%	1.9%
Common effect model Random effects model Heterogeneity: $l^2 = 85\%$, $\tau^2 = 0.2666$, $p < 0.01$ Test for subgroup differences (fixed effect): $\chi^2_{23} = 238.48$, df Test for subgroup differences (random effects): $\chi^2_{23} = 66.90$,	2767 = 23 (p df = 23	< 0.01) (p < 0.01	1)	2921			-3 -2 -1 0 1 2 3 Experimental Control	0.10 0.06	[0.05; [-0.10;	0.16] 0.21]	100.0% 	100.0%

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 clozapinearms 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

	Response to treatment	RR (95% CI)	Events (95% CI)
Sulpiride (n=38)	· · · · · · · · · · · · · · · · · · ·	1.42 (0.65 to 1.88)	69% (32% to 91%)
Levomepromazine (n=40)		1.22 (0.64 to 1.69)	59% (31% to 82%)
Aripiprazole (n=154)		1.14 (0.37 to 1.80)	55% (18% to 88%)
Trifluoperazine (n=20)		1.13 (0.41 to 1.77)	55% (20% to 86%)
Perphenazine (n=167)		1.10 (0.43 to 1.72)	54% (21% to 84%)
Clozapine (n=1072)	+		49%
Thioridazine (n=20)		0.99 (0.33 to 1.68)	48% (16% to 82%)
Olanzapine (n=1095)	4	0.95 (0.78 to 1.14)	46% (38% to 55%)
Ziprasidone (n=225)		0.95 (0.60 to 1.31)	46% (29% to 64%)
Quetiapine (n=412)	-	0.86 (0.57 to 1.19)	42% (28% to 58%)
Amisulpride (n=47)	•	0.84 (0.35 to 1.43)	41% (17% to 69%)
Risperidone (n=859)	-	0.77 (0.60 to 0.95)	37% (29% to 46%)
Chlorpromazine (n=713)		0.67 (0.43 to 0.95)	33% (21% to 46%)
Haloperidol (n=757)		0.65 (0.48 to 0.85)	32% (23% to 42%)
Fluphenazine (n=72)	•	0.63 (0.27 to 1.17)	31% (13% to 57%)
Sertindole (n=216)	_ _	0.55 (0.26 to 1.01)	27% (12% to 49%)
Tiotixene (n=16)		0.30 (0.08 to 0.92)	15% (4% to 45%)
Fluphenazine_LAI (n=30)	•	0.26 (0.04 to 1.15)	12% (2% to 56%)
Pipotiazine_LAI (n=30)		0.26 (0.04 to 1.15)	12% (2% to 56%)
Placebo (n=60)		0.09 (0.04 to 0.30)	5% (2% to 15%)
0.01	0.1 1 10	100	
Fav	vours reference $\leftarrow \rightarrow$ Favours compar	ator	

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						
1.52 (0.24 to 9.46)	Levomepromazi ne	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						
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_L AI	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_LA I	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)	Levomepromazi ne	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_L AI	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

Study	Experim Events	ental Total	Co Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Breier 1999 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Wahlbeck 2000 Clozapine Risperidone Chowdhury 1999 Clozapine Risperidone Schooler 2016 Clozapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$	80 28 5 15 5 24 38	138 43 14 40 11 30 53 329	77 29 3 13 6 20 31	135 43 15 41 9 30 54 327		1.04 0.90 2.22 1.29 0.42 2.00 1.88 1.21 1.21	$\begin{matrix} [0.64; & 1.68] \\ [0.37; & 2.20] \\ [0.42; & 11.83] \\ [0.52; & 3.24] \\ [0.72; & 2.58] \\ [0.62; & 6.46] \\ [0.84; & 4.20] \\ [0.88; & 1.66] \\ [0.88; & 1.67] \end{matrix}$	4.3% 1.3% 0.2% 1.1% 0.5% 0.5% 1.1% 9.1%	2.5% 1.9% 1.0% 1.8% 0.9% 1.5% 2.0% 11.6%
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Kumra 2007 Clozapine Olanzapine Meltzer 2008 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 34\%$, $\tau^2 = 0.0922$, $p = 0.17$	56 4 12 13 22 47 15	72 12 18 21 57 90 40 310	52 2 7 10 23 53 20	75 13 21 19 57 90 39 314	* + + + + + + + + + + + + + + + + + + +	1.55 2.75 4.00 1.46 0.93 0.76 0.57 1.06 1.12	[0.74; 3.25] [0.40; 18.88] [1.05; 15.21] [0.41; 5.15] [0.44; 1.97] [0.42; 1.38] [0.23; 1.40] [0.77; 1.47] [0.73; 1.70]	1.5% 0.2% 0.5% 1.9% 3.3% 1.7% 9.3%	2.1% 0.8% 1.3% 1.4% 2.1% 2.3% 1.9%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Wirshing 1999 Haloperidol Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $r^2 = 0$, $p = 0.83$	5 9 7	22 37 33 92	7 13 7	22 41 34 97	+++	0.63 0.69 1.04 0.77 0.77	[0.16; 2.41] [0.26; 1.88] [0.32; 3.37] [0.40; 1.49] [0.40; 1.49]	0.7% 1.2% 0.7% 2.6%	1.3% 1.7% 1.5% 4.5%
comparison = Chlorpromazine_Olanzapine Conley 1998 Chlorpromazine Olanzapine	0	42	3	42		0.13	[0.01; 2.65]	0.5%	0.4%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	54	145	73	143	-	0.57	[0.36; 0.91]	6.1%	2.5%
comparison = Haloperidol_Placebo Howard 1974 Haloperidol Placebo	8	17	3	16	+	3.85	[0.80; 18.62]	0.2%	1.1%
comparison = Haloperidol_Tiotixene Howard 1974 Haloperidol Tiotixene	8	17	5	16	<u> </u>	1.96	[0.47; 8.11]	0.4%	1.2%
comparison = Placebo_Tiotixene Howard 1974 Placebo Tiotixene	3	16	5	16	+ _	0.51	[0.10; 2.62]	0.5%	1.0%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	59	105	96	216	*	1.60	[1.00; 2.56]	3.6%	2.5%
comparison = Clozapine_Haloperidol Kumra 1996 Clozapine Haloperidol Kane 2001 Clozapine Haloperidol Rosenheck 1997 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 25\%$, $\tau^2 = 0.1059$, $p = 0.26$	7 21 61 15	10 37 205 40 292	7 8 51 9	11 34 218 37 300	* * *	1.33 4.27 1.39 1.87 1.67 1.85	[0.21; 8.29] [1.53; 11.89] [0.90; 2.14] [0.70; 5.01] [1.17; 2.39] [1.07; 3.20]	0.3% 0.5% 4.6% 0.8% 6.1%	0.9% 1.7% 2.5% 1.7% 6.8%
comparison = Chlorpromazine_Risperidone Mercer 1997 Chlorpromazine Risperidone	7	12	3	15		5.60	[1.01; 30.90]	0.1%	1.0%
comparison = Chlorpromazine_Placebo Schiele 1961, 06602 Chlorpromazine Placebo Dean 1958 Chlorpromazine Placebo Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.75$	13 8	20 9 29	2 2	20 9 29		16.71 28.00 19.43 19.56	[2.98; 93.89] [2.07; 379.25] [4.61; 81.95] [4.64; 82.47]	0.1% 0.0% 0.1%	1.0% 0.5% 1.5%
comparison = Chlorpromazine_Thioridazine Schiele 1961, 06602 Chlorpromazine Thioridazine	13	20	15	20	-	0.62	[0.16; 2.43]	0.7%	1.3%
comparison = Chlorpromazine_Trifluoperazine Schiele 1961, 06602 Chlorpromazine Trifluoperazine	13	20	16	20	-+	0.46	[0.11; 1.94]	0.7%	1.2%
comparison = Placebo_Thioridazine Schiele 1961, 06602 Placebo Thioridazine	2	20	15	20		0.04	[0.01; 0.22]	1.8%	0.9%
comparison = Placebo_Trifluoperazine Schiele 1961, 06602 Placebo Trifluoperazine	2	20	16	20		0.03	[0.00; 0.17]	1.9%	0.9%
comparison = Thioridazine_Trifluoperazine Schiele 1961, 06602 Thioridazine Trifluoperazine	15	20	16	20	_ + _	0.75	[0.17; 3.33]	0.5%	1.2%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	40	154	36	146	ł	1.07	[0.64; 1.81]	3.6%	2.4%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	2	13	3	12		0.55	[0.07; 4.01]	0.3%	0.8%

comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	2	13	3	13	<u> </u>	0.61	[0.08;	4.41]	0.3%	0.8%
comparison = Quetiapine_Risperidone Conley 2005 Quetiapine Risperidone Suzuki 2007 Quetiapine Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.45$	3 5	12 10 22	3 3	13 12 25		1.11 3.00 1.84 1.84	[0.18; [0.50; [0.52; [0.51;	6.97] 18.17] 6.53] 6.67]	0.3% 0.2% 0.5%	0.9% 0.9% 1.8%
comparison = Chlorpromazine_Clozapine Hong 1997 Chlorpromazine Clozapine Kane 1988 Chlorpromazine Clozapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.84$	0 5	19 142 161	6 38	21 126 147	\$ \$ \$	0.06 0.08 0.08 0.08	[0.00; [0.03; [0.03; [0.03;	1.17] 0.22] 0.20] 0.21]	0.8% 5.1% 5.9%	0.4% 1.8% 2.2%
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 Breier 1999a Haloperidol Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 40\%$, $\tau^2 = 0.0966$, $p = 0.20$	9 60	37 174 211	20 163	39 352 391	* * *	0.31 0.61 0.56 0.50	[0.11; [0.42; [0.39; [0.27;	0.81] 0.89] 0.79] 0.92]	1.9% 9.3% 11.2% 	1.7% 2.6% 4.3%
comparison = Olanzapine_Risperidone Volavka 2002 Olanzapine Risperidone Alvarez 2006 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Suzuki 2007 Olanzapine Risperidone Kinon 2009 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 43\%$, $\tau^2 = 0.1217$, $p = 0.14$	20 83 5 6 94	39 124 16 15 186 380	13 56 4 3 94	41 123 16 12 192 384	+ + + *	2.27 2.42 1.36 2.00 1.07 1.53 1.68	[0.91; [1.45; [0.29; [0.38; [0.71; [1.15; [1.04;	5.63] 4.06] 6.42] 10.58] 1.59] 2.05] 2.70]	0.8% 2.4% 0.4% 0.3% 6.0% 9.9%	1.8% 2.4% 1.1% 1.0% 2.6% 8.9%
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 Kinon 1993b Fluphenazine Haloperidol Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$	8 3	25 34 59	8 1	25 13 38		1.00 1.16 1.03 1.03	[0.30; [0.11; [0.36; [0.36;	3.28] 12.29] 2.97] 2.98]	0.7% 0.2% 0.9%	1.5% 0.6% 2.1%
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 AstraZeneca 5077IL/0054 Chlorpromazine Quetiapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.91$	9 22	130 119 249	10 25	130 117 247	+00	0.89 0.83 0.85 0.85	[0.35; [0.44; [0.50; [0.50;	2.27] 1.58] 1.45] 1.45]	1.2% 2.7% 3.9%	1.8% 2.2% 4.0%
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	<u> </u>	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	<u> </u>	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 Random effects model Heterogeneity: $l^2 = 62\%$, $\tau^2 = 0.4082$, $p < 0.01$ Test for subgroup differences (fixed effect): $\chi^2_{39} = 146.25$, df = 3 Test for subgroup differences (random effects): $\chi^2_{99} = 132.96$ d	9 (p < 1 f = 39 (J	3358 0.01) p < 0.01)	:	3590	0.01 0.1 1 10 100 Experimental Control	0.95 0.96	[0.86; [0.78;	1.05] 1.19]	100.0% 	 100.0%

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

	Discontinuat	ion due to any reason	OR (95% CI)
Sulpiride (n=38)	•		0.47 (0.02 to 12.65)
Levomepromazine (n=19)			0.49 (0.07 to 3.27)
Olanzapine (n=1216)		+	0.98 (0.74 to 1.31)
Clozapine (n=1272)		•	Reference
Ziprasidone (n=225)			1.09 (0.57 to 2.06)
Risperidone (n=870)			1.13 (0.82 to 1.56)
Sertindole (n=216)			1.48 (0.67 to 3.27)
Chlorpromazine (n=794)		—	1.48 (0.98 to 2.22)
Quetiapine (n=446)		—	1.50 (0.93 to 2.42)
Zotepine (n=25)	-		1.71 (0.47 to 6.26)
Haloperidol (n=832)		- •-	1.79 (1.28 to 2.52)
Fluphenazine_LAI (n=30)		•	1.89 (0.12 to 29.33)
Pipotiazine_LAI (n=30)		•	1.89 (0.12 to 29.33)
Amisulpride (n=47)			2.32 (0.71 to 7.56)
Fluphenazine (n=38)		•	3.03 (1.02 to 9.01)
Placebo (n=74)		•	5.27 (0.65 to 43.05)
Thioridazine (n=20)	-	•	6.43 (0.43 to 96.81)
Trifluoperazine (n=36)		•	8.82 (0.84 to 92.62)
0.01	0.1	1 10	100
	Favours comparato	$r \leftarrow \rightarrow$ Favours reference	

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)	Levomeprom azine	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)	Chlorpromaz ine	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)	Trifluoperazi ne

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									
0.97 (0.02 to 5.43)	Levomeproma zine	NA	NA	NA	NA	NA	0.44 (0.08 to 1.5)	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						
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									
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										
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)	Chlorpromazi ne	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							
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_L AI	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)	Trifluoperazin e

