SUPPLEMENTARY APPENDIX

Antipsychotic-Induced Weight Gain: Dose-Response Meta-Analysis of Randomized Controlled Trials

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Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
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Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4,5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, Appendix4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4, 5

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Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5,6
RESULTS			
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Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, Appendix 7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Not applicable
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-13, Appendix 8-9,11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix 12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12, Appendix 10,13
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15,16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2: PROSPERO registration and protocol

Registration number: CRD42020181467

Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181467

PROTOCOL

Citation

Stefan Leucht, Tasnim Hamza, Spyridon Siafis, Hui Wu, Johannes Schneider-Thoma, John Davis. Dose- response meta-analysis of the efficacy and side-effects of antipsychotic drugs in schizophrenia. PROSPERO 2020 CRD42020181467 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181

Review question

Antipsychotic drugs are efficacious for the treatment of schizophrenia, but they are associated with many side-effects. It is, however, unclear what is the maximally effective dose of each antipsychotic. It is also unclear which side-effects are associated with antipsychotic dose and how these dose versus side-effect relationships look like for each drug. We aim to fill this gap by dose-response meta-analysis of randomized controlled trials. Seven separate publications on overall efficacy and six important side-effects are planned, one for each primary outcome, i.e. 1) overall efficacy, 2) weight gain, 3) extrapyramidal side-effects, 4) prolactin increase, 5) QTc prolongation, 6) sedation, 7) dropouts due to any reason.

This PROSPERO protocol and its registration ID number pertain to the last four planned publications and not to the publications on overall efficacy, weight gain and extrapyramidal side-effects, since data extraction for these outcomes had been started before submission of the protocol. These outcomes are also presented in this protocol, because similar methodology will be followed.

Searches

1. Electronic databases: We will search the Cochrane Schizophrenia Group's Study-Based Register of Trials with the following strategy: (*Amisulpride Dosage* OR *Aripiprazole Dosage* OR *Asenapine Dosage* OR *Brexpiprazole Dosage* OR *Cariprazine Dosage* OR *Clozapine Dosage* OR *Haloperidol Decanoate Dosage* OR *Haloperidol Dosage* OR *Iloperidone Dosage* OR *Lumateperone Dosage* OR *Lurasidone Dosage* OR *Olanzapine Dosage* OR *Paliperidone Dosage* OR *Paliperidone Palmitate Dosage* OR *Quetiapine Dosage* OR *Risperidone Dosage* OR *Sertindole Dosage* OR *Ziprasidone Dosage* OR *Zotepine Dosage*) in Pairwise Comparison Field of Study Records.

2. Previous reviews: Our search will be mainly based on our previous dose-response meta-analysis on the efficacy of antipsychotic drugs (Leucht et al. Am J Psychiatry 2020;177:342-53)

and on our network meta-analysis about the acute effects of antipsychotics in general (Huhn et al. Lancet 2019;394:939-51). For both reviews exhaustive searches had been undertaken.

3. Reference searching: Reference lists of newly included records will be hand-searched for potentially relevant studies.

4. We will contact authors or pharmaceutical companies for missing data of studies published from 1990 onward. We expect most of the studies have been conducted by pharmaceutical companies who hold the data.

5. There will be no language restriction for the search. Studies from mainland China will be excluded due to quality issues in many of these studies (Tong et al. BMC Med Res Methodol 2018;18:96). Studies conducted in China by international companies will be accepted.

There will be no date/time, language, document type, and publication status limitations. All publications will be selected independently by at least two reviewers. In case of doubt, a third reviewer will be involved. If this procedure does not lead to resolution of the issue, the study authors will be contacted.

Types of study to be included

- Open and blinded RCTs which compared at least two fixed doses of an antipsychotic. Studies which compared one fixed-dose of an antipsychotic with placebo will also be included.

- Only the first phase of cross-over studies will be used to avoid carry-over effects (Elbourne et al. Int J Epidemiol 2002;31:140-9).

- Cluster-randomized-trials will be excluded due to their unit-of-analysis-problems (Whiting-O'Keefe et al. Med Care 1984;22:1101-14).

- Studies with a high risk of bias in terms of randomization according the Cochrane risk of bias tool will be excluded.

- The minimum study duration will be three weeks. There will be no a priori defined maximum duration as long as the patients were acutely ill at the start. The rationale is that special populations, in particular people with predominant negative symptoms, or studies on long-acting injectable medication (LAI) need longer trials.

- Studies in stable patients (study defined) on relapse prevention will be excluded.

Condition or domain being studied

Schizophrenia and schizophrenia-related disorders

Participants/population

- Participants with a diagnosis of schizophrenia or schizophrenia-related disorders, e.g. schizophreniform or schizoaffective disorders, as defined by any criteria, Studies with a maximum of 20% of participants with other diagnoses are allowed.

- Studies in participants with predominant negative symptoms (Krause et al. Eur Arch Psychiatry Clin Neurosci 2018;268:625-39), first-episode of schizophrenia (Oosthuizen et al. Int J Neuropsychopharmacol 2004;7:125-31), in children/adolescents (Krause et al. Eur Neuropsychopharmacol 2018;28:659-74) and in elderly patients (Krause et al. Eur Neuropsychopharmacol 2019;29:1003-22) will be analysed separately, because there is evidence that such patients need lower doses and are more vulnerable for side-effects (Schneider-Thoma et al. Lancet Psychiatry 2019;6:753-65). Studies in participants in treatment-resistant illness (study-defined) will be analysed together with the main group "general people with schizophrenia", because there is no clear evidence that the dose effects of antipsychotics differ based on these characteristics (Samara et al. Cochrane Database Syst Rev 2018;5:CD011883), but they will be excluded in a sensitivity analysis.

- Studies in stable patients (relapse prevention studies) will be excluded. Their inclusion would lead to methodological and clinical heterogeneity (e.g. duration is longer and patients are pretreated).

- No other restriction in terms of setting, gender, nationality and ethnicity.

Intervention(s), exposure(s)

- The following antipsychotics in monotherapy: amisulpride, aripiprazole (oral and depot), asenapine (oral and transdermal), brexpiprazole, cariprazine, clozapine, haloperidol (oral and depot), iloperidone, lumateperone, lurasidone, olanzapine (oral and depot), quetiapine, paliperidone (oral and depot), risperidone (oral and depot), sertindole, ziprasidone, zotepine. This selection comprises all so-called second-generation antipsychotics available in Europe and/or the US. Haloperidol was added as a "gold standard" antipsychotic.

- There will be no restriction in terms of route of administration (except for short-acting injections that are used for acute agitation). Antipsychotic compounds given via different route of administration will be considered as separate compounds. For example, oral aripiprazole, aripiprazole maintena and aripiprazole lauroxil will be considered as three separate antipsychotic interventions. In a similar vein for oral asenapine/transdermal asenapine, oral paliperidone/paliperidone depot once monthly, risperidone/risperidone consta/risperidone RBP-7000, olanzapine/olanzapine depot.

- Immediate and extended release formulations of the same antipsychotic (for example quetiapine) will be considered as the same intervention in the main analysis, but they will be analyzed separately in a sensitivity analysis.

- Fixed-dose schedules, and studies in which patients are randomised to different, narrow fixed dose range, for example olanzapine 5mg/day +/- 2.5 mg/day versus olanzapine 10mg/day +/- 2.5mg/day. Flexible-dosing schedules will not be eligible.

Comparator(s)/control

Placebo will be used as the reference in the analyses.

Main outcome(s)

We plan seven separate publications one on overall efficacy and six which focus on different side-effects.

Primary outcomes of each planned review:

1. Overall efficacy:* PANSS total score (Kay and Fiszbein Schizophr Bull 1987;13:261-75) or BPRS (Overall and Gorham Psychol Rep 1962;10:790-812) or if not available any other rating scale on the overall symptoms of schizophrenia.

2. Weight gain:* Weight change (in kg) from baseline to endpoint (continuous outcome). If not available, the mean maximum change from baseline to endpoint will be accepted.

3. Extrapyramidal side effects (EPS):* Mean scores of validated scales to measure EPS. The SAS (Simpson and Angus Acta Psychiatr Scand Suppl 1970;212:11-9) will be preferred to the ESRS (Chouinard Can J Neurol Sci 1980;7:233-44), if available.