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

Study	Experimer Events To	ntal Stal E	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
comparison = Haloperidol_Olanzapine Altamura 2002 Haloperidol Olanzapine Buchanan 2005 Haloperidol Olanzapine Smith 2001 Haloperidol Olanzapine Volavka 2002 Haloperidol Olanzapine Breier 1999a Haloperidol Olanzapine Common effect model Random effects model Helerogeneity: $l^2 = 15\%$, $r^2 = < 0.0001$, $p = 0.32$	7 3 4 16 90	15 34 18 37 174 278	0 3 13 124	13 29 20 39 352 453		23.82 0.84 5.43 1.52 1.97 2.01 1.94	[1.20; 473.07] [0.16; 4.51] [0.55; 54.01] [0.60; 3.86] [1.36; 2.85] [1.45; 2.79] [1.40; 2.70]	0.0% 0.4% 0.1% 1.0% 5.4% 7.0%	0.2% 0.7% 0.4% 1.7% 3.7% 6.8%
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Daniel 1996 Clozapine Risperidone McEvoy 2006 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Wahlbeck 2000 Clozapine Risperidone Chowdhury 1999 Clozapine Risperidone Schooler 2016 Clozapine Risperidone Common effect model Random effects model Heterogenetty: $l^2 = 25\%$, $r^2 = <0.0001$, $\rho = 0.23$	38 9 0 25 18 6 6 25 25	138 43 10 49 40 11 30 53 374	34 9 32 19 1 9 31	135 43 10 16 41 9 30 54 338	+ + + + + + + + + + + + + + + + +	1.13 1.00 0.10 0.35 9.60 0.69 0.66 0.88 0.88	[0.66; 1.94] [0.35; 2.83] [0.00; 2.28] [0.10; 1.23] [0.40; 2.27] [0.88; 105.17] [0.21; 2.30] [0.31; 1.42] [0.64; 1.22] [0.63; 1.23]	3.4% 1.0% 0.5% 1.2% 1.4% 0.1% 0.9% 2.2% 10.6%	3.0% 1.5% 0.2% 1.1% 1.9% 0.4% 1.2% 2.2%
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Conley 2003 Clozapine Olanzapine Kurnra 2007 Clozapine Olanzapine McEvoy 2006 Clozapine Olanzapine Moresco 2004 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Heterogenetly: $l^2 = 5\%$, $\tau^2 = < 0.0001$, $p = 0.40$	32 0 4 25 11 6 35 37 18	72 12 5 18 49 21 12 57 90 40 376	30 1 3 7 12 5 2 36 36 13	75 13 8 21 19 19 11 57 90 39 352		1.20 0.33 0.14 0.57 0.61 3.08 4.50 0.93 1.05 1.64 1.10 1.11	[0.62; 2.31] [0.01; 8.99] [0.01; 3.47] [0.14; 2.40] [0.20; 1.80] [0.81; 11.68] [0.67; 30.23] [0.44; 1.98] [0.58; 1.90] [0.66; 4.07] [0.81; 1.49] [0.81; 1.51]	2.2% 0.2% 0.7% 1.2% 0.3% 0.1% 1.9% 2.9% 1.0%	2.5% 0.2% 0.9% 1.4% 1.0% 2.2% 2.8% 1.8%
comparison = Clozapine_Haloperidol Buchanan 1998 Clozapine Haloperidol Kumra 1996 Clozapine Haloperidol Kane 2001 Clozapine Haloperidol Rosenheck 1997 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effects model Random effects model Hoterogenetly: l^2 = 79%, τ^2 = 0.9824, $p < 0.01$	8 3 13 88 18	38 10 37 205 40 330	3 1 22 157 16	37 11 34 218 37 337	+++++++++++++++++++++++++++++++++++++++	3.02 4.29 0.30 0.29 1.07 0.44 0.80	[0.73; 12.44] [0.37; 50.20] [0.11; 0.78] [0.19; 0.44] [0.44; 2.64] [0.32; 0.60] [0.29; 2.22]	0.3% 0.1% 2.0% 11.9% 1.3% 15.6%	0.9% 0.4% 1.6% 3.6% 1.8% 8.3%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Wirshing 1999 Haloperidol Risperidone Common effect model Random effects model Heterogeneity. $l^2 = 14\%$, $r^2 = < 0.0001$, $p = 0.31$	6 16 5	22 37 33 92	2 19 6	22 41 34 97	++00	3.75 0.88 0.83 1.12 1.08	[0.66; 21.15] [0.36; 2.16] [0.23; 3.05] [0.58; 2.16] [0.55; 2.14]	0.2% 1.4% 0.7% 2.3%	0.7% 1.8% 1.1%
comparison = Chlorpromazine_Olanzapine Conley 1998 Chlorpromazine Olanzapine	13	42	12	42	+	1.12	[0.44; 2.86]	1.1%	1.7%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	28	145	32	143	+	0.83	[0.47; 1.47]	3.6%	2.9%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	30	105	74	216	÷	0.77	[0.46; 1.28]	4.7%	3.1%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	25	49	13	15		0.16	[0.03; 0.79]	1.3%	0.8%
comparison = Olanzapine_Quetiapine McEvoy 2006 Olanzapine Quetiapine Sirota 2006 Olanzapine Quetiapine Suzuki 2007 Olanzapine Quetiapine Common effect model Random effects model Heterogeneity: $l^2 = 22\%$, $\tau^2 = 0.3581$, $p = 0.28$	12 3 3	19 21 15 55	13 2 1	15 19 10 44		0.26 1.42 2.25 0.75 0.81	[0.05; 1.53] [0.21; 9.55] [0.20; 25.37] [0.27; 2.14] [0.21; 3.08]	0.7% 0.2% 0.1% 1.1%	0.7% 0.6% 0.4% 1.6%
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Volavka 2002 Olanzapine Risperidone Alvarez 2006 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Suzuki 2007 Olanzapine Risperidone Kinon 2009 Olanzapine Risperidone Common effect model Random effects model Heterogenetty: $P^2 = 0\%, \tau^2 = < 0.0001, p = 0.54$	12 13 33 3 3 60	19 39 124 16 15 186 399	12 19 39 3 0 58	16 41 123 16 12 192 400	+++	0.57 0.58 0.78 1.00 7.00 1.10 0.92 0.91	[0.13; 2.48] [0.23; 1.43] [0.45; 1.35] [0.17; 5.90] [0.33; 150.06] [0.71; 1.70] [0.68; 1.24] [0.67; 1.23]	0.7% 1.7% 3.9% 0.3% 0.1% 5.3% 12.0%	0.9% 1.8% 3.0% 0.6% 0.2% 3.4%

					1					
comparison = Quetlapine_Risperidone	122	012		2023	83	100000				
McEvoy 2006 Quetiapine Risperidone	13	15	12	16		2.17	[0.33;	14.06]	0.2%	0.6%
Suzuki 2007 Quetiapine Risperidone	1	10	ò	12	· · · ·	3.95	[0.14;	108.09]	0.1%	0.2%
Common effect model		37		41		2.04	[0.65]	6.41]	0.6%	4 692
Heterogeneity: $t^2 = 0\%$, $\tau^2 = 0$, $p = 0.89$					T	2.01	[0.65	0.40]	175	1.57/0
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				221		12722			100000	
comparison = Placabo, Thioridazine	0	20	1	20		0.32	[0.01	; 8.26]	0.2%	0.2%
Schiele 1961, 06602 Placebo Thioridazine	1	20	1	20	1	1.00	[0.06;	17.18]	0.1%	0.3%
comparison = Placebo_Trifluoperazine Schlele 1961_06602_Placebo_Trifluoperazine	1	20	1	20		1.00	10.06	17 181	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 Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.61$					~	0,53	[0.12;	2.32]		0.9%
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%
Random effects model		17		20		2.97	[0.25]	35.51]	0.170	0.4%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$										
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					24-1020-00-00					
Hong 1997 Chlorpromazine Clozapine Honiafeld 1984b Chlorpromazine Clozapine	2	19	2	21		1.12	[0.14	8.82]	0.2%	0.5%
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 Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $p = 0.72$.					P	1.33	[0,83]	2.13]		5.3%
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 <mark>]</mark>	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	-	10	2	10		2.04	10 54	40 441	0.2%	0.894
comparison = Fluphenazine Haloperidol	5	19	2	19		3.04	10.51,	10.11]	0.276	0.0%
Hall 1968 Fluphenazine Haloperidol	5	25	5	25	2	1.00	[0.25	4.00]	0.5%	1.0%
comparison = Chlorpromazine_Sulpiride Toru 1972 Chlorpromazine Sulpiride	1	37	0	38	n <u> n g</u>	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	t	1.00	[0.59	1.69]	3.8%	3.1%
Common effect model	40	249	51	247	5	1.40	10.80	1.721	6.7%	2.9%
Random effects model Heterogeneity: $t^2 = 0\%$, $\tau^2 = 0$, $p = 0.38$					\$	1.17	[0.80;	1.72]	_	6.0%
comparison = Haloperidol_Placebo	3	ß	я	F	·····	0.25	[0.02	9,771	0.3%	0.304
comparison = Palineridone Palineridone Al	2	č		5		0.20	[0.02	0.77]	0.076	0.5%
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%

comparison = Pipotiazine_LAI_Placebo Schlosberg 1978 Pipotiazine_LAI Placebo	21	30	13	15		0.36	[0.07;	1.93]	0.7%	0.7%
comparison = Clopenthixol_LAI_Perphenazine_LAI Ahlfors 1980 Clopenthixol_LAI Perphenazine_LAI	30	87	37	85		0.68	[0.37;	1.26]	3.4%	2.7%
Common effect model 3738 Random effects model					0.01 0.1 1 10 100 Experimental Control	0.99 1.01	[0.89; [0.86;	1.10] 1.17]	100.0%	100.0%

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

	Discontinuation due to inefficacy	RR (95% CI)	Events (95% CI)
Clozapine (n=1146)	•		6%
Fluphenazine_LAI (n=30)		1.15 (0.10 to 8.09)	7% (1% to 51%)
Ziprasidone (n=225)		1.56 (0.32 to 5.80)	10% (2% to 37%)
Pipotiazine_LAI (n=30)		1.71 (0.15 to 9.75)	11% (1% to 62%)
Sulpiride (n=38)	•	1.85 (0.03 to 13.98)	12% (0% to 88%)
Amisulpride (n=47)		1.86 (0.13 to 10.97)	12% (1% to 69%)
Chlorpromazine (n=384)		1.89 (0.86 to 3.85)	12% (5% to 24%)
Olanzapine (n=1077)	-	1.89 (1.36 to 2.60)	12% (9% to 16%)
Risperidone (n=735)	-	2.30 (1.49 to 3.46)	15% (9% to 22%)
Sertindole (n=216)		2.95 (1.41 to 5.52)	19% (9% to 35%)
Quetiapine (n=189)		3.65 (2.00 to 6.04)	23% (13% to 38%)
Haloperidol (n=832)	+	3.74 (2.77 to 4.91)	24% (18% to 31%)
Zotepine (n=25)		4.24 (0.26 to 14.09)	27% (2% to 89%)
Trifluoperazine (n=36)		5.00 (0.46 to 13.90)	32% (3% to 88%)
Placebo (n=74)		6.67 (1.28 to 13.59)	42% (8% to 86%)
Thioridazine (n=20)	÷	6.80 (0.74 to 14.57)	43% (5% to 92%)
Fluphenazine (n=38)		7.18 (3.12 to 11.66)	45% (20% to 74%)
0.01	0.1 1 10 100)	
Favo	purs comparator $\leftarrow \rightarrow$ Favours reference		

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						
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						
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)	Chlorpromaz ine	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)	Trifluoperazi ne	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.

eague table for the outcome: Discontinuation due to inefficacy	/ (F	RR))
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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	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									
0.59 (0.04 to 4.32)	0.67 (0.24 to 1.73)	0.91 (0.04 to 6.36)	Pipotiazine_ LAI	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									
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								
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)	Chlorpromaz ine	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						
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)	Trifluoperazi ne	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

Study	Experimer Events To	ntal otal	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
comparison = Haloperidol_Olanzapine Altamura 2002 Haloperidol Olanzapine Buchanan 2005 Haloperidol Olanzapine Smith 2001 Haloperidol Olanzapine Volavka 2002 Haloperidol Olanzapine Breier 1999a Haloperidol Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $r^2 = 0$, $p = 0.69$	4 3 4 6 62	15 34 18 37 174 278	0 2 1 4 82	13 29 20 39 352 453	+ + + +	- 10.57 1.31 5.43 1.69 1.82 1.93 1.89	[0.51; 217.74] [0.20; 8.41] [0.55; 54.01] [0.44; 6.56] [1.23; 2.71] [1.35; 2.78] [1.31; 2.72]	0.1% 0.5% 0.2% 9.4% 11.1%	0.7% 1.4% 1.1% 2.0% 3.5% 8.8%
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Daniel 1996 Clozapine Risperidone McEvoy 2006 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Wahlbeck 2000 Clozapine Risperidone Chowdhury 1999 Clozapine Risperidone Schooler 2016 Clozapine Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.60$	1 2 5 2 1 0 8	138 43 10 49 40 11 30 53 374	9 4 0 6 2 0 3 21	135 43 10 16 41 9 30 54 338	↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	0.10 0.48 1.00 0.19 1.03 2.71 0.13 0.28 0.30 0.31	[0.01; 0.82] [0.08; 2.75] [0.02; 55.27] [0.14; 7.66] [0.10; 74.98] [0.01; 2.61] [0.11; 0.71] [0.17; 0.53]	2.4% 1.0% 0.1% 2.2% 0.5% 0.1% 0.9% 4.8% 12.1%	1.2% 1.5% 0.4% 2.0% 1.3% 0.6% 0.7% 2.7%
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Conley 2003 Clozapine Olanzapine Kumra 2007 Clozapine Olanzapine McEvoy 2006 Clozapine Olanzapine Metzer 2008 Clozapine Olanzapine Moresco 2004 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Random effect model Heterogeneity: $I^2 = 27\%$, $t^2 = 0.3482$, $p = 0.19$	3 0 1 5 3 1 15 9 2	72 12 5 18 49 21 12 57 90 40 376	4 1 6 6 3 0 7 12 4	75 13 8 21 19 19 11 57 90 39 352	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	0.77 0.33 0.24 0.15 0.25 0.89 3.00 2.55 0.72 0.46 0.77 0.68	$\begin{array}{llllllllllllllllllllllllllllllllllll$	1.0% 0.4% 0.5% 1.4% 2.1% 0.7% 0.1% 1.4% 2.9% 1.0%	1.8% 0.6% 0.6% 2.1% 1.6% 0.6% 2.6% 2.7% 1.5%
comparison = Clozapine_Haloperidol Buchanan 1998 Clozapine Haloperidol Kumra 1996 Clozapine Haloperidol Kane 2001 Clozapine Haloperidol Rosenheck 1997 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 50\%$, $t^2 = 0.6217$, $p = 0.09$	3 0 4 13 2	38 10 37 205 40 330	2 0 17 80 6	37 11 34 218 37 337		1.50 1.10 0.12 0.12 0.27 0.16 0.24	[0.24; 9.54] [0.02; 60.29] [0.04; 0.42] [0.06; 0.22] [0.05; 1.44] [0.10; 0.26] [0.09; 0.63]	0.5% 0.1% 4.3% 19.6% 1.6% 26.1%	1.5% 0.4% 2.2% 3.2% 1.6%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Wirshing 1999 Haloperidol Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.65$	5 6 5	22 37 33 92	1 2 3	22 41 34 97		6.18 3.77 1.85 3.16 3.05	[0.66; 58.03] [0.71; 20.02] [0.40; 8.44] [1.18; 8.46] [1.12; 8.32]	0.2% 0.4% 0.7% 1.3%	1.1% 1.6% 1.8% 4.6%
comparison = Chlorpromazine_Olanzapine Conley 1998 Chlorpromazine Olanzapine	2	42	5	42		0.37	[0.07; 2.02]	1.3%	1.6%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	8	145	11	143		0.70	[0.27; 1.80]	2.8%	2.7%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	14	105	37	216		0.74	[0.38; 1.45]	5.7%	3.1%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	5	49	6	15		0.17	[0.04; 0.68]	2.2%	2.0%
comparison = Olanzapine_Quetiapine McEvoy 2006 Olanzapine Quetiapine Sirota 2006 Olanzapine Quetiapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $r^2 = 0$, $p = 0.87$	6 1	19 21 40	6 1	15 19 34		0.69 0.90 0.73 0.73	[0.17; 2.85] [0.05; 15.47] [0.21; 2.59] [0.21; 2.59]	1.2% 0.3% 1.5%	1.9% 0.8% 2.7%
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Volavka 2002 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Kinon 2009 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $r^2 = 0$, $p = 0.74$	6 4 1 4	19 39 16 186 260	6 2 0 4	16 41 16 192 265		0.77 2.23 3.19 1.03 1.21 1.19	[0.19; 3.12] [0.38; 12.92] [0.12; 84.43] [0.25; 4.19] [0.54; 2.75] [0.52; 2.74]	1.2% 0.5% 0.1% 1.0% 2.8%	2.0% 1.5% 0.6% 2.0% 6.1%

comparison = Quetiapine_Risperidone MEEvoy 2006 Quetiapine Risperidone Conley 2005 Quetiapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $v^2 = 0$, $p = 1.00$	6 3	15 12 27	6 3	16 13 29		1.11 1.11 1.11 1.11	[0.26] [0.18] [0.36] [0.36]	4.72] 6.97] 3.46] 3.46]	0.9% 0.6% 1.5%	1.9% 1.5%
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	· <u> </u>	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 Marjerrison 1964 Placebo Trifluoperazine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $r^2 = 0$, $p = 0.56$	1 2	20 34 54	0 1	20 16 36		3.15 0.94 1.53 1.46	[0.12; [0.08; [0.22; [0.20;	82.16] 11.17] 10.66] 10.51]	0.1% 0.3% 0.5%	0.6% 1.0% 1.6%
comparison = Thioridazine_Trifluoperazine Schiele 1961, 06602 Thioridazine Trifluoperazine	1	20	0	20	s <u></u>	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 McCreadie 1977 Chlorpromazine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.98$	0	14 10 24	0 0	13 10 23		0.93 1.00 0.96 0.96	[0.02; [0.02; [0.06; [0.06;	50.30] 55.27] 16.33] 16.33]	0.1% 0.1% 0.3% 	0.4% 0.4% 0.9%
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 Honigfeld 1984b Chlorpromazine Clozapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.67$	0 10	19 76 95	0 4	21 75 96		1.10 2.69 2.50 2.49	[0.02; [0.80] [0.79; [0.79;	58.28] 8.99] 7.88] 7.91]	0.1% 0.9% 1.1%	0.5% 2.2% 2.7%
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		<mark>0.18</mark>	[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%
Ahlfors 1980 Clopenthixol_LAI Perphenazine_LAI	13	87	13	85		0.97	[0.42	2.24]	3.0%	2.8%
Common effect model Random effects model Heterogeneity: $l^2 = 52\%$, $\tau^2 = 0.5612$, $p < 0.01$ Test for subgroup differences (fixed effect); $\chi^2_{35} = 120.27$, df = 3 Test for subgroup differences (random effects); $\chi^2_{35} = 77.80$, df	35 (p < = 35 (p	3164 0.01) < 0.01)		3307	0.01 0.1 1 10 100 Experimental Control	0.73	[0.63; [0.57;	0.86] 1.01]	100.0% 	 100.0%

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

	Discor	ntinuation due to adverse events	RR (95% CI)	Events (95% CI)
Fluphenazine (n=38)			0.51 (0.07 to 2.95)	6% (1% to 35%)
Olanzapine (n=849)		- • -	0.67 (0.43 to 1.00)	8% (5% to 12%)
Risperidone (n=804)			0.73 (0.47 to 1.11)	9% (6% to 13%)
Haloperidol (n=675)			0.79 (0.52 to 1.19)	9% (6% to 14%)
Clozapine (n=1093)		•		12%
Sertindole (n=216)			1.17 (0.42 to 2.82)	14% (5% to 33%)
Zotepine (n=25)			1.22 (0.36 to 3.34)	14% (4% to 39%)
Quetiapine (n=319)			1.31 (0.73 to 2.25)	15% (9% to 26%)
Ziprasidone (n=225)			1.33 (0.74 to 2.27)	16% (9% to 27%)
Placebo (n=90)			1.70 (0.24 to 5.76)	20% (3% to 68%)
Thioridazine (n=20)			2.19 (0.08 to 7.88)	26% (1% to 92%)
Sulpiride (n=38)			2.31 (0.06 to 8.12)	27% (1% to 95%)
Chlorpromazine (n=533)			2.35 (1.49 to 3.46)	28% (18% to 41%)
Levomepromazine (n=19)			2.35 (0.18 to 7.45)	28% (2% to 87%)
Trifluoperazine (n=36)			2.58 (0.22 to 7.45)	30% (3% to 87%)
Tiotixene (n=16)			2.78 (0.32 to 7.32)	33% (4% to 86%)
Amisulpride (n=47)			3.04 (0.49 to 7.11)	36% (6% to 83%)
Pipotiazine_LAI (n=30)			3.50 (0.38 to 7.78)	41% (4% to 91%)
Fluphenazine_LAI (n=30)			4.43 (0.58 to 8.02)	52% (7% to 94%)
	0.01 0.1	1 10	100	
	Favours con	mparator $\leftarrow \rightarrow$ Favours reference		

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)	Chlorpromazi ne	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)	Levomeproma zine	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)	Trifluoperazin e	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_L AI	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								
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										
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									
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)	Chlorpromazi ne	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)	Levomeproma zine	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)	Trifluoperazin e	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_L AI	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

Study	Experimenta Events Tota	l Co l Events	ontrol Total	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
comparison = Haloperidol_Olanzapine Altamura 2002 Haloperidol Olanzapine Buchanan 2005 Haloperidol Olanzapine Smith 2001 Haloperidol Olanzapine Volavka 2002 Haloperidol Olanzapine Common effect model Random effects model Heterogeneitly: $t^2 = 0\%$, $\tau^2 = 0$, $p = 0.97$	1 1 0 3 0 1 0 3 10	5 0 4 0 8 0 7 0 4	13 29 20 39 101		2.79 0.86 1.11 1.05 1.44 1.40	[0.10; 74.63] [0.02; 44.44] [0.02; 58.71] [0.02; 54.45] [0.23; 8.93] [0.21; 9.11]	0.2% 0.3% 0.2% 0.2%	0.4% 0.3% 0.3% 0.3% 1.4%
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Daniel 1996 Clozapine Risperidone McEvoy 2006 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Wahlbeck 2000 Clozapine Risperidone Chowdhury 1999 Clozapine Risperidone Common effect model Random effects model Heterogenetty: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.81$	16 13 1 4 0 1 5 4 5 4 2 1 4 3 32	B 12 3 1 0 2 9 0 0 2 1 1 0 3 1	135 43 10 16 41 9 30 284		1.34 1.00 0.16 4.08 2.79 1.78 1.38 1.43 1.43	[0.61; 2.96] [0.06; 16.52] [0.01; 3.85] [0.21; 77.90] [0.51; 15.28] [0.13; 23.52] [0.28; 6.80] [0.80; 2.53] [0.79; 2.60]	5.2% 0.5% 1.2% 0.3% 0.4% 1.3% 9.7%	5.1% 0.6% 0.5% 0.5% 0.7% 1.7% 10.6%
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Conley 2003 Clozapine Olanzapine Kurna 2007 Clozapine Olanzapine McEvoy 2006 Clozapine Olanzapine Meltzer 2008 Clozapine Olanzapine Moresco 2004 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0.0591$, $p = 0.63$	7 7 0 1 2 1 5 4 0 2 5 1 6 5 13 9 5 4 37	2 7 2 0 5 1 8 1 9 1 1 0 2 1 7 6 0 4 0 0 6	75 13 8 21 19 19 11 57 90 39 352		1.05 1.08 0.45 2.50 2.05 0.91 7.14 1.00 3.63 - 12.24 1.99 1.83	[0.35; 3.15] [0.02; 58.65] [0.22; 13.41] [0.21; 30.12] [0.22; 18.76] [0.30; 3.31] [1.14; 11.60] [0.65; 229.29] [1.17; 3.37] [1.01; 3.34]	3.0% 0.2% 0.5% 0.4% 0.6% 0.2% 2.6% 1.7% 0.2% 9.8%	3.1% 0.3% 0.4% 0.9% 0.3% 0.8% 2.8% 2.9% 0.5%
comparison = Clozapine_Haloperidol Buchanan 1998 Clozapine Haloperidol Kumra 1996 Clozapine Haloperidol Kane 2001 Clozapine Haloperidol Rosenheck 1997 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effect model Random effects model Heterogeneity: $l^2 = 21\%$, $\tau^2 = 0.1801$, $p = 0.28$	2 3 3 1 2 3 26 20 5 4 33	B 0 0 1 7 3 5 27 0 0	37 11 34 218 37 337		5.14 4.29 0.59 1.03 — 11.62 1.30 1.41	[0.24; 110.70] [0.37; 50.20] [0.09; 3.77] [0.58; 1.83] [0.62; 217.87] [0.79; 2.14] [0.64; 3.13]	0.2% 0.3% 1.4% 11.1% 0.2% 13.3%	0.5% 0.8% 1.3% 7.3% 0.5% 10.4%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Wirshing 1999 Haloperidol Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 10\%$, $\pi^2 = 0.1662$, $p = 0.33$	1 2 0 3 0 3 9	2 0 7 2 3 3 2	22 41 34 97		3.14 0.21 0.13 0.39 0.41	[0.12; 81.35] [0.01; 4.53] [0.01; 2.71] [0.09; 1.71] [0.06; 2.60]	0.2% 1.1% 1.6% 3.0%	0.4% 0.5% 0.5%
comparison = Chlorpromazine_Olanzapine Conley 1998 Chlorpromazine Olanzapine	64	2 1	42		6.83	[0.79; 59.48]	0.4%	1.0%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	5 14	5 12	143		0.39	[0.13; 1.14]	5.6%	3.3%
Howard 1974 Haloperidol Placebo Browne 1988 Haloperidol Placebo Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.69$	0 1 0 2	7 1 6 0 3	16 5 21		0.30 0.85 0.43 0.45	[0.01; 7.79] [0.01; 50.10] [0.04; 5.17] [0.03; 5.73]	0.7% 0.2% 1.0%	0.4% 0.3% 0.7%
comparison = Haloperidol_Tiotixene Howard 1974 Haloperidol Tiotixene	0 1	7 2	16		0.17	[0.01; 3.73]	1.2%	<mark>0.5%</mark>
comparison = Placebo_Tiotixene Howard 1974 Placebo Tiotixene	1 1	6 2	16		0.47	[0.04; 5.73]	0.9%	0.7%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	5 10	5 17	216		0.59	[0.21; 1.63]	5.1%	3.5%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	5 4	93	15		0.45	[0.09; 2.18]	2.0%	1.7%
comparison = Olanzapine Quetiapine McEvoy 2006 Olanzapine Quetiapine Sirota 2006 Olanzapine Quetiapine Common effect model Random effects model Heterogeneity: $t^2 = 35\%$, $t^2 = 1.1386$, $p = 0.22$	1 1 1 2 4	93 100	15 19 34		0.22 2.85 0.57 0.62	[0.02; 2.40] [0.11; 74.34] [0.11; 3.02] [0.05; 7.17]	1.5% 0.2% 1.8% 	0.8% 0.4% 1.3%

					1				
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Volavka 2002 Olanzapine Risperidone Alvarez 2006 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Kinon 2009 Olanzapine Risperidone Common effect model	1 6 0 9	19 39 124 16 186 384	0 2 4 0 10	16 41 123 16 192 388		2.68 0.20 1.51 1.00 0.93 1.01	[0.10; 70.31] [0.01; 4.30] [0.42; 5.50] [0.02; 53.46] [0.37; 2.33] [0.51; 1.99]	0.2% 1.2% 1.8% 0.2% 4.5% 8.0%	0.4% 0.5% 2.4% 0.3% 4.1%
Random effects model Heterogeneity: $t^2 = 0\%$, $\tau^2 = 0$, $p = 0.77$						1.04	[0.52; 2.10]		7.8%
comparison = Quetiapine_Risperidone McEvoy 2006 Quetiapine Risperidone Conley 2005 Quetiapine Risperidone Common effect model Random effects model Heterogenetty: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.87$	3 2	15 12 27	0 0	16 13 29		9.24 6.43 7.82 7.75	[0.44; 195.69] [0.28; 148.77] [0.88; 69.47] [0.87; 69.19]	0.2% 0.2% 0.4%	0.5% 0.5% 1.0%
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%
Random effects model Heterogeneity: $l^2 = 0\%, \epsilon^2 = 0, p = 0.75$		54		50		0.59	[0.06; 5.97]		0.9%
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	0	14	0	13		0.93	10 02: 50 301	0.2%	0.3%
McCreadie 1977 Chlorpromazine Haloperidol	1	10	0	10	<u> </u>	3.32	[0.12; 91.60]	0.2%	0.4%
Common effects model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.63$		24		23		2.04	[0.17; 23.87] [0.15; 25.29]	0.5%	0.7%
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%	<mark>0.3%</mark>
comparison = Chlorpromazine_Clozapine Hong 1997 Chlorpromazine Clozapine Honigfeld 1984b Chlorpromazine Clozapine Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.32$	2 18	19 76 95	2 6	21 75 96	+ • •	1.12 3.57 2.91 2.88	[0.14; 8.82] [1.33; 9.58] [1.21; 6.97] [1.18; 7.01]	0.8% 2.2% 3.1%	1.1% 3.7% 4.8%
comparison = Chlorpromazine_Ziprasidone Kane 2006 Chlorpromazine Ziprasidone	8	154	6	152		<mark>1.33</mark>	[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. <mark>4</mark> 1; 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%	<mark>0.6%</mark>
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 = Chiorpromazine_Quetiapine AstraZeneca 5077IL/0031 Chiorpromazine Quetiapine	21	130	7	<mark>1</mark> 30	-	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 = Fupnenazine_LAI_Pipotiazine_LAI Schlosberg 1978 Fluphenazine_LAI Pipotiazine_LAI	12	30	9	30		1.56	[0.53; 4.53]	2.6%	3.3%

comparison = Fluphenazine_LAI_Placebo Schlosberg 1978 Fluphenazine_LAI Placebo	12	30	2	15		1			4.33	[0.83;	22.75]	0.8%	1.6%
comparison = Pipotiazine_LAI_Placebo Schlosberg 1978 Pipotiazine_LAI Placebo	9 30		2	15		-	<u> </u> .	-	2.79	[0.52;	14.96]	0.9%	1.5%
comparison = Clopenthixol_LAI_Perphenazine_LAI Ahlfors 1980 Clopenthixol_LAI Perphenazine_LAI	5	87	9	85					0.51	[0.17;	1.60]	4.2%	3.0%
$\begin{array}{c c} \mbox{Common effect model} & 3260 \\ \hline \mbox{Random effects model} \\ \mbox{Heterogeneity: } l^2 = 0\%, \tau^2 = 0.0886, p = 0.75 \\ \hline \mbox{Test for subgroup differences (fixed effect): } \chi^2_{39} = 44.41, df = 39 (p = 0.25) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 41.17, df = 39 (p = 0.38) \\ \hline \mbox{Test for subgroup differences (random effects): } \chi^2_{39} = 4$				3221	0.01 Exper	I 0.1 1 rimental	¢ ¢ Cont	10 100 rol	1.34 1.30	[1.12; [1.05;	1.60] 1.63]	100.0% 	100.0%

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.

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)	Levomeprom azine	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	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						
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)	Chlorpromaz ine	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)	Trifluoperazi ne	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

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

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.

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)	Levomeprom azine	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	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								
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							
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)	Chlorpromaz ine	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)	Trifluoperazi ne	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

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

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

Study	Experim Events	ental Total	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Meltzer 2008 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: $t^2 = 9\%$, $\tau^2 = < 0.0001$, $p = 0.36$	29 4 3 9 5	72 21 57 90 40 280	33 2 7 4 5	75 19 57 90 39 280		0.86 2.00 0.40 2.39 0.97 1.00 0.99	[0.45; 1.65] [0.32; 12.41] [0.10; 1.62] [0.71; 8.06] [0.26; 3.66] [0.63; 1.58] [0.61; 1.60]	7.8% 0.7% 2.7% 1.4% 1.8% 14.3%	4.7% 2.3% 3.0% 3.4% 3.1%
comparison = Clozapine_Risperidone Bondolfi 1998 Clozapine Risperidone Breier 1999 Clozapine Risperidone Daniel 1996 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Wahlbeck 2000 Clozapine Risperidone Common effect model Random effects model Heterogeneity: $t^2 = 39\%$, $\tau^2 = 0.4183$, $p = 0.16$	3 2 0 5 3	43 14 10 40 11 118	3 10 7 13 6	43 15 10 41 9 118	*	1.00 0.08 0.02 0.31 0.19 0.23 0.23	[0.19; 5.26] [0.01; 0.53] [0.00; 0.50] [0.10; 0.97] [0.03; 1.28] [0.12; 0.47] [0.09; 0.60]	1.1% 3.3% 2.9% 4.5% 1.9% 13.8%	2.5% 2.2% 1.1% 3.5% 2.1%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone See 1999 Haloperidol Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.72$	6 8	22 10 32	4 6	22 10 32	+++	1.69 2.67 1.97 1.97	[0.40; 7.07] [0.36; 19.71] [0.62; 6.31] [0.61; 6.32]	1.2% 0.5% 1.7% 	2.9% 2.0% 4.9%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	17	145	3	143		6.20	[1.77; 21.65]	1.1%	3.3%
comparison = Chlorpromazine_Placebo Schiele 1961, 06602 Chlorpromazine Placebo	5	20	2	20		3.00	[0.51; 17.74]	0.6%	2.3%
comparison = Chiorpromazine_Thioridazine Schiele 1961, 06602 Chiorpromazine Thioridazine	5	20	2	20		3.00	[0.51; 17.74]	0.6%	2.3%
Schiele 1961, 06602 Chlorpromazine Trifluoperazine	e 5	20	9	20		0.41	[0.11; 1.56]	2.7%	3.1%
comparison = Placebo_Thioridazine Schiele 1961, 06602 Placebo Thioridazine	2	20	2	20		1.00	[0.13; 7.89]	0.7%	1.9%
comparison = Placebo_Trifluoperazine Schiele 1961, 06602 Placebo Trifluoperazine Marjerrison 1964 Placebo Trifluoperazine Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.41$	2	20 34 54	9 9	20 16 36	\$ \$ \$	0.14 0.05 0.08 0.08	[0.02; 0.75] [0.01; 0.28] [0.03; 0.29] [0.02; 0.28]	3.3% 4.6% 7.9% 	2.4% 2.4% 4.8%
comparison = Thioridazine_Trifluoperazine Schiele 1961, 06602 Thioridazine Trifluoperazine	2	20	9	20		0.14	[0.02; 0.75]	3.3%	2.4%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	27	154	40	146	-	0.56	[0.32; 0.98]	13.6%	4.9%
comparison = Olanzapine_Quetiapine Sirota 2006 Olanzapine Quetiapine	6	21	5	19		1.12	[0.28; 4.51]	1.5%	3.0%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	4	13	3	12		1.33	[0.23; 7.74]	0.9%	2.4%
comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	4	13	2	13		2.44	[0.36; 16.55]	0.6%	2.1%
comparison = Quetiapine_Risperidone Conley 2005 Quetiapine Risperidone	3	12	2	13		1.83	[0.25; 13.47]	0.6%	2.0%
comparison = Chlorpromazine_Haloperidol McCreadie 1977 Chlorpromazine Haloperidol	1	10	3	10		0.26	[0.02; 3.06]	1.1%	1.5%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	44	74	49	73	-	0.72	[0.37; 1.41]	8.0%	4.6%
comparison = Olanzapine_Risperidone Volavka 2002 Olanzapine Risperidone Alvarez 2006 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.41$	5 31	39 124 163	13 47	41 123 164	***	0.32 0.54 0.49 0.49	[0.10; 1.00] [0.31; 0.93] [0.30; 0.79] [0.30; 0.80]	4.4% 14.2% 18.7% 	3.5% 4.9% 8.4%
comparison = Chlorpromazine_Levomepromazine Lal 2006 Chlorpromazine Levomepromazine	10 8	19	3	19		3.88	[0.84; 17.97]	0.7%	2.7%
comparison = Fluphenazine_Haloperidol Hall 1968 Fluphenazine Haloperidol	19	25	18	25		1.23	[0.35; 4.37]	1.7%	3.3%