4. Mean prolactin increase (in ng/ml)

5. Mean QTc prolongation (in msec)

6. Sedation

7. Drop out due to any reason (all-cause discontinuation). This outcome is a measure of effectiveness, because it comprises dropouts due to adverse events, inefficacy and others.

Outcomes will be measured at study endpoint.

*The PROSPERO protocol does not pertain to the publication of these outcomes, since their data extraction has started before submission of the protocol.

*** Measures of effect**

Weight, prolactin and QTc will be analysed with the mean difference (MD), Efficacy and extrapyramidal sideeffects will be analysed with the standardized mean difference (SMD). The other outcomes are dichotomous outcomes which will be analysed with odds ratios. Also see section ‘strategy for data synthesis’.

For continuous rating scales we will prefer the mean change from baseline to endpoint of these scales over the at endpoint values, if available. Moreover, we will always prefer the broadest scores of rating scales. E.g. for the ESRS scale, we prefer the ESRS total score to the score composed of the subscores of parkinsonism, dystonia and dyskinesia. If those are not available, we will accept the parkinsonism subscore of the ESRS.

Additional outcome(s)

The following secondary outcomes will be analysed in the six separate reviews.

1. Overall efficacy: none.

2. Weight gain:*

- Number of participants with weight (>=7% change from baseline will be preferred, but any study-definition will be eligible, dichotomous outcome).

3. Extrapyramidal side effects (EPS):*

- The number of participants with at least one extrapyramidal side-effect. If not available, the number of participants with 'extrapyramidal disorder' (study defined) will be extracted. If neither of these outcomes is available, the number of participants with increased SAS/ESRS score will be extracted.

- The number of participants who received antiparkinson medication at least once.

- The mean change of the total scores of validated scales to measure akathisia from baseline to endpoint or, if not available, the mean endpoint values of these scales. The Barnes Akathisia Scale (BAS, Barnes Br J Psychiatry 1989;154:672-6) will be preferred to other scales, if available. The BAS total score will be preferred to the BAS global score, because the latter is a more subjective score.

- The number of participants with akathisia. If this outcome is not reported as an adverse event, the number of participants with increased BAS score will be extracted.

4. Prolactin:

- The number of participants with prolactin increase (study defined)

5. QTc prolongation

- The number of participants with QTc prolongation (study defined, but if available > 470msec for women and > 450msec for men)

6. We do not plan secondary outcomes for the reviews on sedation and on drop-out due to any reason.

Outcomes will be measured at study endpoint.

*The PROSPERO protocol does not pertain to the publication of these outcomes, since their data extraction has started before submission of the protocol.

*** Measures of effect**

Except the akathisia scores which will be analyzed using standardized mean differences (SMD), all other outcomes are dichotomous for which odds ratios will be use as measures of effect. Also see section 'strategy for data synthesis'.

Data extraction (selection and coding)

1. Selection of trials: At least two reviewers will independently inspect the titles and abstracts of nonduplicated references identified through the search and will exclude those not pertinent. Discrepancies between the two reviewers will be resolved by discussion reaching consensus. If doubts still remain, the full text will be obtained and eligibility will be assessed. Full texts of included references will be obtained and independently assessed by two reviewers for eligibility.

Again, disagreements will be resolved by discussion and, if needed, a third author will be involved. When required, further information will be requested from study authors.

2. Data extraction: Two authors will independently extract data from all selected trials in a Microsoft Access database. When disagreement arises, we will resolve it by discussion and, if needed, involving a third senior author. Where this is not sufficient, we will contact the study authors.

- For continuous outcomes, we will prefer change scores to follow-up data, but we will also accept the latter when the former are not available.

- When authors of original studies used imputation methods to handle missing data, we will prefer them to completers' data. Furthermore, data based on mixed-models of repeated measurement (MMRM), multiple imputation will be preferred over last-observation carried forward (LOCF), if available.

- For dichotomous outcomes, if only completer analyses are presented, we will assume that participants lost to follow-up did not have the outcome. We think that another assumption would overestimate the risk.

- Missing SDs will be calculated from 1) standard error (SE), 2) other measures of variability (95%

confidence intervals, ranges etc), 3) test statistics 4) imputed from the SDs of the other studies using a validated method (Furukawa et al. J Clin Epidemiol 2006;59:7-10) according to the Cochrane Handbook (Higgins and Green 2011).

Risk of bias (quality) assessment

Two independent review authors will assess the risk of bias in the selected studies using the 'Cochrane Collaboration risk of bias' tool. When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author.

Strategy for data synthesis

- The effect sizes for continuous outcomes will be the mean difference (MD), if possible, because this measure can be interpreted more easily by clinicians. To use MD will be possible for weight (in kg), prolactin increase (ng/ml) and QTc prolongation (msec). For other outcomes such as rating scales for overall efficacy or EPS we will use the standardized mean difference (SMD as Hedges' g), because we expect that various EPS scales have been used in the studies. The effect sizes for dichotomous outcomes will be the odds ratio (OR). All effect sizes will be accompanied by their 95% confidence intervals.

- We will conduct a one-stage dose response meta-analysis in a frequentist framework using restricted-cubic splines with the R package 'dosresmeta' developed by (Crippa and Orsini BMC Med Res Methodol 2016;16:91, Crippa et al. Stat Methods Med Res 2019;28:1579-96). We will use knot points at the 25th, 50th and 75th percentile.

- For the outcome overall efficacy we will try to identify the 95% effective doses (ED95) as we did in our previous dose-response meta-analysis (Leucht et al. Am J Psychiatry 2020;177:342-53).

- We will produce absolute dose-response curves: we will synthesize the effects in the placebo arms and we will transform the relative dose-response curves estimated in previous steps to absolute curves.

- For drugs with enough data we will use the Wald statistic to explore whether there is evidence of an overall dose-response relationship and we will report the p-values.

- Small study effects and the possibility of publication bias will be assessed with funnel plots and Egger's test for each antipsychotic, when there are at least 10 studies available.

Analysis of subgroups or subsets

Overall efficacy: We will primarily analyse each antipsychotic separately. As there are no major efficacy differences between antipsychotics, we will also pool all antipsychotics after converting their doses to risperidone equivalents based on two criteria: a) a "scientific" criterion using dose-equivalence based on 95% Effective Doses (Leucht et al. Am J Psychiatry 2020;177:342-53), if a dose-equivalence is not available for a drug the Minimum-Effective-Dose-Method (Leucht et al. Schizophr-Bull 2014;40:314-26, Rothe et al. Schizophr-Res 2018;193:23-8), then Classical-Mean-Dose-Method (Leucht et al. Schizophr-Bull 2015;41:1397-402, Davis Arch-Gen-Psychiatry 1976;33:858-61)), Daily-Defined-Dose-Method (Leucht et al. Schizophr Bull 2016;42 Suppl 1:S90-4) and finally the Delphi conference of the International-Consensus-Study-of-Antipsychotic-Dosing (Gardner et al. Am-J-Psychiatry 2010;167:686-93). b) In a secondary analysis we will convert doses based on "clinical" judgment of experts involved in the International-Consensus-Study-of-Antipsychotic-Dosing (Gardner et al. Am-J-Psychiatry 2010;167:686-93) supplemented by similar judgements by the reviewer team for drugs that were not reported in the consensus statement.

- Side-effects: Antipsychotics differ clearly in their side-effects profiles. Therefore, dose-response analyses will be conducted separately for each antipsychotic drug.

Predefined sensitivity analyses of the primary outcomes will be:

- Exclusion of studies that compared only a single dose of an antipsychotic with placebo. Such studies are no true dose-finding studies. It can be expected that their inclusion will lead to more heterogeneity, because they are different in design.

- Immediate (IR) and extended release (XR) formulations will be analyzed separately (i.e. for quetiapine).

- We will exclude studies in treatment resistant patients (study defined).

- We will exclude open RCTs for subjective outcomes.

Contact details for further information

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Professor John Davis. University of Chicago at Illinois

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

01 March 2020

Anticipated completion date

31 December 2021

Funding sources/sponsors

TH and GS are funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 825162. HW is funded by the Shanghai General Hospital Excellent Young Medical Talents Project B.

Conflicts of interest

In the last 3 years, Stefan Leucht has received honoraria as a consultant/advisor and/or for lectures from LB Pharma, Otsuka, Lundbeck, Boehringer Ingelheim, LTS Lohmann, Janssen, Johnson&Johnson, TEVA, MSD, Sandoz, SanofiAventis, Angelini, Recordati, Sunovion, Geodon Richter.