Test for subgroup differences (fixed effect): $\chi^2_{24} = 67.49$, df = Test for subgroup differences (random effects): $\chi^2_{24} = 62.40$, e	0.01) p < 0.01)		0.001 E	0.1 1 10 xperimental Control	1000					
Common effect model1407Random effects model1407Heterogeneity: $l^2 = 55\%$, $\tau^2 = 0.5944$, $p < 0.01$				1347 		0.77	[0.64; [0.58;	0.93] 1.17]	100.0% 	 100.0%
comparison = Pipotiazine_LAI_Placebo Schlosberg 1978 Pipotiazine_LAI Placebo	3	30	0	15		3.95	[0.19;	81.49]	0.2%	1.1%
comparison = Fluphenazine_LAI_Placebo Schlosberg 1978 Fluphenazine_LAI Placebo	4	30	0	15		- 5.26	[0.27; 1	04.49]	0.2%	1.1%
comparison = Fluphenazine_LAI_Pipotiazine_LAI Schlosberg 1978 Fluphenazine_LAI Pipotiazine_LAI	4	30	3	30		1.38	[0.28;	6.80]	1.0%	2.6%
comparison = Amisulpride_Olanzapine Kahn 2018 Amisulpride Olanzapine	6	47	6	46		0.98	[0.29;	3.28]	2.1%	3.4%
comparison = Chlorpromazine_Sulpiride Toru 1972 Chlorpromazine Sulpiride	27	37	22	38	*	1.96	[0.74;	5.18]	2.4%	3.9%

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)	Chlorpromazi ne	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

Study	Total	Expe Mean	rimental SD	Total	Mean	Control SD	Mean Difference	MD	95%-CI	Weight (common)	Weight (random)
comparison = Clozapine_Risperidone Breier 1999 Clozapine Risperidone McEvoy 2006 Clozapine Risperidone Common effect model Random effect model Heterogeneity: / ² = 61%, t ² = 73.2767, p = 0.11	13 39 52	12.20 -7.60	7.7000 13.1100	14 11 25	50.70 15.40	27.9000 17.9000	\$ \$ + +	-38.50 -23.00 -28.55 -29.89	[-53.70; -23.30] [-34.35; -11.65] [-37.64; -19.45] [-44.99; -14.79]	3.2% 5.7% 8.9%	5.5% 5.9% 11.4%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone	16	13.20	14.5700	18	26.37	27.8400		-13.17	[-27.88; 1.54]	3.4%	5.5%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	113	-0.97	60.5600	106	-28.37	60.5600		27.40	[11.35; 43.45]	2.9%	5.4%
comparison = Clozapine_Olanzapine McEvoy 2006 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.39$	39 60 99	-7.60 -3.20	13.1100 17.3000	16 60 76	-4.10 4.12	9.2000 17.3000		-3.50 -7.32 -5.38 -5.38	[-9.60; 2.60] [-13.51; -1.13] [-9.73; -1.04] [-9.73; -1.04]	19.8% 19.3% 39.1% 	6.3% 6.3% 12.5%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	39	-7.60	13.1100	13	-13.20	18.0000		5.60	[-5.01; 16.21]	6.5%	5.9%
comparison = Olanzapine_Quetiapine McEvoy 2006 Olanzapine Quetiapine	16	-4.10	9.2000	13	-13.20	18.0000		9.10	[-1.67; 19.87]	6.4%	5.9%
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Kinon 2009 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $c^2 = 0$, $p = 0.53$	16 179 195	-4.10 -26.46	9.2000 55.8653	11 188 199	15.40 -12.14	17.9000 55.8653	\$ \$ { }	-19.50 -14.32 -16.90 -16.90	[-31.00; -8.00] [-25.75; -2.89] [-25.00; -8.79] [-25.00; -8.79]	5.6% 5.6% 11.2%	5.9% 5.9% 11.7%
comparison = Quetiapine_Risperidone McEvoy 2006 Quetiapine Risperidone Conley 2005 Quetiapine Risperidone Common effect model Random effects model Heterogeneity: $l^2 = 9\%$, $\tau^2 = 8.5645$, $p = 0.29$	13 6 19	-13.20 8.20	18.0000 21.8412	11 12 23	15.40 50.60	17.9000 21.8412	\$ \$ +	-28.60 -42.40 -32.90 -33.14	[-43.01; -14.19] [-63.80; -21.00] [-44.86; -20.95] [-45.84; -20.43]	3.6% 1.6% 5.2%	5.6% 4.8% 10.4%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	135	-28.20	68.7500	137	-0.30	68.7500		-27.90	[-44.24; -11.56]	2.8%	5.4%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	9	24.40	21.8412	6	8.20	21.8412		16.20	[-6.36; 38.76]	1.4%	4.7%
comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	9	24.40	21.8412	12	50.60	21.8412		-26.20	[-45.08; -7.32]	2.1%	5.1%
comparison = Chlorpromazine_Ziprasidone Kane 2006 Chlorpromazine Ziprasidone	154	-1.60	55.8653	153	-17.00	55.8653		15.40	[2.90; 27.90]	4.7%	5.8%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	47	- 6.50	55.8653	46	-5.00	55.8653		-1.50	[-24.21; 21.21]	1.4%	4.7%
comparison = Chlorpromazine_Quetiapine AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine	130	-3.80	55.8653	130	-23.50	55.8653		19.70	[6.12; 33.28]	4.0%	5.7%
Common effect model Random effects model Heterogeneity: $l^2 = 86\%$, $\tau^2 = 352.0106$, $p < 0.01$ Test for subgroup differences (fixed effect): $\chi_{13}^2 = 119.80$, df Test for subgroup differences (random effects): $\chi_{13}^2 = 103.64$	1033 = 13 (p , df = 1	< 0.01) 3 (p < 0.1	01)	957			-60 -40 -20 0 20 40 Experimental Control	-6.55 -8.28	[-9.27; -3.83] [-17.60; 1.05]	100.0% 	 100.0%

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 clozapinearms 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



Favours comparator $\leftarrow \rightarrow$ Favours reference

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	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)	Trifluoperazi ne	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)	Chlorpromaz ine	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)	Levomeprom azine

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							
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	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)	Trifluoperazi ne	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)	Chlorpromaz ine	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)	Levomeprom azine

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

Study	Experim Events	ental Total	Co Events	ntrol Total	Odds Ratio	OR	95%-CI	Weight (common)	Weight (random)
comparison = Clozapine_Risperidone	22	170	10	125	i	1.02	14 03: 3 591	5.0%	4 504
Azorin 2001 Clozapine Risperidone	33	138	19	135	1 million	1.92	[1.03; 3.58]	5.0%	4.0%
McEvov 2006 Clozanine Risperidone	20	40	13	45	1	2.01	[0.69: 8.65]	1 1%	2.0%
Common effect model	LL	230	7	194	0	2.01	[1 26- 3 23]	B 5%	2.070
Random effects model		2.99		101	4	2.01	[1.25: 3.22]	0.070	9.8%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.94$						2.51	[read and		0.010
comparison = Clozapine_Olanzapine		-		-					
Bitter 2004 Clozapine Olanzapine	41	12	27	/5		2.35	[1.21; 4.56]	3.9%	4.3%
Shaw 2006 Clozapine Olanzapine	2	12	2	13		1.10	[0.13; 9.34]	0.5%	0.9%
McEvov 2006 Clozanine Olanzanine	22	40	19	10		4.74	[0.21, 105.54]	1.6%	2 496
Tollefson 2001 Clozapine Olanzapine	41	90	23	90		2.44	[1.30: 4.57]	4.3%	4.5%
Common effect model	7.1	241	20	218	0	2.27	[1.50; 3.42]	10.5%	4.070
Random effects model					•	2.26	[1.50; 3.41]		12.5%
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $p = 0.92$									
comparison = Clozapine_Haloperidol	20	20	42	27		2.05	[0 94, E 40]	2.46/	2.00/
Kumma 1996 Clozapine Haloperidel	20	10	13	37		2.05	12.06- 270.62	2.1%	0.7%
Rosenberk 1997 Clozapine Haloperidol	187	205	177	218		24.00	[1 33 4 35]	5 1%	4 7%
Common effect model	101	253		266	•	2.59	[1.60: 4.19]	7.4%	
Random effects model					•	2.52	[1.55; 4.11]		8.4%
Helefogeneity: $r = 42.\%$, $t' = 40.0001$, $p = 0.16$									
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone	14	22	15	22		0.82	[0.23; 2.85]	1.9%	2.1%
comparison = Chlorpromazine Olanzapine									
Conley 1998 Chlorpromazine Olanzapine	22	42	15	42	-	1.98	[0.83; 4.75]	2.4%	3.3%
comparison = Haloperidol_Placebo	2	47	4	16		2.24	10 20: 24 641	0.3%	0.7%
Howard 1974 Halopendor Placebo	5	11	10	10		5.21	[0.50, 54.04]	0.370	0.770
comparison = Haloperidol Tiotixene									
Howard 1974 Haloperidol Tiotixene	3	17	0	16		- 7.97	[0.38; 167.53]	0.1%	0.4%
comparison = Placebo_Tiotixene					1				
Howard 1974 Placebo Tiotixene	1	16	0	16		3.19	[0.12; 84.43]	0.2%	0.4%
comparison = Risperidone_Sertindole									
Kane 2010b Risperidone Sertindole	15	105	25	216	Ť	1.27	[0.64; 2.53]	4.8%	4.2%
comparison = Clozapine_Quetiapine					1				
McEvoy 2006 Clozapine Quetiapine	22	49	5	15		1.63	[0.48; 5.48]	1.4%	2.1%
comparison = Olanzapine_Quetiapine					1				
McEvoy 2006 Olanzapine Quetiapine	6	19	5	15		0.92	[0.22; 3.92]	1.3%	1.6%
Sirota 2006 Olanzapine Quetlapine	0	21	0	19		0.91	[0.02; 47.94]	0.2%	0.3%
Common effect model		40		34		0.92	[0.24; 3.58]	1.5%	
Random effects model Heterogeneity: $l^2 = 0.95$, $\tau^2 = 0$, $p = 0.99$					\rightarrow	0.92	[0.24; 3.58]	100	1.9%
comparison = Olanzapine_Risperidone	E	10	2	16	1	4 99	10.24. 6 441	1.09/	1 60/
Alvarez 2006 Olanzapine Risperidone	5	124	8	123		0.60	10 19 1 901	2.6%	2 3%
Chen 2012 Olanzapine Risperidone	11	16	10	16		1.32	[0.31: 5.70]	1.1%	1.6%
Kinon 2009 Olanzapine Risperidone	12	186	11	192		1.13	[0.49; 2.64]	3.5%	3.4%
Common effect model		345		347	4	1.02	[0.58; 1.79]	8.2%	
Random effects model					\$	1.02	[0.58; 1.81]		8.9%
Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $p = 0.77$									
comparison = Quetiapine_Risperidone					1				
McEvoy 2006 Quetlapine Risperidone	5	15	4	16		1.50	[0.32; 7.14]	0.9%	1.5%
Conley 2005 Quetiapine Risperidone	3	12	5	13		0.53	[0.10; 2.98]	1.2%	1.2%
Common effect model		27		29		0.94	[0.30; 2.91]	2.1%	0.701
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.38$						0.94	(u.au; z.aa)	_	2.1%
comparicon = Chiamannanina Discolo									
Schiele 1961, 06602 Chlorpromazine Placebo	4	20	3	20		1.42	10.27: 7.341	0.8%	1.3%
			-		1			9	
comparison = Chlorpromazine_Thioridazine					1				
Schiele 1961, 06602 Chlorpromazine Thioridazine	4	20	5	20		0.75	[0.17; 3.33]	1.4%	1.6%
comparison = Chloropoporine Triflueneronine									
Schiele 1961, 06602 Chlorpromazine Trifluoperazine	4	20	4	20	<u></u>	1.00	[0.21; 4.71]	1.1%	1.5%
comparison = Placebo_Thioridazine Schiele 1961_06602_Placebo_Thioridazine	2	20	F	20		0.52	10 11 2 60	1.50/	1.494
Contere rao i, couce riacebo michaeline	5	20	5	20		0.05	[0.11, 2.00]	1.070	1.470
comparison = Placebo_Trifluoperazine									
Schlele 1961, 06602 Placebo Trifluoperazine	3	20	4	20		0.71	[0.14; 3.66]	1.2%	1.3%
comparison = Thioridazine Trifluonerazine									
Schiele 1961, 06602 Thioridazine Trifluoperazine	5	20	4	20		1.33	[0.30; 5.93]	1.0%	1.6%
							90 N.		

comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	4	154	10	146		0.36	[0.11;	1.18]	3.4%	2.2%
comparison = Fluphenazine Quetiapine										
Conley 2005 Fluphenazine Quetiapine	4	13	3	12		1.33	[0.23;	7.74]	0.7%	1.2%
comparison = Fluphenazine_Risperidone										
Conley 2005 Fluphenazine Risperidone	4	13	5	13		0.71	[0.14;	3.61]	1.2%	1.4%
comparison = Chlorpromazine_Clozapine										
Hong 1997 Chlorpromazine Clozapine	4	19	5	21		0.85	[0.19;	3.79]	1.3%	1.6%
Honigfeld 1984b Chlorpromazine Clozapine	14	76	16	75		0.83	[0.37;	1.85]	4.5%	3.6%
Kane 1988 Chlorpromazine Clozapine	18	142	26	126		0.56	[0.29;	1.08]	8.2%	4.3%
Common effect model		237		222	•	0.67	[0,42;	1.09]	14.0%	
Random effects model					•	0.67	[0.42;	1.09]		9.5%
Heterogeneity: $t^2 = 0\%$, $\tau^2 = 0$, $p = 0.71$										
comparison = Chlorpromazine Ziprasidone										
Kane 2006 Chlorpromazine Ziprasidone	44	154	29	152		1.70	[0.99;	2.90]	7.1%	5.0%
comparison = Chlorpromazine_Haloperidol										
McCreadie 1977 Chlorpromazine Haloperidol	3	10	8	10		0.11	[0.01;	0.84]	1.9%	0.9%
comparison = Clozapine_Ziprasidone										
Sacchetti 2009 Clozapine Ziprasidone	17	74	4	73	i	5.14	[1.64;	16.16]	1.1%	2.3%
comparison = Chlorpromazine_Levomepromazine					i.					
Lal 2006 Chlorpromazine Levomepromazine	3	19	5	19		0.52	[0.11;	2.60]	1.4%	1.4%
comparison = Chlorpromazine_Sulpiride										
Toru 1972 Chlorpromazine Sulpiride	10	37	8	38		1.39	[0.48;	4.03]	2.0%	2,6%
comparison = Amisulpride_Olanzapine										
Kahn 2018 Amisulpride Olanzapine	10	47	21	46	- 18 -	0.32	[0.13;	0.80]	5.7%	3.1%
comparison = Chlorpromazine_Quetiapine										
AstraZeneca 5077IL/0031 Chlorpromazine Quetlapine	25	130	19	130		1.39	[0.72;	2.67]	5.2%	4.3%
Common effect model		2412		2412		1.38	[1.19;	1.61]	100.0%	<u></u>
Random effects model					0	1.31	[1.06;	1.61]		100.0%
Heterogeneity: $l^2 = 33\%$, $\tau^2 = 0.1531$, $p = 0.02$							3			
Test for subgroup differences (fixed effect): χ^2_{29} = 59.90, df = 29	9 (p < 0	0.01)			0.01 0.1 1 10 100					
Test for subgroup differences (random effects): χ^2_{29} = 58.92, df	= 29 (0	< 0.01)			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.

8.10 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)	Chlorpromazi ne	-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)	Levomeproma zine	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

Study	Total	Expe Mean	rimental SD	Total	Mean	Control SD	Mean Differe	nce MD	95%-CI	Weight (common)	Weight (random)
comparison = Clozapine_Risperidone Azorin 2001 Clozapine Risperidone Bondolfi 1998 Clozapine Risperidone Daniel 1996 Clozapine Risperidone McEvoy 2006 Clozapine Risperidone Volavka 2002 Clozapine Risperidone Common effect model Random effects model Heterogeneity: $J^2 = 0\%$, $\tau^2 = 0$, $p = 0.94$	136 43 10 41 38 268	2.40 2.70 80.56 1.40 4.20	5.7600 5.7269 5.8100 17.9300 4.7000	134 43 10 11 39 237	0.20 1.10 78.97 1.77 2.30	5.7600 5.7269 5.1200 4.2100 2.8000	*	2.20 1.60 1.59 -0.37 1.90 1.93 1.93	[0.83; 3.57] [-0.82; 4.02] [-3.21; 6.39] [-6.40; 5.66] [0.17; 3.63] [0.98; 2.88] [0.98; 2.88]	4.4% 1.4% 0.4% 0.2% 2.8% 9.2%	3.6% 2.9% 1.6% 1.2% 3.4%
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Shaw 2006 Clozapine Olanzapine Conley 2003 Clozapine Olanzapine Metzer 2008 Clozapine Olanzapine Moresco 2004 Clozapine Olanzapine Tollefson 2001 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Volavka 2002 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: f^2 = 54%, τ^2 = 2.2854, p = 0.03	72 12 5 41 21 6 57 90 38 342	4.10 3.80 1.54 1.40 92.80 66.80 5.00 2.30 4.20	5.6000 6.0000 4.0000 17.9300 6.8600 9.4000 6.8000 4.9000 4.7000	75 13 8 16 19 9 57 90 38 325	3.30 3.60 3.40 2.81 98.40 80.00 3.50 1.80 5.40	5.3000 4.0000 5.3500 13.2300 5.7300 13.9000 5.9000 5.0000 4.6000	++++++++	0.80 0.20 -1.86 -1.41 -5.60 -13.20 1.50 0.50 -1.20 -0.03 -0.57	$\begin{bmatrix} -0.96; 2.56] \\ [-3.83; 4.23] \\ [-6.96; 3.24] \\ [-9.90; 7.08] \\ [-9.50; -1.70] \\ [-24.99; -1.41] \\ [-0.84; 3.84] \\ [-0.95; 1.95] \\ [-3.29; 0.89] \\ [-0.88; 0.81] \\ [-2.06; 0.92] \end{bmatrix}$	2.7% 0.5% 0.3% 0.1% 1.5% 4.0% 1.9% 11.7%	3.3% 1.9% 1.5% 0.7% 2.0% 0.4% 3.0% 3.5% 19.5%
comparison = Clozapine_Haloperidol Buchanan 1998 Clozapine Haloperidol Kumra 1996 Clozapine Haloperidol Volavka 2002 Clozapine Haloperidol Common effect model Random effects model Heterogeneity: l^2 = 33%, t^2 = < 0.0001, p = 0.22	28 10 38 76	4.20 0.90 4.20	3.4000 6.4700 4.7000	33 11 36 80	0.40 0.94 0.20	3.2000 2.8900 0.2000	*	3.80 -0.04 4.00 3.67	[2.13; 5.47] [-4.40; 4.32] [2.50; 5.50] [2.59; 4.75] [2.59; 4.75]	3.0% 0.4% 3.7% 7.2%	3.4% 1.8% 3.5% 8.7%
comparison = Haloperidol_Olanzapine Buchanan 2005 Haloperidol Olanzapine Volavka 2002 Haloperidol Olanzapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$	31 36 67	87.27 0.20	20.0000 0.2000	27 38 65	88.95 5.40	16.7800 4.6000	* \$	1.68 -5.20 -5.12 -5.12	[-11.15; 7.79] [-6.66; -3.74] [-6.56; -3.67] [-6.56; -3.67]	0.1% 3.9% 4.0%	0.6% 3.5% 4.1%
comparison = Haloperidol_Risperidone Claus 1992 Haloperidol Risperidone Volavka 2002 Haloperidol Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.47$	22 36 58	73.90 0.20	13.1300 0.2000	22 39 61	73.20 2.30	12.2000 2.8000	*	0.70 -2.10 -2.06 -2.06	[-6.79; 8.19] [-2.98; -1.22] [-2.94; -1.19] [-2.94; -1.19]	0.1% 10.8% 10.9%	0.9% 3.8% 4.7%
comparison = Haloperidol_Quetiapine Emsley 2000 Haloperidol Quetiapine	141	0.70	5.7269	140	1.40	5.7269	ł	-0.70	[-2.04; 0.64]	4.7%	3.6%
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	86	2.50	3.3000	162	3.10	4.5000	4	-0.60	[-1.58; 0.38]	8.7%	3.8%
comparison = Clozapine_Quetiapine McEvoy 2006 Clozapine Quetiapine	41	1.40	17.9300	13	0.50	8.3400		- 0.90	[-6.22; 8.02]	0.2%	0.9%
comparison = Olanzapine_Quetiapine McEvoy 2006 Olanzapine Quetiapine Sirota 2006 Olanzapine Quetiapine Common effect model Random effects model Heterogeneity: $l^2 = 0\%$, $\pi^2 = 0$, $p = 0.83$	16 21 37	2.81 2.30	13.2300 3.6700	13 19 32	0.50 -0.90	8.3400 3.6700	+ \$ \$	- 2.31 3.20 3.13 3.13	[-5.60; 10.22] [0.92; 5.48] [0.94; 5.32] [0.94; 5.32]	0.1% 1.6% 1.7%	0.8% 3.0% 3.8%
comparison = Olanzapine_Risperidone McEvoy 2006 Olanzapine Risperidone Volavka 2002 Olanzapine Risperidone Alvarez 2006 Olanzapine Risperidone Chen 2012 Olanzapine Risperidone Kinon 2009 Olanzapine Risperidone Common effect model Random effects model Heterogeneity: $f^2 = 46\%$, $\tau^2 = 0.9202$, $p = 0.12$	16 38 124 16 179 373	2.81 5.40 3.50 2.70 1.85	13.2300 4.6000 6.9000 4.0000 3.9700	11 39 123 16 188 377	1.77 2.30 2.97 1.00 1.29	4.2100 2.8000 7.6500 4.2000 4.2500	**	- 1.04 3.10 0.53 1.70 0.56 1.02 1.33	[-5.90; 7.98] [1.39; 4.81] [-1.29; 2.35] [-1.14; 4.54] [-0.28; 1.40] [0.35; 1.69] [0.09; 2.58]	0.2% 2.9% 2.5% 1.0% 11.8% 18.5%	1.0% 3.4% 3.3% 2.6% 3.9% 14.2%
comparison = Quetiapine_Risperidone McEvoy 2006 Quetiapine Risperidone Conley 2005 Quetiapine Risperidone Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$	13 12 25	0.50 -1.20	8.3400 11.2200	11 13 24	1.77 -0.65	4.2100 2.4300	-++0-0	-1.27 -0.55 -0.99 -0.99	[-6.44; 3.90] [-7.03; 5.93] [-5.03; 3.05] [-5.03; 3.05]	0.3% 0.2% 0.5%	1.5% 1.1%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	154	-2.19	5.7269	146	-1.52	5.7269	4	-0.67	[-1.97; 0.63]	5.0%	3.6%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	13	-2.60	5.7000	12	-1.20	11.2200	<u> </u>	-1.40	[-8.46; 5.66]	0.2%	0.9%
comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	13	-2.60	5.7000	13	-0.65	2.4300	-+	-1.95	[-5.32; 1.42]	0.7%	2.3%
comparison = Chlorpromazine_Ziprasidone Kane 2006 Chlorpromazine Ziprasidone	154	1.32	5.7269	153	0.23	5.7269	Ļ	1.09	[-0.19; 2.37]	5.1%	3.6%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	73	0.84	4.6000	73	-2.62	4.7000	-	3.46	[1.95; 4.97]	3.7%	3.5%
comparison = Chlorpromazine_Levomepromazine Lal 2006 Chlorpromazine Levomepromazine	12	75.40	18.4000	17	75.60	12.9000		-0.20	[-12.28; 11.88]	0.1%	0.4%
comparison = Amisulpride_Olanzapine Kahn 2018 Amisulpride Olanzapine	33	2.70	2.9000	39	4.20	3.6000	4	-1.50	[-3.00; 0.00]	3.7%	3.5%

comparison = Chlorpromazine_Quetiapine AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine	130	0.45	5.7269	130	1.36	5.7269			+			-0.91	[-2.30; 0.48]	4.3%	3.6%
Common effect model	2096			2099								0.20	[-0.09; 0.49]	100.0%	
Random effects model									þ			0.31	[-0.47; 1.09]		100.0%
Heterogeneity: $I^2 = 81\%$, $\tau^2 = 3.9230$, $p < 0.01$							1	1	1	1					
Test for subgroup differences (fixed effect): $\chi_{18}^2 = 178.14$, df	= 18 (p	< 0.01)					-20	-10	0	10	20				
Test for subgroup differences (random effects): χ^2_{18} = 175.8	, df = 1	B (p < 0	.01)				Expe	erimenta	al Co	ontrol					

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

Study	Total	Expe Mean	rimental SD	Total	Mear	Control SD	Mean D	ifference	MD	95%-CI	Weight (common)	Weight (random)
comparison = Risperidone_Sertindole Kane 2010b Risperidone Sertindole	105	4.10	15.6000	216	22.70	22.4000	-		-18.60	[-22.82; -14.38]	61.8%	22.7%
comparison = Chlorpromazine_Ziprasidone Kane 2006 Chlorpromazine Ziprasidone	142	400.70	40.5000	145	396.60	45.5000	-	*	4.10	[-5.86; 14.06]	11.1%	20.8%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	71	-3.58	39.3000	67	6.04	43.3000			-9.62	[-23.44; 4.20]	5.8%	19.0%
comparison = Chlorpromazine_Levomepromazine Lal 2006 Chlorpromazine Levomepromazine	12	437.00	24.0000	11	429.00	25.0000		-	- 8.00	[-12.07; 28.07]	2.7%	15.8%
comparison = Chlorpromazine_Quetiapine AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine	130	15.00	38.3000	130	-4.80	23.2000			- 19.80	[12.10; 27.50]	18.6%	21.7%
Common effect model Random effects model Heterogeneity: $l^2 = 95\%$, $\tau^2 = 227.2294$, $p < 0.01$ Test for subgroup differences (fixed effect): $\chi^2_A = 82.45$, df = Test for subgroup differences (random effects): $\chi^2_A = 82.45$,	460 4 (ρ < 0 tf = 4 (μ	0.01) 0 < 0.01)		569			-20 -10 Experimental	0 10 20 Control	-7.69 0.37	[–11.01; –4.37] [–13.85; 14.58]	100.0% 	100.0%

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

Study	Total	Exper Mean	imental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%–CI	Weight (common)	Weight (random)
comparison = Haloperidol_Olanzapine Buchanan 2005 Haloperidol Olanzapine	34	-18.10	5.9000	29	-18.10	5.7000		0.00	[-0.50; 0.50]	10.3%	13.7%
comparison = Clozapine_Haloperidol Kumra 1996 Clozapine Haloperidol	10	-44.90	9.5000	11	-27.90	12.1000		-1.49	[-2.48; -0.50]	2.6%	8.0%
$\label{eq:comparison} \begin{array}{l} \mbox{Clozapine Olanzapine}\\ \mbox{Kumra 2007 Clozapine Olanzapine}\\ \mbox{Meltzer 2008 Clozapine Olanzapine}\\ \mbox{Common effect model}\\ \mbox{Random effects model}\\ \mbox{Heterogeneity: } r^2 = 43\%, \tau^2 = 0.0819, \end{tabular} = 0.18 \end{array}$	18 21 39	-50.50 -62.40	15.0000 9.6200	21 19 40	-46.40 -54.80	19.4000 7.8500	\$ \$ }	-0.23 -0.84 -0.53 -0.53	[-0.86; 0.40] [-1.49; -0.19] [-0.98; -0.07] [-1.13; 0.07]	6.3% 6.0% 12.3% 	11.9% 11.7% 23.6%
comparison = Clozapine_Ziprasidone Sacchetti 2009 Clozapine Ziprasidone	73	-7.20	10.8000	71	-8.30	13.9000	-	0.09	[-0.24; 0.41]	23.6%	15.9%
comparison = Clozapine_Risperidone Wahlbeck 2000 Clozapine Risperidone	10	-35.00	11.0000	9	-44.00	10.0000		0.82	[–0.13; 1.76]	2.8%	8.4%
comparison = Olanzapine_Risperidone Alvarez 2006 Olanzapine Risperidone	120	-7.75	21.9900	115	0.92	21.9900	-	-0.39	[-0.65; -0.13]	37.8%	16.6%
comparison = Paliperidone_Paliperidone_LAI Actrn12618001113246 Paliperidone Paliperidone_LAI	32	-62.05	12.9200	33	-65.22	9.6400	-	0.28	[-0.21; 0.76]	10.6%	13.8%
Common effect model Random effects model Heterogeneity: $l^2 = 71\%$, $\tau^2 = 0.2017$, $p < 0.01$ Test for subgroup differences (fixed effect): $\chi_6^2 = 22.29$, df = Test for subgroup differences (random effects): $\chi_6^2 = 21.28$,	318 6 (p < 0 df = 6 (j	0.01) v < 0.01)		308			-2 -1 0 1 2 Experimental Control	-0.18 -0.19	[–0.34; –0.02] [–0.56; 0.18]	100.0% 	 100.0%

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

Study	Total	Exper Mean	rimental SD	Total	Mean	Control SD	Standardised Mean Difference	SMD	95%-CI	Weight (common)	Weight (random)
comparison = Clozapine_Olanzapine Bitter 2004 Clozapine Olanzapine Naber 2005 Clozapine Olanzapine Common effect model Random effects model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.99$	50 50 100	-13.70 -13.70	21.2000 29.3000	45 49 94	-18.50 -21.90	18.9000 38.4000	**	0.24 0.24 0.24 0.24	[-0.17; 0.64] [-0.16; 0.63] [-0.05; 0.52] [-0.05; 0.52]	8.2% 8.5% 16.7% 	10.0% 10.4% 20.4%
comparison = Haloperidol_Olanzapine Buchanan 2005 Haloperidol Olanzapine	34	-59.40	19.1000	29	-59.70	20.7000		0.01	[-0.48; 0.51]	5.4%	7.3%
comparison = Aripiprazole_Perphenazine Kane 2007a Aripiprazole Perphenazine	104	-1.70	16.2400	103	-2.60	15.2200		0.06	[-0.22; 0.33]	18.0%	16.8%
comparison = Fluphenazine_Quetiapine Conley 2005 Fluphenazine Quetiapine	11	-24.40	19.1530	10	-27.90	19.1530		- 0.18	[-0.68; 1.03]	1.8%	2.8%
comparison = Fluphenazine_Risperidone Conley 2005 Fluphenazine Risperidone	11	-24.40	19.1530	12	-28.40	19.1530		- 0.20	[-0.62; 1.02]	2.0%	3.0%
comparison = Quetiapine_Risperidone Conley 2005 Quetiapine Risperidone	10	-27.90	19.1530	12	-28.40	19.1530		0.03	[-0.81; 0.86]	1.9%	2.9%
comparison = Clozapine_Haloperidol Rosenheck 1997 Clozapine Haloperidol	158	-47.61	19.3100	153	-43.09	19.0400	-	-0.24	[-0.46; -0.01]	26.8%	20.6%
comparison = Chlorpromazine_Quetiapine AstraZeneca 5077IL/0031 Chlorpromazine Quetiapine	128	-31.50	18.6000	125	-27.50	19.3000		-0.21	[-0.46; 0.04]	21.8%	18.6%
comparison = Paliperidone_Paliperidone_LAI Actrn12618001113246 Paliperidone Paliperidone_LAI	32	-79.22	11.2300	33	-75.27	14.7900		-0.30	[-0.79; 0.19]	5.6%	7.5%
Common effect model Random effects model Heterogeneity: $I^2 = 14\%, \tau^2 = 0.0152, p = 0.32$ Test for subgroup differences (fixed effect): $\chi_8^2 = 10.44, df = 1$	588 8 (p = 0	0.24)		571			-1 -0.5 0 0.5	-0.07 -0.04	[–0.18; 0.05] [–0.19; 0.11]	100.0% 	 100.0%
Handom errects model Heterogeneity: $l^2 = 14\%$, $\tau^2 = 0.0152$, $p = 0.32$ Test for subgroup differences (fixed effect): $\chi^2_6 = 10.44$, df = l Test for subgroup differences (random effects): $\chi^2_6 = 10.44$, dc	8 (p = 0 if = 8 (p	0.24) o = 0.24)					-1 -0.5 0 0.5 Experimental Control	1	[-0.19; 0.11]		100.