Yes

Language

English

Country

China, Germany, Switzerland, United States of America

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

05 July 2020

Date of first submission

22 April 2020

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Differences between protocol and review

For the primary outcome we pooled available different formulations for each drug by converting them to oral equivalences to have a more comprehensive interpretation and reported different formulations in sensitivity analyses. Other than that, we performed several more sensitivity analyses to test the robustness of our results from available data, which were analysing standardized mean difference (SMD) as effect size in lurasidone and risperidone LAI (consta) (body mass index (BMI) was reported instead of weight gain in two studies that investigated relatively rare high doses), comparing the pooled data in sertindole FDA review (only from where data of 8mg/d arms were reported) with data from individual studies and investigating dose-response relationship of weight gain rate (weight gain divided by study duration, kg/week).

For the secondary outcome when the numbers of participants with important weight gain not reported, they were imputed from mean scores using a validated imputation method and a cut-off of 7% increase from baseline. We excluded studies with imputed number of patients with

weight gain in sensitivity analyses.

For asenapine and sertindole, knot points at the 10^{th}, 50^{th} and 90^{th} were used, because 25^{th}, 50^{th} and 75^{th} quantiles could not form three unique knot points for these two drugs.

Despite of clinical judgement and visual inspection, we also applied the variance partition coefficient (VPC) across the dose range to quantify heterogeneity.

Appendix 3: Search strategy

Database: Cochrane Schizophrenia Group's Study-Based Register of Trials. Details are also described on the Cochrane Schizophrenia Group's website: https://schizophrenia.cochrane.org/.

Date: 9th March 2020

Strategy: (*Amisulpride Dosage* OR *Aripiprazole Dosage* OR *Asenapine Dosage* OR *Brexpiprazole Dosage* OR *Cariprazine Dosage* OR *Clozapine Dosage* OR *Haloperidol Decanoate Dosage* OR *Haloperidol Dosage* OR *Iloperidone Dosage* OR *Lumateperone Dosage* OR *Lurasidone Dosage* OR *Olanzapine Dosage* OR *Paliperidone Dosage* OR *Paliperidone Palmitate Dosage* OR *Quetiapine Dosage* OR *Risperidone Dosage* OR *Sertindole Dosage* OR *Ziprasidone Dosage* OR *Zotepine Dosage*) in Pairwise Comparison Field of Study Records

Search Results

There were 1249 references from 357 studies.

References to database details

1. Shokraneh, Farhad; Adams, Clive E. Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis. Health Information and Libraries Journal 2020; Accepted

2. Shokraneh, Farhad; Adams, Clive E. Cochrane Schizophrenia Group's Study-Based Register of Randomized Controlled Trials: Development and Content Analysis. Schizophrenia Bulletin Open 2020; Under Review.

3. Shokraneh, Farhad; Adams, Clive E. Study-based registers reduce waste in systematic reviewing: discussion and case report. Systematic Reviews 2019; 8: 129. DOI 10.1186/s13643-019-1035-3

4. Shokraneh, Farhad; Adams, Clive E. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. BioImpacts 2017; 7(4): 209-217. DOI 10.15171/bi.2017.25

Update search in PubMed

Our research group has done a broader update search in PubMed, which we have used and adapted to this project

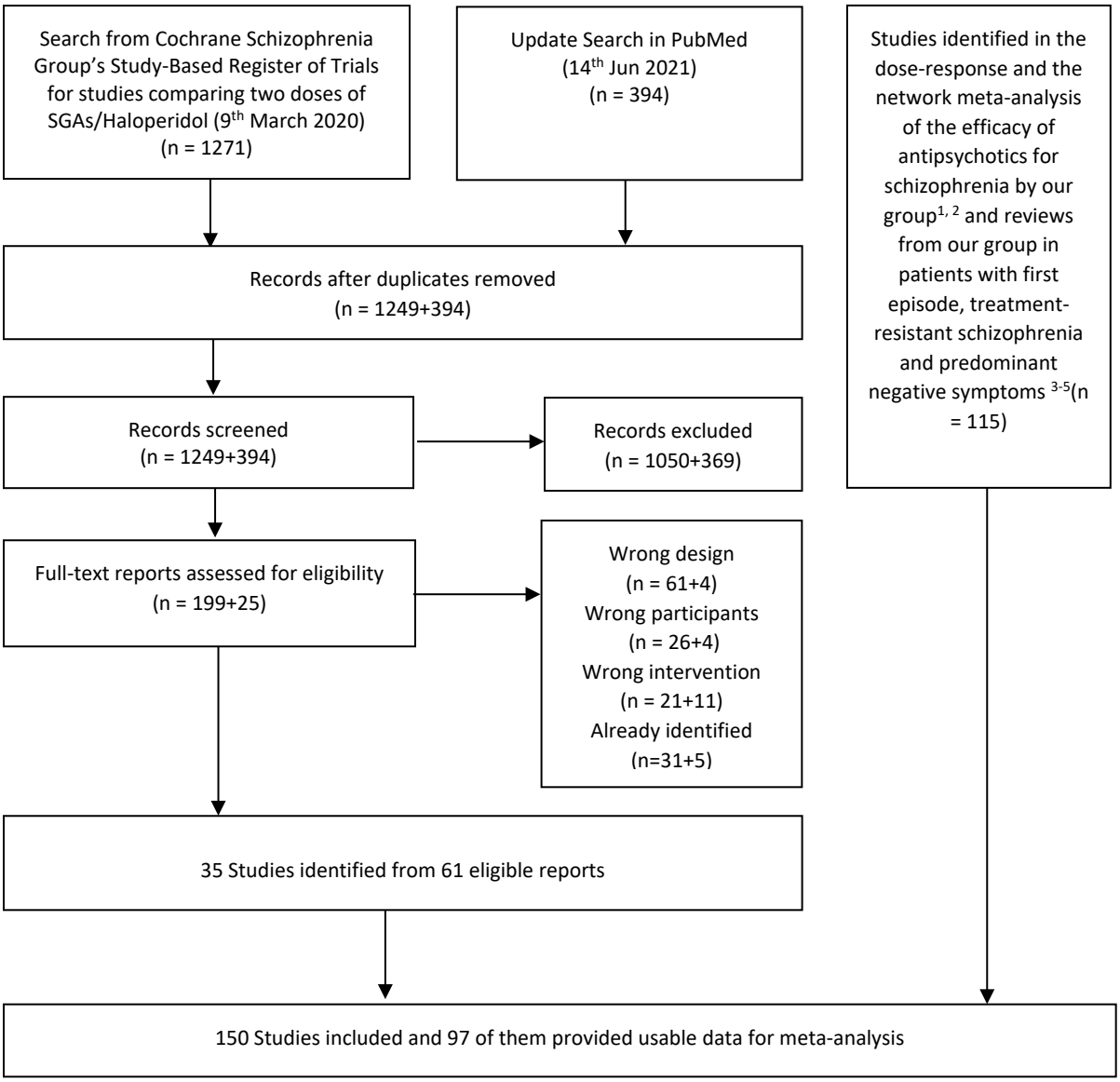
Date: 14th June 2021

Strategy: (amisulpride OR aripiprazole OR asenapine OR benperidol OR brexpiprazole OR cariprazine OR chlorpromazine OR clopenthixol OR clozapine OR flupenthixol OR fluphenazine OR fluspirilene OR haloperidol OR Iloperidone OR levomepromazine OR methotrimeprazine OR loxapine OR lumateperone OR lurasidone OR molindone OR olanzapine OR paliperidone OR penfluridol OR perazine OR perphenazine OR pimozide OR quetiapine OR sertindole OR sulpiride OR thioridazine OR thiothixene OR trifluoperazine OR ziprasidone OR zotepine OR zuclopenthixol OR risperidone) AND random* from 9.3.2020 to 14.6.2021

Search Results

394 reports.

Appendix 4: PRISMA flow chart



References

1. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. American Journal of Psychiatry. 2020;177:342-353.

2. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Bäckers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394:939-951.

3. Zhu Y, Li C, Huhn M, Rothe P, Krause M, Bighelli I, et al. How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis. Eur Neuropsychopharmacol. 2017;27(9):835-44.