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



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



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.

Levomeproma zine	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)	Chlorpromazi ne	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

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



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



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.

Levomeproma zine	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)	Chlorpromazi ne	-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

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



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



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.

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)	Levomeproma zine	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)	Chlorpromazi ne	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	-0.76 (-1.54 to	-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

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



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



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.

Levomeproma zine	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)	Chlorpromazi ne	-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

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



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



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.

Levomeproma zine	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)	Chlorpromazi ne	-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

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



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



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.

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)	Chlorpromazi ne

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



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



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.

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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)	Levomeproma zine	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)	Chlorpromazi ne

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



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



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.

Amisulpride	NA	NA	-0.24 (-0.82 to 0.35)	NA	NA	NA	NA	NA	NA	NA
0.05 (-0.93 to 1.03)	Levomeproma zine	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)	Chlorpromazi ne	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

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



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



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.

Levomeproma zine	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)	Chlorpromazi ne	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)
-0.70 (-1.42 to 0.02) -0.85 (-1.54 to -0.15)	-0.37 (-0.88 to 0.15) -0.51 (-1.04 to 0.02)	-0.13 (-0.29 to 0.03) -0.27 (-0.49 to -0.06)	-0.10 (-0.26 to 0.07) -0.24 (-0.45 to -0.03)	-0.09 (-0.38 to 0.20) -0.23 (-0.50 to 0.04)	-0.02 (-0.62 to 0.58) -0.16 (-0.78 to 0.45)	-0.00 (-0.25 to 0.25) -0.14 (-0.33 to 0.04)	Risperidone -0.14 (-0.38 to 0.09)	-0.06 (-0.70 to 0.58) Quetiapine	-0.14 (-0.43 to 0.15) -0.14 (-0.42 to 0.14)	0.02 (-0.76 to 0.81) 0.15 (-0.65 to 0.95)	-0.32 (-0.60 to -0.04) NA
-0.70 (-1.42 to 0.02) -0.85 (-1.54 to -0.15) -0.85 (-1.56 to -0.14)	-0.37 (-0.88 to 0.15) -0.51 (-1.04 to 0.02) -0.51 (-1.02 to -0.01)	-0.13 (-0.29 to 0.03) -0.27 (-0.49 to -0.06) -0.28 (-0.42 to -0.14)	-0.10 (-0.26 to 0.07) -0.24 (-0.45 to -0.03) -0.24 (-0.39 to -0.10)	-0.09 (-0.38 to 0.20) -0.23 (-0.50 to 0.04) -0.24 (-0.51 to 0.04)	-0.02 (-0.62 to 0.58) -0.16 (-0.78 to 0.45) -0.17 (-0.76 to 0.42)	-0.00 (-0.25 to 0.25) -0.14 (-0.33 to 0.04) -0.15 (-0.38 to 0.08)	Risperidone -0.14 (-0.38 to 0.09) -0.15 (-0.32 to 0.02)	-0.06 (-0.70 to 0.58) Quetiapine -0.00 (-0.21 to 0.20)	-0.14 (-0.43 to 0.15) -0.14 (-0.42 to 0.14) Haloperidol	0.02 (-0.76 to 0.81) 0.15 (-0.65 to 0.95) -0.17 (-0.60 to 0.26)	-0.32 (-0.60 to -0.04) NA NA
-0.70 (-1.42 to 0.02) -0.85 (-1.54 to -0.15) -0.85 (-1.56 to -0.14) -0.93 (-1.72 to -0.13)	-0.37 (-0.88 to 0.15) -0.51 (-1.04 to 0.02) -0.51 (-1.02 to -0.01) -0.59 (-1.21 to 0.03)	-0.13 (-0.29 to 0.03) -0.27 (-0.49 to -0.06) -0.28 (-0.42 to -0.14) -0.35 (-0.74 to 0.03)	-0.10 (-0.26 to 0.07) -0.24 (-0.45 to -0.03) -0.24 (-0.39 to -0.10) -0.32 (-0.71 to 0.07)	-0.09 (-0.38 to 0.20) -0.23 (-0.50 to 0.04) -0.24 (-0.51 to 0.04) -0.31 (-0.76 to 0.14)	-0.02 (-0.62 to 0.58) -0.16 (-0.78 to 0.45) -0.17 (-0.76 to 0.42) -0.24 (-0.94 to 0.45)	-0.00 (-0.25 to 0.25) -0.14 (-0.33 to 0.04) -0.15 (-0.38 to 0.08) -0.22 (-0.64 to 0.20)	Risperidone -0.14 (-0.38 to 0.09) -0.15 (-0.32 to 0.02) -0.22 (-0.62 to 0.17)	-0.06 (-0.70 to 0.58) Quetiapine -0.00 (-0.21 to 0.20) -0.08 (-0.48 to 0.32)	-0.14 (-0.43 to 0.15) -0.14 (-0.42 to 0.14) Haloperidol -0.08 (-0.44 to 0.29)	0.02 (-0.76 to 0.81) 0.15 (-0.65 to 0.95) -0.17 (-0.60 to 0.26) Fluphenazine	-0.32 (-0.60 to -0.04) NA NA NA

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



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



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.

Levomeproma zine	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)	Chlorpromazi ne	-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

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



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



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.

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)	Levomeproma zine	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)	Chlorpromazi ne

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


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



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.

Clozapine	NA	-0.14 (-0.59 to 0.31)	-0.45 (-1.19 to 0.28)	45 (-1.19 to 0.28) NA		NA	NA	NA	-0.86 (-1.10 to -0.63)
-0.12 (-0.81 to 0.57)	Levomeproma zine	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 NA		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)	Chlorpromazi ne

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



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



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)	Chlorpromazi ne

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



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



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.

Chlorpromazi ne	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

<u>c High cut-off</u>

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





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



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.

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	NA -0.15 (-1.04 to 0.75)		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)	Levomeproma zine	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)	Chlorpromazi ne

12.1.2 The criteria from Samara et al⁸¹

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



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



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

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



No response to at least 2 retrospective periods of antipsychotic treatment

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



No response to at least 2 retrospective periods of antipsychotic treatment SMD (95% CI)

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)	Chlorpromazi ne

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



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

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



No response to a combination of retrospective and prospective criteria for treatment resistance , SMD (95% CI)

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.

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)	Levomeproma zine	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)	Chlorpromazi ne

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



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



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)	Levomeproma zine	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)	Chlorpromazi ne

<u>b Less than 18 years old</u>

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.

<u>a High dose</u>

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



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)	Levomeproma zine	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)	Chlorpromazi ne	-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

<u>b Low dose</u>

Number of studies: k = 19

Number of pairwise comparisons: m = 26

Number of treatments: n = 9

Number of designs: d = 11

Network plot



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



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

12.4 Publication year

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

<u>a Early</u>

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



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)	Chlorpromazi ne

<u>b Late</u>

Number of studies: k = 22

Number of pairwise comparisons: m = 34

Number of treatments: n = 11

Number of designs: d = 14

Network plot



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


League table

Levomeproma zine	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)	Chlorpromazi ne	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.

<u>a High</u>

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)	Levomeproma zine	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)	Chlorpromazi ne

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.

<u>b Low</u>

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)
-0.40 (-0.94 to 0.14) -0.47 (-1.04 to 0.09)	-0.22 (-0.46 to 0.02) -0.29 (-0.49 to -0.09)	-0.17 (-0.37 to 0.04) -0.24 (-0.50 to 0.03)	0.00 (-0.36 to 0.37) -0.07 (-0.35 to 0.21)	Risperidone -0.07 (-0.32 to 0.18)	-0.13 (-0.48 to 0.22) Haloperidol	NA -0.17 (-0.61 to 0.27)	-0.32 (-0.62 to -0.02)
-0.40 (-0.94 to 0.14) -0.47 (-1.04 to 0.09) -0.65 (-1.36 to 0.07)	-0.22 (-0.46 to 0.02) -0.29 (-0.49 to -0.09) -0.46 (-0.95 to 0.02)	-0.17 (-0.37 to 0.04) -0.24 (-0.50 to 0.03) -0.41 (-0.92 to 0.10)	0.00 (-0.36 to 0.37) -0.07 (-0.35 to 0.21) -0.24 (-0.76 to 0.28)	Risperidone -0.07 (-0.32 to 0.18) -0.24 (-0.75 to 0.26)	-0.13 (-0.48 to 0.22) Haloperidol -0.17 (-0.61 to 0.27)	NA -0.17 (-0.61 to 0.27) Fluphenazine	-0.32 (-0.62 to -0.02) NA NA

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.

<u>a Short</u>

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)	Chlorpromazi ne	-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.

<u>b Long</u>

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

Levomeproma zine	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)	Chlorpromazi ne	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

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Altamura 2002	+	+	8	+	+	8
	AstraZeneca 5077IL/0031	+	+	8	+	+	8
	AstraZeneca 5077IL/0054	+	+	8	+	+	8
	Azorin 2001	+	+	-	+	+	-
	Bitter 2004	+	+	-	+	+	-
	Bondolfi 1998	+	+	-	+	+	-
	Breier 1999	-	+	8	+	+	8
	Breier 1999a	+	+	-	+	+	-
	Buchanan 1998	-	+	8	+	+	8
	Buchanan 2005	-	+	-	+	+	-
	Chen 2012	-	-	-	+	+	•
	Chowdhury 1999	-	-	-	-	+	8
	Claus 1992	+	+	8	+	+	8
	Conley 1998	+	+	-	+	+	•
	Conley 2003	-	+	8	+	+	8
	Conley 2005	+	+	8	+	+	8
	Emsley 2000	+	+	-	+	+	-
	Hall 1968	-	+	-	+	+	-
	Hong 1997	-	+	-	+	+	-
	Honigfeld 1984b	+	+	-	+	+	-
	Kahn 2018	+	8	-	+	+	8
	Kane 1988	+	+	-	+	+	-
Study	Kane 2001	+	8	8	+	+	8
	Kane 2006	+	+	-	+	+	-
	Kane 2010b	+	+	-	+	+	-
	Kinon 1993b	-	-		+	+	8
	Kinon 2009	+	+	-	+	+	-

Kumra 1996	+	+	8	+	+	8
Kumra 2007	+	+	8	+	+	8
Lal 2006	+	+	×	+	+	8
McEvoy 2006	+	+	×	-	+	8
Meltzer 2008	+	+	-	+	+	-
Meyer-Lindenberg 1997	+	+	-	+	+	-
Moresco 2004	+	♦	×	+	+	8
Naber 2005	+	+	∞	+	+	8
Rosenheck 1997	-	+	×	+	+	8
Sacchetti 2009	+	+	-	+	+	-
Schooler 2016	-	\bigotimes	×	+	+	8
See 1999	-	-	×	+	+	8
Shaw 2006	+	+	-	+	+	-
Sirota 2006	+	-	-	+	+	-
Tollefson 2001	+	+	-	+	+	-
Volavka 2002	-	+	-	+	+	-
Wahlbeck 2000	+	-	8	+	+	8
Wirshing 1999	+	+	-	+	+	-

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.

Judgement High
Some concerns
Low
No information Not applicable

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.



Older treatment more efficacious than comparison average ← 💛 Newer treatment more efficacious than comparison average

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 \longleftarrow \longrightarrow 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) framework⁸¹ and the official online tool (<u>https://cinema.ispm.unibe.ch/</u>). 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. Withinstudy 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 metaanalysis).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 guideline⁸³ 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 document⁸² 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 evi	dence				
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 Y
Chlorpromazine vs Levomepromazine	1	Major concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low Y
Chlorpromazine vs Olanzapine	1	Some concerns	Low risk		No concerns	Some concerns	No concerns	Moderate ¥
Chlorpromazine vs Ouetiapine	2	Maire concerns	Low risk		Maine concerns.	No concerns	Major concerns	Very low Y
Chlorpromazine vs Ziprasidone	1	Some concerns	Low risk		Some concerns	Some concerns	No concerns	
Clozanine vs Haloneridol	- 5	Maire concare	Low risk		No conceros	Some concerns	No concerns	
Clozapine vs Olanzapine	10	Some concerns	Low risk		Maire margans	No concerns	No concerns	
Clozapine vs Quetiapine	10	Some concerns	Low risk		No concerns	No concerns		
Clozapine vs Queriapine	1	Como concerns	Low risk	No concerns	Como concerno	Come concerns	No concerns	Moderate ~
Clozapine vs Rispendone	0	Some concerns	Low risk	No concerns	Some concerns E	No concerns	No concerns	Low
Closepine vs Ziprasidone	1	Some concerns	LOW TISK	No concerns	and the concerns		NO CONCERNS	Low
Clozapine vs Zotepine	1	Some concerns	Low risk		Major concerns		Major concerns	Very low Y
Fluphenazine vs Haloperidol	2	Major concerns	Low risk		Major concerns			Low V
Fluphenazine vs Quetiapine	1	Major concerns	Low risk		Major concerns			Low V
Fluphenazine vs Risperidone	1	Major concerns	Low risk		Major concerns.	No concerns	No concerns	Low Y
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 Y
Haloperidol vs Risperidone	4	Some concerns	Some concerns	No concerns	Some concerns 🗆	Some concerns	No concerns	Low Y
Olanzapine vs Quetiapine	2	Some concerns 🗆	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate Y
Olanzapine vs Risperidone	4	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low Y
Quetiapine vs Risperidone	2	Some concerns	Low risk	No concerns	Some concerns	Some concerns	No concerns	Low Y
Risperidone vs Sertindole	1	Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low 🖌
			Indirect ev	idence				
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 V
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 Y
Amisulpride vs Sertindole		Some concerns	Low risk	No concerns	Some concerns	Some concerns	Major concerns	Very low Y
Amisulpride vs Ziprasidone		Some concerns	Low risk		Major concerns	No concerns	Major concerns	Very low
Amisulpride vs Zotepine		Some concerns	Low risk		Major concerns	No concerns	Maint concerns	Very low
Chlorpromazine vs Fluphenazine		Maire concurre -	Low risk		Maire concorns		Major concorro	Verylow
Chlorpromazine vs Haloperidol		Some concerns	Low risk		Major concerns		Major concerns	Very low
Chlorpromazine vs Risperidone		Some concerns	Low risk		No concerns	Marce concerns	Maunt concerns	Very low
Chlorpromazine vs Sertindole		Some concerns	Low risk		Maire cruceens	No concerns	Major concorns	Verylow
Chlorpromazine vs Zotenine		Some concerns	Low risk		Maint conserved		Maine concerns	Verylow
Clozapine vs Flunhenazine		Maine	Low rick		Some concerns	Some concerns	Maine	Very low
Clozapine vs evomenromazine		Maine en	Low rick		Maine concerns	No concerns	Maine ex-	
Clozapine vs Sertindolo		Some concerne	Low risk		No concerne	Maure	Maint or	Very low
	-	Some concerns	Low risk		NO CONCEINS			Very low V
Fluphenazine vs Levomepromazine	**		LOW TISK			No concerns	- Major concerns	Very low Y
Fluphenazine vs Olanzapine		Some concerns	LOW TISK		Some concerns	Some concerns	Major concerns	Very low Y
Fuphenazine vs Sertindole		Some concerns	Low risk		wajar cancerns		Major concerns	Very low
Fuphenazine vs Ziprasidone		Some concerns	Low risk				Phagon considering	Very low V
Fluphenazine vs Zotepine		Some concerns	Low risk	No concerns	Major concerns	No concerns	Major concerns	Very low Y
Haloperidol vs Levomepromazine	-	Major concerns	Low risk	No concerns	Major concerns 🗆	No concerns	Major concerns	Very low V
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		With concerns	Low risk		Mappi demonstra		Major concerning	Very low 🖌	1
Levomepromazine vs Sertindole	-	Some concerns	Low risk		Mingen som minis 🗖		thages surround	Very low 💙	1
Levomepromazine vs Ziprasidone	-	Some concerns	Low tisk		Magili sonsannis	No:concerns	Pages same and	Very low 🖌	I
Levomepromazine vs Zotepine	-	Some concerns	Low risk	No concerns	Mages conserved		billion and control of the	Very low 🖌	1
Olanzapine vs Sertindole		Some concerns 🗖	Low risk		Some concerns	Some concerns	Magin concerned 🗖	Very low 🖌	1
Olanzapine vs Ziprasidone	-	Some concerns 🗆	Low risk	No concerns	Mager contourns	No concerns	Mager orthogram	Very low 🖌	1
Olanzapine vs Zotepine		Some concerns 🗆	Low risk		inger somerine 🗆	No concerns	Mager concorring	Very low 🖌	1
Quetiapine vs Sertindole	144	Some concerns 🗖	Low risk		Magar surround		Mallor carlos real	Very low 🖌	I
Quetiapine vs Ziprasidone	-	Some concerns	Low risk		Major amonum	No concerns	Philip Amount	Very low 🖌	1
Quetiapine vs Zotepine	-	Some concerns 🗆	Low risk		Manu commun.		Million characteris	Very low 🖌	1
Risperidone vs Ziprasidone		Some concerns	Low risk	No concerns	Migue conserve.		Migni concernita.	Very low 💙	1
Risperidone vs Zotepine	1	Some concerns 🗆	Low risk		Majul automore.		higher enterents	Very low 🖌	1
Sertindole vs Ziprasidone	22	Some concerns	Low risk		906 manana 🗖	No concerns	Materia contractina 📮	Very low 🖌	1
Sertindole vs Zotepine	-	Some concerns 🗆	Low risk		Magin concernes	No concerns	Matter Streeting	Very low 🖌	1
Ziprasidone vs Zotepine		Some concerns	Low risk	No concerns	man somerin 🗆	No concerns	there conserved	Very low 💙	1

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 questions⁸³ 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.

		Number of studies in each com	parison	Within-study assessment of bias	Across-study assessment of bias	Overall judgement			
	Pairwise comparison	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			
Gro	up 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			

Overall bias of Pairwise Comparisons Table

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	۰
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	٠
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:Trifluonerazine	1 (40)	2 (90)	No bias detected	No bias detected	No bias detected	
27	Quetianine Richeridone	2 (39)	3 (61)	No bias detected	No bias detected	No bias detected	
20	DisperidenceCertindele	1 (216)	1 (015)	No bias detected	No bias detected	No bias detected	-
20		((10)	1 (313)		No bias detected	No bias detected	•
29 Grou	Informazine: Influoperazine	1 (40)	1 (40)	No bias detected +	No bias detected =	No bias detected	
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	•
Grou	ıp 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:7insasidone	NA (NA)	NA (NA)		No bias detected	No bias detected	-
40	Amisulpride:Zotanina				No biss detected	No biss detected	
40	Chlororomazion:Elunbonazion	NA (NA)	NA (NA)		No biss detected	No bias detected	-
40	Chlorpromatine/Cartic-to-to-	NA (NA)	ΝΔ (ΝΔ)		No bias detected	No bias detected	
-15	Chlorpromazine.Serundole		NA (NA)		No bias detected	No biss detected	-
50	Cheerine: Cotepine				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	۰

64	Fluphenazine:Trifluoperazine	NA (NA)	NA (NA)	No bias detected \$	No bias detected	٥
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	٥
67	Haloperidol:Sertindole	NA (NA)	NA (NA)	No bias detected \$	No bias detected	٠
68	Haloperidol:Sulpiride	NA (NA)	NA (NA)	No bias detected 🕈	No bias detected	٥
69	Haloperidol:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected	٥
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	0
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	٥
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	٥
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	٥
81	Levomepromazine:Ziprasidone	NA (NA)	NA (NA)	No bias detected +	No bias detected	٥
82	Levomepromazine:Zotepine	NA (NA)	NA (NA)	No bias detected +	No bias detected	٠
83	Olanzapine:Placebo	NA (NA)	NA (NA)	No bias detected	No bias detected	٥
84	Olanzapine:Sertindole	NA (NA)	NA (NA)	No bias detected +	No bias detected	٥
85	Olanzapine:Sulpiride	NA (NA)	NA (NA)	No bias detected	No bias detected	٠
86	Olanzapine:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected	٥
87	Olanzapine:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected	٥
88	Olanzapine:Ziprasidone	NA (NA)	NA (NA)	No bias detected 🗢	No bias detected	٥
89	Olanzapine:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected	٥
90	Placebo:Quetiapine	NA (NA)	NA (NA)	No bias detected +	No bias detected	٠
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	٥
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	٥
95	Placebo:Zotepine	NA (NA)	NA (NA)	No bias detected	No bias detected	٥
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	٥
98	Quetiapine:Thioridazine	NA (NA)	NA (NA)	No bias detected	No bias detected	0
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	٥
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	٥
104	Risperidone:Trifluoperazine	NA (NA)	NA (NA)	No bias detected \$	No bias detected	٥
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	0
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	٥
109	Sertindole:Trifluoperazine	NA (NA)	NA (NA)	No bias detected	No bias detected	٥
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	٥
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	٥

115 Sulpiride:Zotepine	NA (NA)	NA (NA)	No bias detected \$	No bias detected	0
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	٠
118 Trifluoperazine:Ziprasidone	NA (NA)	NA (NA)	No bias detected \$	No bias detected	٥
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	٥

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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

		% contribution of evidence from pairwise comparisons with suspected bias		Evaluation of contribution from evidence with suspected bias		Bias assessment for	NMA treatment	NMR treatment effect at the smallest	Evaluation of small-study effects		Overall risk of bias	
	NMA esumate	Favouring first treatment	Favouring second treatment	set all to "No substantial contribution"		indirect evidence	effect	observed variance	set all to "No evidence"		calculate overall RoB	
mb	ed/only direct											
1	Amisulpride:Olanzapine	0	0	No substantial contribution from bias	٥		0.23 (-0.42,0.86)	0.3 (-11.2,12.53)	No evidence of small-study effects		Low risk 0	
2	Chlorpromazine:Clozapine	0	1	No substantial contribution from bias	٥		-0.44 (-0.68,-0.19)	-0.52 (-0.91,-0.13)	No evidence of small-study effects		Low risk 0	
3	Chlorpromazine:Levomepromazine	0	0	No substantial contribution from bias	٠		-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	٥		-0.38 (-0.64,-0.1)	-0.5 (-0.93,-0.08)	No evidence of small-study effects		Low risk Ø	
5	Chlorpromazine:Placebo	0	0	No substantial contribution from bias	0		0.52 (-0.18,1.22)	2.75 (-12.97,16.74)	No evidence of small-study effects		Low risk Ø	
6	Chlorpromazine:Quetiapine	0	0	No substantial contribution from bias	0		-0.01 (-0.29,0.26)	0.06 (-0.32,0.44)	No evidence of small-study effects		Low risk 0	
7	Chlorpromazine:Sulpiride	0	0	No substantial contribution from bias	۰		-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	٠	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	•		-0.21 (-0.96,0.53)	-0.56 (+12.07,16.99)	No evidence of small-study effects		Low risk 0	
10	Chlorpromazine:Ziprasidone	0	0	No substantial contribution from bias	•		-0.24 (-0.62,0.15)	0.14 (-0.63,0.97)	No evidence of small-study effects		Low risk 0	
11	Clozapine:Haloperidol	1	0	No substantial contribution from bias	•		0.32 (0.12,0.52)	0.3 (0,0.57)	No evidence of small-study effects		Low risk Ø	
12	Clozapine:Olanzapine	0	0	No substantial contribution from bias	٠		0.05 (-0.11,0.24)	0.02 (+0.23,0.26)	No evidence of small-study effects		Low risk 0	
13	Clozapine:Quetiapine	6	0	No substantial contribution from bias	۰		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	٠		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	۰		0.2 (-0.2,0.59)	0.67 (-0.18,1.53)	No evidence of small-study effects		Low risk Ø	
16	Clozapine:Zotepine	0	0	No substantial contribution from bias	0		0.07	19.23	No evidence of small-study effects		Low risk e	

17	Fluphenazine:Haloperidol	0	0	No substantial contribution from bias 0		-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		0.01 (-0.48,0.49)	-0.01 (-0.98,0.85)	No evidence of small-study effects	0	Low risk	0
19	Fluphenazine:Risperidone	0	12	No substantial contribution from bias \$		-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		-0.26 (-0.46,-0.05)	-0.28 (-0.57,0.01)	No evidence of small-study effects	0	Low risk	0
21	Haloperidol:Quetiapine	0	0	No substantial contribution from bias		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 Risperidor		-0.13	-0.03	No evidence of small-study effects		Some concerns	•
23	Olanzapine:Quetiapine	0	0	No substantial contribution from bias \$		0.37	0.56	No evidence of small-study effects	•	Low risk	•
24	Olanzapine:Risperidone	0	8	No substantial contribution from bias		0.13	0.25	No evidence of small-study effects	0	Low risk	•
25	Placebo:Thioridazine	0	0	No substantial contribution from bias		-0.61	-10.53	No evidence of small-study effects		Low risk	
26	Placebo:Trifluoperazine	0	0	No substantial contribution from bias		-0.73	-1.89	No evidence of small-study effects	•	Law risk	
27	Oustinging Pingeridan	0		No substantial contribution from bios		(-1.51,0.07) -0.23	(-19.76,14.98) -0.31	No evidence of small study effects	•	Law side	
21	Quebapine:Kispendone		a	No substantial contribution from bias		(-0.54,0.09)	(-0.77,0.16) -0.11	No evidence of small-study effects	•	LOW NSK	•
28	Risperidone/Sertindole	0	0	No substantial contribution from bias		(-0.18,0.82)	(-13.58,16.37)	No evidence of small-study effects	•	Low nsk	-
29 indi	Thioridazine:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	(-0.89,0.65)	(-10.26,43.24)	No evidence of small-study effects	•	Low risk	•
30	Chlorpromazine:Haloperidol	0	0	No substantial contribution from bias	No bias detected	-0.12	-0.22	No evidence of small-study effects		Low risk	
31	Chlorpromazine:Risperidone	0	5	No substantial contribution from bias \$	No bias detected	-0.25	-0.25	No evidence of small-study effects	•	Low risk	•
32	Haloperidol:Levomepromazine	0	0	No substantial contribution from bias	No bias detected	-0.57	2.34	No evidence of small-study effects	•	Low risk	•
33	Halmaridal-Disrahn	0	0	No substantial contribution from hias 🔹 🕏	Suspected bias favouring	0.64	(-30.34,18.53)	No evidence of small-study effects		Low risk	-
	help belde Abberrander		•	No substantial contribution from blas	Haloperidol	(-0.14,1.4)	(-12.76,16.94) 0.8	No endence of small study cheeds		Law data	-
34	Amisulpride: Cintanine	0	0	No substantial contribution from bias	No bias detected	(-0.11,1.3) 0.17	(-10.78,13.15) 0.28	No evidence of small-study effects	•	Low risk	÷
	Annaugh national prime	•	•	No substantial contribution from blas	No bias detected	(-0.51,0.83)	(-11.21,12.52) 0.87	No evidence of small-study effects	•	Low risk	-
30	Amisulpride:huphenazine	0	0	No substantial contribution from bias	No bias detected	(-0.22,1.36)	(-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	(-0.2, 1.16)	(-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	(-1.12,0.97)	(-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	(0.13,2.13)	(-17.17,21.78)	No evidence of small-study effects	0	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	0
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	۰	Low risk	۰
42	Amisulpride:Sentindole	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	۰	Low risk	0
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	۰	Low risk	•
44	Amisulpride:Thioridazine	0	0	No substantial contribution from bias 0	No bias detected	0.52 (-0.48,1.49)	-10.29 (-32.01,14.26)	No evidence of small-study effects	0	Low risk	0
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	٠	Low risk	•
46	Amisulpride:Ziprasidone	0	0	No substantial contribution from bias 0	No bias detected	0.37 (-0.42,1.14)	0.92 (-10.64,13.24)	No evidence of small-study effects	۰	Low risk	0
47	Amisulpride:Zotepine	0	0	No substantial contribution from bias	No bias detected	0.24	16.09 (-6.22.50.2)	No evidence of small-study effects	٠	Low risk	•
48	Chlorpromazine:Fluphenazine	0	0	No substantial contribution from bias	No bias detected	-0.02	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	-0.33	No evidence of small-study effects		Low risk	•
50	Chlorpromazine:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.37	18.7	No evidence of small-study effects	•	Low risk	•
51	Clozapine: Fluphenazine	1	0	No substantial contribution from bias +	No bias detected	0.41	0.59	No evidence of small-study effects	•	Low risk	
52	Clozapine Levomeoromazine	1	0	No substantial contribution from bias	No bias detected	-0.25	(-0.24,1.55)	No evidence of small-study effects		Low risk	
53	Clozapine Olacabo	1	0	No substantial contribution from hiss d	No bias datasted	(-1.04,0.54)	(-30.05,18.85) 3.32	No evidence of small-study effects	•	Low sitk	
54	Clozanine:Sertioriole	0		No substantial contribution from bias	No bias detected	(0.2, 1.7) 0.51	(-12.44,17.2) 0.3	No evidence of small-study effects		Low risk	-
	ClassicsCubida	1	0	No substantial contribution from bios	No biss datasted	(-0.02,1.05)	(-13.31,16.66) 5.35	No oridance of small study effects		Les site	
					No bias detected	(-0.68,0.66)	(-19.55,20.88) -6.98	No evidence of small-study effects	•	LOWINSK	-
20			0	No substantial contribution from bias	No bias detected	(-0.4, 1.09)	(-32.74,6.98) -0.04	No evidence of small-study effects	•	sow risk	-
57	Gozapine:Trifluoperazine		0	No substantial contribution from bias	No bias detected	(-0.56,1)	(-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	(+1.58,0.24)	(-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	(-0.8,0.1)	(-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	(-0.32,1.39)	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	۰	Low risk	۰
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	0	Low risk	0
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	0
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	0
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	٠	Low risk	٠
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	0	Low risk	0
67	Haloperidol/Sertindole	0	0	No substantial contribution from bias Ø	No bias detected	0.19 (-0.35,0.74)	-0.11 (-13.58,16.37)	No evidence of small-study effects	•	Low risk	0
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	0
69	Haloperidol:Thioridazine	0	0	No substantial contribution from bias	No bias detected	0.03	-7.27 (-33.01,6.69)	No evidence of small-study effects	۰	Low risk	•
70	Haloperidol:Trifluoperazine	0	0	No substantial contribution from bias	No bias detected	-0.08	-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	0.37	No evidence of small-study effects	•	Low risk	•
72	Haloperidol:Zotepine	0	0	No substantial contribution from bias	No bias detected	-0.25	18.9	No evidence of small-study effects	•	Low risk	•
-						(+0.97,0.48)	(4-41,58.42)				