4. Samara MT, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, et al. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. JAMA Psychiatry. 2016;73(3):199-210.

5. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis.

Appendix 5: Dose conversion scheme

Table 1: Dose conversion scheme

Drug formulation	Dose	Oral equivalence
Aripiprazole lauroxil (1)	441 mg/4 weeks	10.71429 mg/d[b]
	882 mg/4 weeks	21.42857 mg/d[b]
Aripiprazole maintena	396.4 mg/4 weeks	14.15714 mg/d[a]
Asenapine HP3070 (2)	3.8 mg/d	10mg/d[b]
	7.6 mg/d	20mg/d[b]
Olanzapine LAI	210 mg/2 weeks	15 mg/d[a]
	300 mg/2 weeks	21.42857 mg/d[a]
	405 mg/4 weeks	14.44643 mg/d[a]
Paliperidone LAI (3)	25 mg/4 weeks	2 mg/d[b]
	50 mg/4 weeks	4 mg/d[b]
	100 mg/4 weeks	8 mg/d[b]
	150 mg/4 weeks	12 mg/d[b]
Risperidone consta	25 mg/2 weeks	1.785714 mg/d[a]
	50 mg/2 weeks	3.571429 mg/d[a]
	75 mg/2 weeks	5.357143 mg/d[a]
Risperidone RBP-7000	90 mg/4 weeks	3.214286 mg/d[a]
	120 mg/4 weeks	4.285714 mg/d[a]
Risperidone ISM	75mg/4 weeks	3mg/d[c]
	100mg/4 weeks	4mg/d[c]

We converted long injectable doses to daily oral equivalences in these ways: [a] dividing the LAI doses by the number of days; [b] according to the published dose equivalences; [c] dose equivalence recommendations from Laboratorios Farmacéuticos ROVI (personal contact).

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Appendix 6: Description of included studies

Table 2: Description of included studies

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
1	Arvanitis 1997(1)	acute exacerbation of (sub-) chronic schizophrenia (DSM-III-R)	6	Placebo	0	51	80,39	56,86	n,i,	n.i.	n.i.
				Haloperidol	12	52	80,77	59,62	n,i,	n.i.	n.i.
				Quetiapine_IR	75	53	73,58	73,71	n,i,	n.i.	n.i.
				Quetiapine_IR	150	48	81,25		n,i,	n.i.	n.i.
				Quetiapine_IR	300	52	71,15		n,i,	n.i.	n.i.
				Quetiapine_IR	600	51	74,51		n,i,	n.i.	n.i.
				Quetiapine_IR	750	54	70,37		n,i,	n.i.	n.i.
2	Beasley 1996a(2)	schizophrenia (DSM-III-R)	6	Placebo	0	50	66,00	66,00	79,42	n.i.	n.i.
				Olanzapine	1	52	76,92	76,92	82,69	n.i.	n.i.
				Olanzapine	10	50	74,00	74,00	80,45	n.i.	n.i.
3	Beasley 1996b(3)	acute exacerbation of schizophrenia (DSM-III-R)	6	Placebo	0	68	91,18	70,59	80,25	n.i.	n.i.
				Haloperidol	16,4	69	89,86	57,97	83,02	n.i.	n.i.
				Olanzapine	6,6	65	92,31	64,62	80,03	n.i.	n.i.
				Olanzapine	11,6	64	87,50	71,88	78,25	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Olanzapine	16,3	69	78,26	78,26	79,89	n.i.	n.i.
4	Beasley 1997(4)	acute exacerbation of schizophrenia (DSM-III-R)	6	Haloperidol	17,6	81	59,26	81,48	73,77	n.i.	n.i.
				Olanzapine	1	88	65,91	87,50	70,79	n.i.	n.i.
				Olanzapine	6,7	87	65,52	86,21	69,74	n.i.	n.i.
				Olanzapine	11,3	86	63,95	84,88	71,64	n.i.	n.i.
				Olanzapine	16,4	89	64,04	89,89	71,35	n.i.	n.i.
5	Bugarski-Kirola(5)	acute exacerbation of schizophrenia (DSM-IV)	4	Placebo	0	79	73,42	56,96	n,i,	n.i.	n.i.
				Olanzapine	15	63	73,02	61,90	n,i,	n.i.	n.i.
6	Cantillon 2014(6)	acute exacerbation of schizophrenia or schizoaffective disorder (DSM-IV-TR)	4	Placebo	0	39	69,23	5,13	n,i,	n.i.	n.i.
				Aripiprazole	15	20	90,00	5,00	n,i,	n.i.	n.i.
7			6	Placebo	0	119	73,95	42,02	87,2	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
	Casey 2008(7)	acute exacerbation of schizophrenia (DSM-IV-TR)		Risperidone	6	120	78,33	35,83	88,2	n.i.	n.i.
8	Chouinard 1993(8)	chronic schizophrenia (DSM-III-R)	8	Placebo	0	22	71,11	94,07	n,i,	n.i.	n.i.
				Haloperidol	20	21			n,i,	n.i.	n.i.
				Risperidone	2	24			n,i,	n.i.	n.i.
				Risperidone	6	22			n,i,	n.i.	n.i.
				Risperidone	10	22			n,i,	n.i.	n.i.
				Risperidone	16	24			n,i,	n.i.	n.i.
9	Cooper 2000a(9)	acute episode of schizophrenia or acute exacerbation of (sub-) chronic schizophrenia	8	Placebo	0	53	69,81	100,00	72,7	n.i.	n.i.
				Zotepine	240,57	53	69,81	98,11	70,6	n.i.	n.i.
10	Correll 2015(10)	schizophrenia (DSM-IV-TR)	6	Placebo	0	184	64,13	65,76	77,8	n.i.	26,5
				Brexpiprazole	0,25	90	67,78	70,00	78	n.i.	26,2
				Brexpiprazole	2	182	60,99	65,93	80	n.i.	27,3

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Brexpiprazole	4	180	61,67	66,11	80,1	n.i.	27,1
11	Correll 2020(11)	acute exacerbation of schizophrenia (DSM-5)	4	Placebo	0	150	82,00	28,00	85,9	n.i.	28,2
				Lumateperone	40	150	75,33	28,00	85,8	n.i.	28,4
				Lumateperone	60	150	73,33	22,00	86,3	n.i.	28,7
12	Correll 2020b(12)	acute exacerbation of schizophrenia (DSM-5)	12	Placebo	0	132	74,24	54,55	n,i,	n.i.	28,36
				Risperidone ISM	75[a]	129	75,97	56,59	n,i,	n.i.	28,04
				Risperidone ISM	100[a]	129	75,19	51,94	n,i,	n.i.	28,58
13	Cutler 2008(13)	schizophrenia (DSM-IV)	4	Placebo	0	152	75,00	30,26	81,1	172	27,2
				Iloperidone	24	303	80,86	36,63	82,2	173,8	27,3
				Ziprasidone	160	151	74,83	33,77	80,5	172,7	27
14	Cutler 2008a(14)	acute schizophrenia (DSM-IV)	6	Placebo	0	117	65,81	30,77	87,51	n.i.	n.i.
				Quetiapine_IR	800	116	59,48	25,00	90,33	n.i.	n.i.
				Quetiapine_XR	400	114	69,30	34,21	92,06	n.i.	n.i.
				Quetiapine_XR	600	105	78,10	32,38	90,99	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Quetiapine_XR	800	113	72,57	34,51	93,12	n.i.	n.i.
15	Daniel 1999(15)	acute exacerbation of (sub-) chronic schizophrenia or schizoaffective disorder (DSM-III-R)	6	Placebo	0	92	68,48	60,87	79,47	n.i.	n.i.
				Ziprasidone	80	106	70,75	72,64	76,67	n.i.	n.i.
				Ziprasidone	160	104	74,04	70,19	75,49	n.i.	n.i.
16	Danion 1999(16)	schizophrenia of residual type (DSM-III-R)	12	Placebo	0	83	62,65	98,80	68,7	n.i.	n.i.
				Amisulpride	50	84	61,90	100,00	68,1	n.i.	n.i.
				Amisulpride	100	75	66,67	97,33	66,6	n.i.	n.i.
17	Davidson 2007(17)	schizophrenia acute episode (DSM-IV)	6	Placebo	0	123	67,48	49,59	75,8	n.i.	n.i.
				Olanzapine	10	128	75,00	46,88	74,7	n.i.	25,8
				Paliperidone	3	127	60,63	48,82	73,8	n.i.	25,7
				Paliperidone	9	125	63,20	52,00	74,1	n.i.	n.i.
				Paliperidone	15	115	63,48	43,48	76,5	n.i.	26,6
18	Downing 2014(18)	acute exacerbation of schizophrenia	6	Placebo	0	295	61,36	62,03	81,4	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
		(DSM-IV)		Risperidone	4	143	60,84	65,03	82,7	n.i.	n.i.
19	Durgam 2014(19)	acute exacerbation of schizophrenia (DSM-IV-TR)	6	Placebo	0	151	66,89	52,98	74,4	172	25,2
				Cariprazine	1,5	145	64,14	53,10	71,7	n.i.	24,9
				Cariprazine	3	146	73,29	48,63	74,8	n.i.	25,6
				Cariprazine	4,5	147	70,07	51,02	72,4	n.i.	24,8
				Risperidone	4	140	70,00	47,86	75,1	171	25,8
20	Garcia 2009(20)	acute exacerbation of schizophrenia	6	Placebo	0	64	62,50	92,19	70,3	n.i.	n.i.
				Haloperidol	10	60	58,33	95,00	69,9	n.i.	n.i.
21	Garry 1962b(21)	chronic schizophrenia (clinical diagnosis)	12	Placebo	0	26	n.i.	n.i.	n,i,	n.i.	n.i.
				Haloperidol	10	26	n.i.	n.i.	n,i,	n.i.	n.i.
22	Gopal 2010(22)	schizophrenia (DSM-IV)	13	Placebo	0	136	69,12	37,50	83	n.i.	28
				Paliperidone_LAI	50[a]	94	69,15	37,23	86,4	n.i.	29
				Paliperidone_LAI	100 [a]	97	62,89	36,08	84,6	n.i.	29
				Paliperidone_LAI	150 [a]	30	73,33	66,67	84,3	n.i.	29

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
23	Honer 2010(23)	schizophrenia or schizoaffective disorder (DSM-IV)	8	Quetiapine_IR	799	43	74,42	86,05	81,7	n.i.	28,4
				Quetiapine_IR	1144	88	65,91	90,91	83,7	n.i.	28,6
24	Ishigooka 2018(24)	schizophrenia (DSM-IV-TR)	6	Placebo	0	116	43,97	n.i.	60,8	n.i.	23,1
				Brexpiprazole	1	115	44,35	n.i.	60,4	n.i.	22,9
				Brexpiprazole	2	115	53,04	n.i.	61,7	n.i.	23
				Brexpiprazole	4	113	48,67	n.i.	64,1	n.i.	23,8
25	Iyo 2021(25)	acute exacerbation of schizophrenia (DSM-IV-TR)	6	Placebo	0	235	51,06	77,87	71,9	n.i.	25,2
				Lurasidone	40	247	48,18	74,09	72,21	n.i.	25,3
26	Janssen CR012625 (26)	schizophrenia with acute symptoms (DSM-IV)	6	Placebo	0	138	52,17	n.i.	61,07	162,29	23,12
				Olanzapine	10	47	40,43	n.i.	60,27	161,53	22,98
				Paliperidone	6	136	51,47	n.i.	60,71	162,19	23,06
27	Johnson NCT00397 033(27)	acute exacerbation of schizoaffective disorder (DSM-IV)	6	Placebo	0	107	62,62	49,53	80	n.i.	n.i.
				Paliperidone	5,7	109	64,22	44,04	74,4	n.i.	n.i.
				Paliperidone	11,06	100	64,00	43,00	78,4	n.i.	n.i.
28			6	Placebo	0	65	70,77	9,23	79,2	170	27,3

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
	Johnson NCT00524043(28)	acute exacerbation of schizophrenia (DSM-IV)		Paliperidone	1,5	66	75,76	12,12	77,8	169,3	26
				Paliperidone	6	70	67,14	15,71	73,1	167	26,2
29	Kahn 2007(29)	acute schizophrenia (DSM-IV)	6	Placebo	0	118	56,78	57,63	64,75	n.i.	n.i.
				Quetiapine_IR	400	123	56,10	57,72	65,63	n.i.	n.i.
				Quetiapine_XR	400	113	69,03	55,75	64,05	n.i.	n.i.
				Quetiapine_XR	600	113	53,98	58,41	62,88	n.i.	n.i.
				Quetiapine_XR	800	121	57,85	58,68	64,58	n.i.	n.i.
30	Kane 2002(30)	schizophrenia or schizoaffective disorder, acute relapse (DSM-IV)	4	Placebo	0	106	69,81	50,94	83,3	n.i.	n.i.
				Aripiprazole	15	102	74,51	59,80	85,3	n.i.	n.i.
				Aripiprazole	30	102	68,63	57,84	87,8	n.i.	n.i.
				Haloperidol	10	104	65,38	65,38	84,8	n.i.	n.i.
31	Kane 2003(31)	schizophrenia (DSM-IV)	12	Placebo	0	98	81,63	46,94	84,3	n.i.	n.i.
				Risperidone_Consta	25[b]	99	68,69	37,37	89,3	n.i.	n.i.
				Risperidone_Consta	50[b]	103	81,55	42,72	88,1	n.i.	n.i.
				Risperidone_Consta	75[b]	100	68,00	39,00	87,8	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
32	Kane 2007b(32)	acute episode of schizophrenia (DSM-IV)	6	Placebo	0	127	51,97	83,46	71,2	167,4	25,3
				Olanzapine	10	128	46,88	86,72	71,7	167,6	25,3
				Paliperidone	6	123	50,41	86,18	71,2	168,1	25,1
				Paliperidone	9	122	59,02	86,07	70,2	169,4	24,4
				Paliperidone	12	130	52,31	85,38	70,9	168,4	24,9
33	Kane 2010a(33)	acute exacerbation of schizophrenia (DSM-IV-TR)	6	Placebo	0	123	52,03	61,79	74,5	n.i.	26
				Asenapine	10	114	65,79	62,28	77,6	n.i.	26,7
				Asenapine	20	106	63,21	63,21	77,8	n.i.	26,2
				Haloperidol	8	115	54,78	59,13	76,5	n.i.	26,5
34	Kane 2014(34)	acute exacerbation of schizophrenia (DSM-IV-TR)	12	Placebo	0	172	80,81	31,98	86,6	n.i.	28,5
				Aripiprazole_Maintena	396,4[a]	168	77,38	30,95	86	n.i.	28,4
35	Kane 2015(35)	schizophrenia (DSM-IV-TR)	6	Placebo	0	184	60,33	59,78	85	n.i.	26,6
				Brexpiprazole	1	120	64,17	62,50	80,3	n.i.	26,7
				Brexpiprazole	2	186	65,59	63,44	84,8	n.i.	26,3
				Brexpiprazole	4	184	61,41	56,52	84,8	n.i.	27,1
36			6	Quetiapine_IR	50	209	64,59	n.i.	n,i,	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
	King 1998(36)	acute exacerbation of chronic or subchronic schizophrenia (DSM-IIIR)		Quetiapine_IR	450	200	64,00	n.i.	n,i,	n.i.	n.i.
				Quetiapine_IR	450	209	69,86	n.i.	n,i,	n.i.	n.i.
37	Kinon 2006c(37)	schizophrenia or schizoaffective disorder (DSM-IV)	8	Olanzapine	10	199	67,34	44,22	89,95	n.i.	30,06
				Olanzapine	20	200	67,50	46,50	88,59	n.i.	29,68
				Olanzapine	40	200	69,50	45,00	88,63	n.i.	30,18
38	Kinon 2011(38)	schizophrenia (DSM-IV)	4	Placebo	0	122	57,38	91,80	73	n.i.	n.i.
				Olanzapine	15	62	54,84	91,94	73,9	n.i.	n.i.
39	Kramer 2010(39)	schizophrenia (DSM-IV)	9	Placebo	0	84	46,43	64,29	73,8	n.i.	26
				Paliperidone_LAI	50[a]	79	51,90	63,29	74,5	n.i.	26
				Paliperidone_LAI	100[a]	84	50,00	65,48	71,6	n.i.	25
40	Landbloom 2016(40)	schizophrenia of paranoid, disorganized, or undifferentiated subtype (DSM-IV-TR)	6	Placebo	0	103	52,43	71,84	77,1	n.i.	n.i.
				Asenapine	5	98	59,18	68,37	81,6	n.i.	n.i.
				Asenapine	10	113	61,06	75,22	78,6	n.i.	n.i.
				Olanzapine	15	46	60,87	63,04	80,7	n.i.	n.i.
41	Lauriello 2008(41)	schizophrenia (DSM-IV or DSM-IV-TR)	8	Placebo	0	98	62,24	54,08	82,2	n.i.	28,3
				Olanzapine_LAI	405[a]	100	73,00	54,00	87,3	n.i.	29,4
				Olanzapine_LAI	210[b]	106	74,53	57,55	87	n.i.	28,7