Normal Name Normal Normal </th <th>73 Levomepromazine:Olanzapine</th> <th>0</th> <th>0</th> <th>No substantial contribution from bias</th> <th>•</th> <th>No bias detected</th> <th>0.31 (-0.5,1.12)</th> <th>-2.63 (-18.83,30.07)</th> <th>No evidence of small-study effects</th> <th>0</th> <th>Low risk</th> <th>0</th>	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	0	Low risk	0
Normal	74 Levomepromazine:Placebo	0	0	No substantial contribution from bias	٥	No bias detected	1.21 (0.18,2.24)	3.11 (-29.49,38.91)	No evidence of small-study effects	0	Low risk	0
Normal	75 Levomepromazine:Quetiapine	0	0	No substantial contribution from bias	٠	No bias detected	0.67 (-0.14, 1.49)	-2.02 (-18.23,30.62)	No evidence of small-study effects	٠	Low risk	٠
n n	76 Levomepromazine:Risperidone	0	4	No substantial contribution from bias	٥	No bias detected	0.44 (-0.38,1.26)	-2.33 (-18.52,30.33)	No evidence of small-study effects	0	Low risk	0
No. No. <td>77 Levomepromazine:Sertindole</td> <td>0</td> <td>0</td> <td>No substantial contribution from bias</td> <td>•</td> <td>No bias detected</td> <td>0.76 (-0.19,1.71)</td> <td>-1.48 (-27.81,47.5)</td> <td>No evidence of small-study effects</td> <td></td> <td>Low risk</td> <td>•</td>	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	•
No Normal Mathematical Matematical Mathematical Matematical Mathematical Mathemati	78 Levomepromazine:Sulpiride	0	0	No substantial contribution from bias	0	No bias detected	0.26 (-0.75,1.22)	2.49 (-28.06,35.97)	No evidence of small-study effects	0	Low risk	0
i i	79 Levomepromazine:Thioridazine	0	0	No substantial contribution from bias	٠	No bias detected	0.6 (-0.43, 1.63)	-11.66 (-44.06,31.09)	No evidence of small-study effects	٠	Low risk	•
b impact and set of the se	80 Levomepromazine:Trifluoperazine	0	0	No substantial contribution from bias	٠	No bias detected	0.49 (-0.61, 1.54)	-2.32 (-29.18,46.82)	No evidence of small-study effects	۰	Low risk	•
Participant Participant <	81 Levomepromazine:Ziprasidone	0	0	No substantial contribution from bias	٠	No bias detected	0.45	-1.82 (-18.2.30.58)	No evidence of small-study effects		Low risk	
Bayeshan	82 Levomepromazine:Zotepine	0	0	No substantial contribution from bias		No bias detected	0.32	15.02 (-0.76.68.05)	No evidence of small-study effects	0	Low risk	0
Appendix Appendix <th< td=""><td>83 Olanzapine:Placebo</td><td>0</td><td>0</td><td>No substantial contribution from bias</td><td>•</td><td>No bias detected</td><td>0.9 (0.13.1.65)</td><td>3.3 (-12.47.17.17)</td><td>No evidence of small-study effects</td><td></td><td>Low risk</td><td></td></th<>	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	
Massach	84 Olanzapine:Sertindole	0	0	No substantial contribution from bias	٠	No bias detected	0.45	0.27 (-13.31.16.64)	No evidence of small-study effects	٠	Low risk	•
American American <th< td=""><td>85 Olanzapine:Sulpiride</td><td>0</td><td>0</td><td>No substantial contribution from bias</td><td>•</td><td>No bias detected</td><td>-0.06</td><td>534</td><td>No evidence of small-study effects</td><td></td><td>Low risk</td><td>•</td></th<>	85 Olanzapine:Sulpiride	0	0	No substantial contribution from bias	•	No bias detected	-0.06	534	No evidence of small-study effects		Low risk	•
Disputique Control Contro Control <thcontrol< th=""> <</thcontrol<>	86 Olanzapine:Thioridazine	0	0	No substantial contribution from bias	•	No bias detected	0.29	-7 (.32.74.6.06)	No evidence of small-study effects		Low risk	•
Image: Another interpretation of the second of th	87 Olanzapine:Trifluoperazine	0	0	No substantial contribution from bias		No bias detected	0.17	-0.06	No evidence of small-study effects		Low risk	•
Amplitude <	88 Olanzapine:Ziprasidone	0	0	No substantial contribution from bias	•	No bias detected	0.14	0.65	No evidence of small-study effects	•	Low risk	•
International (1) Internation (1) Internat	89 Olanzapine:Zotepine	Ó	0	No substantial contribution from bias	•	No bias detected	0.01	(-0.21, 1.52)	No evidence of small-study effects	•	Low risk	
National Action National A	90 Placebo-Quetianine	0	0	No substantial contribution from bias	•	No bias detected	(-0.71,0.71) -0.54	-2.66	No evidence of small-study effects		Low risk	
Notice of the second	91 PlaceborRisseridone	0	3	No substantial contribution from bias	•	No bias detected	(-1.29,0.22) -0.77	(-16.66,13.01) -3.07	No evidence of small-study effects	•	Low ritk	-
Maintana	03 Reselve feetindele		0	No substantial contribution from bios		No bios detected	(-1.53,0.01) -0.45	(-16.93,12.68) -3.11	No evidence of small study effects		Law side	-
m m	22 Placebolsertinosie	0			•	No bias detected	-0.96	(-11.77,9.66) 3.06	No evidence of small-study effects	•	LOW PISK	
m minute	93 Macebosupinde	0	0	No substantial contribution from bias	•	No bias detected	(-1.89,-0.02)	(-33.35,28.42) -2.47	No evidence of small-study effects	-	Low risk	-
> Maximum 0 Maximum Maximum <	94 Placeboi/prasidone			No substantial contribution from bias	•	No bias detected	(-1.56,0.03) -0.88	(-16.59,13.15)	No evidence of small-study effects	•	Low risk	•
a bit added added bases bit added added bases bit added added bases disk ad	95 PlaceboiZotepine	0	0	No substantial contribution from bias	•	No bias detected	(-1.91,0.13)	(-4.89,42.48) -0.44	No evidence of small-study effects	•	Low risk	•
interconduction intercondu	96 Quetiapine:Sertindole	0	0	No substantial contribution from bias	•	No bias detected	(-0.5,0.68)	(-13.91,16.13)	No evidence of small-study effects	•	Low risk	•
i is independence	97 Quetiapine:Sulpiride	0	0	No substantial contribution from bias	•	No bias detected	(-1.12,0.24)	(-20.11,20.23)	No evidence of small-study effects	•	Low risk	•
0 0 <td>98 Quetiapine:Thioridazine</td> <td>0</td> <td>0</td> <td>No substantial contribution from bias</td> <td>•</td> <td>No bias detected</td> <td>(-0.82,0.68)</td> <td>(-33.35,6.44)</td> <td>No evidence of small-study effects</td> <td>•</td> <td>Low risk</td> <td>•</td>	98 Quetiapine:Thioridazine	0	0	No substantial contribution from bias	•	No bias detected	(-0.82,0.68)	(-33.35,6.44)	No evidence of small-study effects	•	Low risk	•
100 100 <td>99 Quetiapine:Trifluoperazine</td> <td>0</td> <td>0</td> <td>No substantial contribution from bias</td> <td>•</td> <td>No bias detected</td> <td>(-0.99,0.59)</td> <td>(-12.15,16.91)</td> <td>No evidence of small-study effects</td> <td>•</td> <td>Low risk</td> <td>•</td>	99 Quetiapine:Trifluoperazine	0	0	No substantial contribution from bias	•	No bias detected	(-0.99,0.59)	(-12.15,16.91)	No evidence of small-study effects	•	Low risk	•
10 designed damps 0 0 Notes detected 173 mail 173 mai	100 Quetiapine:Ziprasidone	0	0	No substantial contribution from bias	•	No bias detected	(-0.67,0.22)	(-0.75,0.93)	No evidence of small-study effects	•	Low risk	•
101 Rperdare-Sayore 4 6 Restantion comband on the law Note stered Company Press association Restantion comband on the law Restantion comband on the l	101 Quetiapine:Zotepine	0	0	No substantial contribution from bias	•	No bias detected	-0.30 (-1.11,0.4)	(1.96,38.21)	No evidence of small-study effects	•	Low risk	•
101 Reperties/Entroder 3 0 No state state is No bia detect No	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	۰
101 Repartment 3 0 No subtract distribution from basis No bias detected 0 No bias detected <td>103 Risperidone:Thioridazine</td> <td>3</td> <td>0</td> <td>No substantial contribution from bias</td> <td>•</td> <td>No bias detected</td> <td>(-0.61,0.93)</td> <td>-7.25 (-33.02,6.66)</td> <td>No evidence of small-study effects</td> <td>•</td> <td>Low risk</td> <td>•</td>	103 Risperidone:Thioridazine	3	0	No substantial contribution from bias	•	No bias detected	(-0.61,0.93)	-7.25 (-33.02,6.66)	No evidence of small-study effects	•	Low risk	•
101 Reparatore 4 0 Roustand combination from bias No bias detected One of the statement o	104 Risperidone:Trifluoperazine	3	0	No substantial contribution from bias	۰	No bias detected	(-0.76,0.83)	-0.33 (-11.85,17.24)	No evidence of small-study effects	•	Low risk	۰
101 Rugarizand/Categorie 5 0 No statistical contribution from bias No bias detected 101/2 (22,35,4m) No or odden contribution from No Isoland 102/2 (22,35,4m) No or odden contribution from Isoland 101/2 (22,35,4m) No or odden contribution from Isoland No bias detected 101/2 (22,35,4m) No or odden contribution from Isoland No bias detected 101/2 (22,35,4m) No or odden contribution from Isoland No bias detected 101/2 (22,35,4m) No or odden contribution from Isoland No bias detected 101/2 (22,35,4m) No or odden contribution from No	105 Risperidone:Ziprasidone	4	0	No substantial contribution from bias	0	No bias detected	(-0.42,0.44)	0.4 (-0.47,1.28)	No evidence of small-study effects		Low risk	•
107 Serindele Ziporide 0 No bias detected A31 (272)224281 No bias detected A31 (272)22481 No bias detected A31 (272)255553 No bias detected A31 (272)55553 No bias detected A31 (272)55553 No bias detected A31 (272)55553 No bias detected A31 (272)55553 No bias detected A31 (272)5553 No bias detected A31 (242)600 No bias detected A31 (242)600 No bias detected A31 (242)600 A44 (151)240 No bias detected A31 (242)600 No bias detected A31 (242)600 A44 (151)240 No bias detected A31 (242)600 A44 (151)240 No bias detected A31 (242)210 A32 (252)2137 No bias detected A31 (242)210 A32 (252)2137 No bias detected A31 (242)210 A32 (242)2121 No bias detected A31 (242)210 A32 (242)213 No bias detected A31 (242)210 A32 (242)2137 No bias detected A31 (242)211 A32 (242)2137 No bias detected A31 (242)211 A32 (242)2137 No bias detected A31 (242)231 No bias dete	106 Risperidone:Zotepine	5	0	No substantial contribution from bias	0	No bias detected	-0.12 (-0.84,0.6)	18.94 (2.28,38.44)	No evidence of small-study effects	0	Low risk	0
101 Serindale/Triologenzine 0 0 No bial detected -0.07 (-0.77)(-0.17) No bial detected -0.07 (-0.77)(-0.77) No bial detected -0.07 (-0.77)(-0.7) No bial detected	107 Sertindale:Sulpiride	0	0	No substantial contribution from bias	0	No bias detected	-0.51 (-1.37,0.34)	2.42 (-27.3,28.68)	No evidence of small-study effects	0	Low risk	0
10 Sentidale Trifuggerative 0 No bias detected 127 127 (21.008) 124.20 127 (21.008) No bias detected 127 121.2008) No bias detected 127 121.2008) No bias detected 121.2008 (20.71.2008)	108 Sertindole:Thioridazine	0	0	No substantial contribution from bias	٥	No bias detected	-0.16 (-1.07,0.74)	-10.47 (-27.35,6.25)	No evidence of small-study effects	•	Low risk	٥
110 SerindeleZpesidore 0 0 No bas detected 101 041 041 044 (No bas No bas detected 10070,040 No bas detected 10070,040 No bas detected 1040 No bas detected 1040 1060,0040 No bas detected 1040 1040,0040 No bas detected 1040 1040,0040 No bas detected 1040,0040 1040,0040 No bas detected 1040,0040 1040,0040 1060,0040 1060,0040 1060,0040 1060,0040 1060,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040 1040,0040,000 1040,0040,000 1040,0040,000 1040,0040,000 1040,0040,000	109 Sertindole:Trifluoperazine	0	0	No substantial contribution from bias	0	No bias detected	-0.27 (+1.23,0.65)	-2.42 (-17.33,20.82)	No evidence of small-study effects	•	Low risk	٥
111 Seried decide 0.44 15.04	110 Sertindole:Ziprasidone	0	0	No substantial contribution from bias	0	No bias detected	-0.31 (-0.97,0.34)	0.44 (-16.1,14.03)	No evidence of small-study effects	0	Low risk	0
112 Supirise Thronisation 0 0 No bias detected 033 (137,128) -400 (137,128) No bias detected 033 (137,128) No bias detected 031 (137,128) No bias detected 031 (147,128) No bias detected 031 (140,138) No b	111 Sertindole:Zotepine	0	0	No substantial contribution from bias	٥	No bias detected	-0.44 (-1.31,0.44)	16.69 (0.81,44.14)	No evidence of small-study effects	0	Low risk	•
13 Supirida 0 No basideteridad contribution from bias No basideteridad 023 (27252137) No evidence of small-study effect. Icon risk	112 Sulpiride:Thioridazine	0	0	No substantial contribution from bias	0	No bias detected	0.35 (-0.59,1.28)	-4.08 (-51.87,16.98)	No evidence of small-study effects	0	Low risk	0
114 SoprisdezZepresidene 0 0 No basidetendal contribution from bias No basidetendal 172 (200,000) 172 (200,000) No evidence of small-study effect. 0 Low risk Low ris	113 Sulpiride:Trifluoperazine	0	0	No substantial contribution from bias	0	No bias detected	0.23 (+0.73,1.21)	-3.22 (-27.25,21.37)	No evidence of small-study effects	0	Low risk	0
115 SubjickeZitepine 0 No loss detected 007 (493,00) 17.35 (493,00) No evidence of small-study effects Icor risk 116 TrickstaineZitepine 0 0 No substantial contribution from bias No bias detected -0.5 (493,00) 7.59 (493,00) No evidence of small-study effects Icor risk Icor risk 117 TrickstaineZitepine 0 0 No substantial contribution from bias No bias detected -0.35 (493,00) 7.59 (493,00) No evidence of small-study effects Icor risk Icor risk 117 TrinkstaineZitepine 0 0 No substantial contribution from bias No bias detected -0.35 (493,00) 7.59 (197,051) No evidence of small-study effects Icor risk 118 TrifkognezineZitepine 0 0 No substantial contribution from bias No bias detected -0.45 (493,00) 7.64,412,33 No evidence of small-study effects Icor risk 118 TrifkognezineZitepine 0 0 No substantial contribution from bias No bias detected -0.45 (423,02) 7.64,423,33 No evidence of small-study effects Icor risk 119 TrifkognezineZitepine 0 0 No substantial contribution from bias No bias detected -0.41 (423,02) 16,42,43,43 No evidence of small-stud	114 Sulpiride:Ziprasidone	0	0	No substantial contribution from bias	٠	No bias detected	0.2 (-0.52,0.95)	-4.77 (-20.06,20.08)	No evidence of small-study effects	٠	Low risk	۰
116 This detected -0.15 7.95 No evidence of small-subcy effects Icor risk • 117 This detected -0.15 7.95 (32.33.5) No evidence of small-subcy effects • Icor risk Icor risk • Icor risk Icor risk Icor risk Icor risk Icor risk Icor risk	115 Sulpiride:Zotepine	0	0	No substantial contribution from bias	۰	No bias detected	0.07 (+0.88,1.03)	17.35 (-4.05,38.2)	No evidence of small-study effects	•	Low risk	•
117 This detected -0.8 -0.8 239 No evidence of small-study effects Iou mail Iou mail </td <td>116 Thioridazine:Ziprasidone</td> <td>0</td> <td>0</td> <td>No substantial contribution from bias</td> <td>٥</td> <td>No bias detected</td> <td>-0.15 (-0.95,0.65)</td> <td>7.59 (-6.32,33.5)</td> <td>No evidence of small-study effects</td> <td>0</td> <td>Low risk</td> <td>0</td>	116 Thioridazine:Ziprasidone	0	0	No substantial contribution from bias	٥	No bias detected	-0.15 (-0.95,0.65)	7.59 (-6.32,33.5)	No evidence of small-study effects	0	Low risk	0
118 TrifluoperazineZiperaidone 0 0 No substantial contribution from bias No bias detected ^{0,05} (644,081) ^{0,17} (1644,12.24) No evidence of small-study effects (or risk e) Iou risk e) Lou risk Lou risk Lou risk Lou risk Lou risk Lou risk	117 Thioridazine:Zotepine	0	0	No substantial contribution from bias	0	No bias detected	-0.28 (-1.29,0.73)	23.59 (0.77,69.11)	No evidence of small-study effects	•	Low risk	•
119 TrillaperazineZotepine 0 0 No substantial contribution from bias No bias detected -0.16 (±12.048) 19.46 (±43.07) No evidence of small-study effects Icou risk • 120 ZprasidoneZotepine 0 0 No substantial contribution from bias • No bias detected -0.13 (±43.056) 18.43 (±43.056) No evidence of small-study effects • Low risk •	118 Trifluoperazine:Ziprasidone	0	0	No substantial contribution from bias	0	No bias detected	-0.03 (-0.84,0.81)	0.7 (-16.84,12.34)	No evidence of small-study effects	•	Low risk	0
120 ZpraśdoneZotepine 0 0 No substantial contribution from bias • No bias detected (432,066) (183,38.15) No evidence of small-study effects • Low risk •	119 Trifluoperazine:Zotepine	0	0	No substantial contribution from bias	0	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	0	No bias detected	-0.13 (-0.92,0.66)	18.43 (1.83,38.15)	No evidence of small-study effects	0	Low risk	0

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