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Olanzapine_LAI	300[b]	100	72,00	58,00	85,5	n.i.	28,9
42	Lecrubier 2006(42)	schizophrenia, residual, disorganised or catatonic (DSM-IV)	26	Placebo	0	34	64,71	97,06	75,42	1,72	n.i.
				Amisulpride	150	70	71,43	97,14	71,68	1,71	n.i.
				Olanzapine	5	70	60,00	95,71	70,2	1,69	n.i.
				Olanzapine	20	70	74,29	94,29	70,61	1,71	n.i.
43	Lieberman 2015(43)	schizophrenia (DSM-IV)	4	Placebo	0	85	76,47	20,00	n,i,	n.i.	29,8
				Lumateperone	60	84	78,57	15,48	n,i,	n.i.	28,9
				Lumateperone	120	84	85,71	19,05	n,i,	n.i.	28,5
				Risperidone	4	82	89,02	19,51	n,i,	n.i.	28,3
44	Lindenmayer 2008(44)	schizophrenia, acute exacerbation (DSM-IV)	6	Placebo	0	84	77,38	44,05	85,6	n.i.	29,2
				Quetiapine_IR	300	90	71,11	47,78	86,7	n.i.	28,9
				Quetiapine_IR	600	86	68,60	44,19	87	n.i.	29,4
				Quetiapine_XR	300	91	64,84	51,65	82,7	n.i.	28,2
				Quetiapine_XR	600	92	66,30	51,09	91,6	n.i.	30,9
				Quetiapine_XR	800	89	77,53	56,18	89,3	n.i.	29,8
45	Lindenmayer 2011(45)	schizophrenia or schizoaffective disorder	8	Quetiapine_IR	600	31	87,10	16,13	93,81	n.i.	31,01

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
		with suboptimal treatment response (DSM-IV-R)		Quetiapine_IR	1200	29	96,55	10,34	91,34	n.i.	30,18
46	Litman 2016(46)	schizophrenia (DSM-IV)	4	Placebo	0	55	80,00	12,73	n,i,	n.i.	n.i.
				Risperidone	4	31	83,87	16,13	n,i,	n.i.	n.i.
47	Litmann 2014(47)	schizophrenia, symptomatic patients but medically stable (DSM-IV)	4	Placebo	0	41	95,12	31,71	n,i,	n.i.	28,48
				Olanzapine	15	22	100,00	22,73	n,i,	n.i.	28,41
48	Loebel 2015a(48)	acute exacerbation of schizophrenia (DSM-IV-TR)	6	Placebo	0	112	69,64	72,32	n,i,	n.i.	n.i.
				Lurasidone	20	101	64,36	72,28	n,i,	n.i.	n.i.
				Lurasidone	97,37	199	59,80	72,86	n,i,	n.i.	n.i.
49	Loo 1997(49)	schizophrenia with predominant negative symptoms (DSM-III-R)	26	Placebo	0	72	75,00	88,89	71,3	n.i.	n.i.
				Amisulpride	100	69	66,67	91,30	69,4	n.i.	n.i.
50	Marder 1994(50)	schizophrenia (DSM-III-R)	8	Placebo	0	66	86,36	60,61	n,i,	n.i.	n.i.
				Haloperidol	20	66	90,91	62,12	n,i,	n.i.	n.i.
				Risperidone	2	63	85,71	65,08	n,i,	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Risperidone	6	64	85,94	65,63	n,i,	n.i.	n.i.
				Risperidone	10	65	93,85	64,62	n,i,	n.i.	n.i.
				Risperidone	16	64	82,81	59,38	n,i,	n.i.	n.i.
51	Marder 2007c(51)	acute exacerbation of schizophrenia (DSM-IV)	6	Placebo	0	110	74,55	45,45	89,89	173,6	29,8
				Olanzapine	10	110	80,00	40,00	89,64	174,6	29,5
				Paliperidone	6	112	67,86	41,07	87,34	172,1	29,6
				Paliperidone	12	112	68,75	41,07	87,09	173,1	29,1
52	McEvoy 2007b(52)	acute exacerbation of schizophrenia (DSM-IV)	6	Placebo	0	108	76,85	45,37	83,84	n.i.	n.i.
				Aripiprazole	10	106	77,36	50,00	82,89	n.i.	n.i.
				Aripiprazole	15	106	74,53	53,77	81,67	n.i.	n.i.
				Aripiprazole	20	100	82,00	52,00	86,15	n.i.	n.i.
53	Meltzer 2004(53)	acute schizophrenia or schizoaffective disorder (DSM-IV)	6	Placebo	0	98	75,51	53,06	n,i,	n.i.	n.i.
				Haloperidol	10	98	70,41	41,84	n,i,	n.i.	n.i.
54	Meltzer 2007a(54)	acute exacerbation of schizophrenia (DSM-IV-TR)	6	Placebo	0	149	74,50	n.i.	77,9	n.i.	26,9
				Risperidone	6	154	72,73	n.i.	79,2	n.i.	27,5

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
55	Meltzer 2012(55)	schizophrenia with a recent acute exacerbation of psychotic symptoms	6	Haloperidol	2	87	62,07	n.i.	n,i,	n.i.	n.i.
				Risperidone	2	86	60,47	n.i.	n,i,	n.i.	n.i.
				Risperidone	6	87	60,92	n.i.	n,i,	n.i.	n.i.
56	Meltzer 2014(56)	treatment resistant schizophrenia or schizoaffective disorder (DSM-IV)	24	Risperidone_Consta	50[b]	82	73,17	31,71	n,i,	n.i.	n.i.
				Risperidone_Consta	100[b]	78	71,79	34,62	n,i,	n.i.	n.i.
57	Meltzer 2015(57)	acute exacerbation of schizophrenia (DSM-IV-TR)	12	Placebo	0	208	66,83	45,19	79	n.i.	27
				Aripiprazole_Lauroxil	441[a]	207	68,12	47,83	80,8	n.i.	27,7
				Aripiprazole_Lauroxil	882[a]	208	68,75	47,12	80,3	n.i.	27,3
58	Meltzer 2020(58)	treatment-resistant schizophrenia or schizoaffective disorder (DSM-IV-TR)	24	Lurasidone	80	34	41,18	35,29	n.i.	n.i.	30,5
				Lurasidone	240	33	45,45	33,33	n.i.	n.i.	32,4
59	Nasrallah 2010(59)	schizophrenia (DSM-IV-TR)	13	Placebo	0	127	61,42	52,76	81,7	n.i.	27,5
				Paliperidone_LAI	25[a]	131	64,89	51,15	81,7	n.i.	27,6

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Paliperidone_LAI	50[a]	129	72,09	53,49	80,8	n.i.	27,3
				Paliperidone_LAI	100[a]	131	64,89	49,62	81,2	n.i.	27,7
60	Nasser 2016(60)	acute exacerbation of schizophrenia (DSM-IV-TR)	8	Placebo	0	119	68,07	21,01	91,84	173,1	29,58
				Risperidone_RBP-7000	90[a]	116	80,17	24,14	90,6	175,3	29,38
				Risperidone_RBP-7000	120[a]	119	70,59	25,21	89,01	174	30,71
61	NCT00563706(61)	schizophrenia (DSM-IV-TR)	4	Placebo	0	37	78,38	n.i.	n,i,	n.i.	n.i.
				Risperidone	4	43	76,74	n.i.	n,i,	n.i.	n.i.
62	NCT00711269(62)	schizophrenia (DSM-IV)	6	Placebo	0	133	54,14	n.i.	n,i,	n.i.	n.i.
				Lurasidone	40	131	66,41	n.i.	n,i,	n.i.	n.i.
				Lurasidone	80	131	62,60	n.i.	n,i,	n.i.	n.i.
				Risperidone	4	65	53,85	n.i.	n,i,	n.i.	n.i.
63	NCT00905307(63)	schizophrenia (DSM-IV-TR)	6	Placebo	0	95	61,05	61,05	n,i,	n.i.	26,4
				Aripiprazole	15	50	68,00	68,00	n,i,	n.i.	24,7
				Brexpiprazole	0,25	42	64,29	61,90	n,i,	n.i.	26,8
				Brexpiprazole	1	89	59,55	56,18	n,i,	n.i.	27,1
				Brexpiprazole	2,5	90	66,67	62,22	n,i,	n.i.	25,9

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Brexpiprazole	5	93	59,14	63,44	n,i,	n.i.	25,3
64	NCT01098110(64)	schizophrenia (DSM-IV-TR)	6	Placebo	0	174	46,55	n.i.	62,58	n.i.	23,49
				Asenapine	10	176	42,61	n.i.	62,51	n.i.	23,64
				Asenapine	20	182	54,40	n.i.	64,28	n.i.	24,15
65	NCT01104766(65)	acute exacerbation of schizophrenia (DSM-IV-TR)	6	Placebo	0	153	63,40	60,78	78,3	n.i.	26,5
				Aripiprazole	10	152	61,84	65,13	79,5	n.i.	26,9
				Cariprazine	3	155	63,87	65,81	77,2	n.i.	26
				Cariprazine	6	157	63,69	64,33	78,1	n.i.	26,3
66	NCT01614899(66)	schizophrenia (DSM-IV-TR)	6	Placebo	0	152	58,55	n.i.	64,47	n.i.	24
				Lurasidone	40	150	54,67	n.i.	65	n.i.	24,45
				Lurasidone	80	155	52,26	n.i.	62,72	n.i.	23,33
67	NCT02469155(67)	acute exacerbation of schizophrenia (DSM-V)	6	Placebo	0	174	75,86	20,11	n,i,	n.i.	n.i.
				Lumateperone	20	174	71,84	14,94	n,i,	n.i.	n.i.
				Lumateperone	60	174	70,69	17,24	n,i,	n.i.	n.i.
				Risperidone	4	174	75,86	22,99	n,i,	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
68	NCT02876900(68)	acute exacerbation of schizophrenia (DSM-V)	6	Placebo	0	206	63,59	73,79	n,i,	171,8	25,9
				Asenapine_HP3070	3,8	205	63,90	76,59	n,i,	172,5	26,6
				Asenapine_HP3070	7,6	206	53,88	77,18	n,i,	171,8	26,24
69	Pandina 2010(69)	schizophrenia (DSM-IV)	13	Placebo	0	164	66,46	53,05	77,8	170,5	26,83
				Paliperidone_LAI	25[a]	160	72,50	53,75	79,3	173,1	26,77
				Paliperidone_LAI	100[a]	165	66,67	52,12	76,8	170,7	26,36
				Paliperidone_LAI	150[a]	163	64,42	51,53	77,8	171,2	26,65
70	Patil 2007(70)	schizophrenia (DSM-IV-TR)	4	Placebo	0	63	77,78	98,41	74,1	n.i.	24,4
				Olanzapine	15	34	73,53	100,00	74,8	n.i.	25,1
71	Peuskens 1995(71)	chronic schizophrenia (DSM-III-R)	8	Haloperidol	10	226	66,37	n.i.	n,i,	n.i.	n.i.
				Risperidone	1	229	72,49	n.i.	n,i,	n.i.	n.i.
				Risperidone	4	227	66,96	n.i.	n,i,	n.i.	n.i.
				Risperidone	8	230	62,61	n.i.	n,i,	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Risperidone	12	226	62,83	n.i.	n,i,	n.i.	n.i.
				Risperidone	16	224	62,50	n.i.	n,i,	n.i.	n.i.
72	Potkin 2003(72)	schizophrenia or schizoaffective disorder (DSM-IV)	4	Placebo	0	103	70,87	n.i.	85,2	n.i.	n.i.
				Aripiprazole	20	101	72,28	n.i.	87,2	n.i.	n.i.
				Aripiprazole	30	101	65,35	n.i.	84	n.i.	n.i.
				Risperidone	6	99	71,72	n.i.	82,4	n.i.	n.i.
73	Potkin 2007c(73)	acute exacerbation of schizophrenia (DSM-IV)	6	Placebo	0	62	79,03	32,26	90	n.i.	n.i.
				Asenapine	10	60	76,67	41,67	89	n.i.	n.i.
				Risperidone	6	60	60,00	41,67	85	n.i.	n.i.
74	Protocol 128-301(74)	schizophrenia or schizoaffective disorder (DSM-III-R)	12	Haloperidol	10	120	n.i.	n.i.	n,i,	n.i.	n.i.
				Haloperidol	20	118	n.i.	n.i.	n,i,	n.i.	n.i.
				Ziprasidone	40	116	n.i.	n.i.	n,i,	n.i.	n.i.
				Ziprasidone	120	115	n.i.	n.i.	n,i,	n.i.	n.i.
				Ziprasidone	200	128	n.i.	n.i.	n,i,	n.i.	n.i.
75	Puech 1998(75)	chronic or subchronic schizophrenia with acute exacerbation (DSM-III-R)	4	Amisulpride	100	61	68,85	93,44	69,2	n.i.	n.i.
				Amisulpride	400	64	67,19	92,19	68,7	n.i.	n.i.
				Amisulpride	800	65	47,69	93,85	67,6	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Amisulpride	1200	65	69,23	89,23	66,3	n.i.	n.i.
				Haloperidol	16	64	56,25	100,00	68,2	n.i.	24
76	Schmidt 2014(76)	acute exacerbation of schizophrenia (DSM-IV)	6	Placebo	0	101	58,42	81,19	73,3	170,3	25,3
				Olanzapine	15	93	52,69	81,72	71,3	169,7	24,7
77	Shen 2014(77)	acute schizophrenia (DSM-IV-TR)	6	Placebo	0	78	66,67	21,79	86	173,3	n.i.
				Olanzapine	15	77	59,74	24,68	92,1	172,1	n.i.
78	Simpson 1999(78)	schizophrenia or schizoaffective disorder (DSM-III-R)	16	Clozapine	100	14	42,86	86,00	n,i,	n.i.	n.i.
				Clozapine	300	17	41,18		n,i,	n.i.	n.i.
				Clozapine	600	17	41,18		n,i,	n.i.	n.i.
79	Study 006(79)	schizophrenia (DSM-IV)	6	Placebo	0	50	84,00	40,00	89,3	n.i.	29,4
				Lurasidone	40	50	72,00	40,00	87,4	n.i.	29,5
				Lurasidone	120	49	73,47	44,90	90,2	n.i.	29,6
80	Study 049(80)	acute exacerbation of schizophrenia (DSM-IV)	6	Placebo	0	72	76,39	56,94	84,8	n.i.	n.i.
				Haloperidol	10	73	79,45	46,58	88,4	n.i.	n.i.
				Lurasidone	20	71	71,83	53,52	83,8	n.i.	n.i.
				Lurasidone	40	69	66,67	49,28	87,2	n.i.	n.i.
				Lurasidone	80	71	73,24	40,85	91	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
81	Study 115 2000(81)	acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R)	6	Placebo	0	83	65,06	60,24	78,37	n.i.	n.i.
				Haloperidol	15	85	70,59	64,71	81,22	n.i.	n.i.
				Ziprasidone	40	87	60,92	63,22	79,05	n.i.	n.i.
				Ziprasidone	120	78	70,51	69,23	78,64	n.i.	n.i.
				Ziprasidone	200	86	63,95	67,44	78,62	n.i.	n.i.
82	Study 196(82)	schizophreniform or schizoaffective disorder or catatonic or residual subtypes of schizophrenia (DSM-IV)	6	Placebo	0	90	77,78	28,89	93,5	n.i.	31,2
				Lurasidone	80	90	75,56	38,89	92,2	n.i.	30,7
83	Study 229(83)	schizophrenia (DSM-IV)	6	Placebo	0	128	70,31	51,56	80,92	n.i.	26,9
				Lurasidone	40	125	65,60	44,80	79,46	n.i.	27
				Lurasidone	80	123	61,79	48,78	77,37	n.i.	26,8
				Lurasidone	120	124	74,19	48,39	77,37	n.i.	26,1
84	Study 231(84)	acute exacerbation of schizophrenia (DSM-IV)	6	Placebo	0	116	75,86	31,03	75,2	n.i.	25,8
				Lurasidone	40	120	77,50	36,67	76,4	n.i.	26,3
				Lurasidone	120	119	78,15	40,34	75,4	n.i.	25,5

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Olanzapine	15	123	77,24	33,33	76	n.i.	26
85	Study 233(85)	acute exacerbation of schizophrenia (DSM-IV-TR)	6	Placebo	0	122	63,11	55,74	75,85	n.i.	26,1
				Lurasidone	80	125	76,80	60,00	76,1	n.i.	25,7
				Lurasidone	160	121	67,77	52,07	74,4	n.i.	25,6
				Quetiapine_XR	600	120	64,17	57,50	72,1	n.i.	25,5
86	Study 3000(86)	acute exacerbation of schizophrenia (DSM-IV)	6	Placebo	0	127	70,87	50,39	n,i,	n.i.	n.i.
				Haloperidol	15	124	69,35	46,77	n,i,	n.i.	n.i.
				Iloperidone	4	121	67,77	47,11	n,i,	n.i.	n.i.
				Iloperidone	8	125	75,20	39,20	n,i,	n.i.	n.i.
				Iloperidone	12	124	73,39	54,03	n,i,	n.i.	n.i.
87	Study 3004(86)	schizophrenia and schizoaffective disorder (DSM-IV)	6	Placebo	0	156	67,31	57,05	n,i,	n.i.	n.i.
				Iloperidone	7,16	153	69,28	60,13	n,i,	n.i.	n.i.
				Iloperidone	14,58	154	70,78	59,09	n,i,	n.i.	n.i.
				Risperidone	7,02	153	75,16	60,13	n,i,	n.i.	n.i.
88	Study 3005(86)	acute exacerbation of schizophrenia and schizoaffective disorder (DSM-IV)	6	Placebo	0	160	58,75	68,75	n,i,	n.i.	n.i.
				Iloperidone	14,42	244	59,84	66,80	n,i,	n.i.	n.i.
				Iloperidone	22,17	145	68,28	70,34	n,i,	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Risperidone	7,09	157	61,15	75,80	n,i,	n.i.	n.i.
89	Study 93202 2002(87)	schizophrenia acute relapse (DSM-III-R)	4	Placebo	0	35	82,86	51,43	78,77	n.i.	n.i.
				Aripiprazole	30	34	94,12	55,88	82,75	n.i.	n.i.
				Haloperidol	20	34	88,24	50,00	81,66	n.i.	n.i.
90	Study 94202 2002(87)	schizophrenia acute relapse (DSM-IV)	4	Placebo	0	64	82,81	51,56	84,22	n.i.	n.i.
				Aripiprazole	2	59	79,66	55,93	82,04	n.i.	n.i.
				Aripiprazole	10	60	81,67	43,33	80,63	n.i.	n.i.
				Aripiprazole	30	61	75,41	49,18	79,86	n.i.	n.i.
				Haloperidol	10	63	82,54	58,73	82,78	n.i.	n.i.
91	Study RGH-MD-03(88)	schizophrenia (DSM-IV-TR)	6	Placebo	0	130	79,23	29,23	87,3	n.i.	28,6
				Cariprazine	3,83	128	82,03	36,72	85,7	n.i.	28,1
				Cariprazine	8,7	134	75,37	31,34	87,6	n.i.	29
92	Study RGH-MD-05(89)	schizophrenia (DSM-IV-TR)	6	Placebo	0	147	74,83	17,69	73,3	n.i.	25,8
				Cariprazine	5,58	151	78,15	18,54	73,5	n.i.	25,6
				Cariprazine	8,39	148	76,35	20,27	72,9	n.i.	25,1
93		schizophrenia (DSM-IV)	4	Placebo	0	83	78,31	57,83	79	n.i.	n.i.
				Risperidone	4	85	78,82	58,82	81,65	n.i.	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
	Study RIS-USA-72 1996(90)			Risperidone	8	78	82,05	48,72	83,46	n.i.	n.i.
94	Takahashi 2013(91)	schizophrenia (DSM-IV-TR)	13	Placebo	0	164	50,61	0,00	n,i,	n.i.	23,9
				Paliperidone_LAI	75[a]	160	63,13	0,00	n,i,	n.i.	23,5
95	van Kammen 1996(92)	schizophrenia (DSM-III-R)	05,07, 2021	Placebo	0	48	93,75	47,92	n,i,	n.i.	n.i.
				Sertindole	8	52	63,46	40,38	n,i,	n.i.	n.i.
				Sertindole	12	51	74,51	54,90	n,i,	n.i.	n.i.
				Sertindole	20	54	72,22	33,33	n,i,	n.i.	n.i.
96	Zborowski 1995(93)	schizophrenia (DSM-III-R/DSM-IV)	8	Placebo	0	116	77,59	63,79	77,75	173,23	n.i.
				Haloperidol	16	115	74,78	59,13	77,61	171,96	n.i.
				Sertindole	20	117	76,07	68,38	77,34	173,23	n.i.
				Sertindole	24	113	75,22	62,83	83,1	172,97	n.i.
97	Zimbroff 1997(94)	schizophrenia (DSM-III-R/DSM-IV)	8	Placebo	0	73	78,08	56,16	79,1	173,6	n.i.
				Haloperidol	4	71	83,10	53,52	77,3	174,4	n.i.
				Haloperidol	8	67	80,60	53,73	78	172,5	n.i.
				Haloperidol	16	70	75,71	55,71	80,6	173,4	n.i.
				Sertindole	12	76	80,26	63,16	79,4	174,5	n.i.

	Study name	Diagnosis	Study duration (week)	Intervention	Dose (mg/d)	N	Men%	Race-White%	Weight baseline (kg)	Height (cm)	BMI (kg/m^2)
				Sertindole	20	68	76,47	63,24	79,7	172,1	n.i.
				Sertindole	24	72	69,44	59,72	78,5	174	n.i.

N= number of participants randomised, ICD 9/10 = International Classification of Diseases, 9th/10th Revision, DSM-III, -III-R, -IV, -IV-TR, -V = different versions of the Diagnostic and Statistical Manual of Mental Disorders, n.i. = not indicated, IR= immediate release, XR= extended release, LAI= long-acting injectable, a: mg/4 weeks, b: mg/2 weeks, c: mg/kg body weight/day. Some reports provided data for several studies.

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Appendix 7: Risk of bias assessment

Assessments of the risk of bias of individual studies used in the meta-analysis

Table 3: Risk of bias for individual studies assessed by Cochrane risk of bias tool 1[1]

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Arvanitis 1997	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Beasley 1996a	Low	Low	Low	Low	Low	Low	Low	Low
Beasley 1996b	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Beasley 1997	Low	Low	Low	Low	Low	Low	Low	Low
Bugarski-Kirola	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Cantillon 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Moderate
Casey 2008	Unclear	Unclear	Unclear	Unclear	Low	High	Low	Moderate
Chouinard 1993	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Cooper 2000a	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Correll 2015	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Correll 2020	Low	Low	Low	Low	Low	Low	Low	Low
Correll 2020b	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Cutler 2008	Low	Low	Low	Low	High	Low	Low	Moderate
Cutler 2008a	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Daniel 1999	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Danion 1999	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Davidson 2007	Low	Low	Low	Low	Low	Low	Low	Low
Downing 2014	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Durgam 2014	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Garcia 2009	Low	Unclear	Low	Low	Low	High	Low	Moderate
Garry 1962b	Low	Unclear	Unclear	Unclear	High	High	Low	High

Gopal 2010	Low	Low	Low	Low	Low	Low	Low	Low
Honer 2010	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Ishigooka 2018	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Iyo 2021	Low	Low	Low	Low	Low	Low	Low	Low
Janssen CR012625	Unclear	Unclear	Low	Low	Unclear	Unclear	Low	Moderate
Johnson NCT00397033	Low	Low	Low	Low	Low	Low	Low	Low
Johnson NCT00524043	Low	Low	Low	Low	Low	Low	Low	Low
Kahn 2007	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Kane 2002	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Kane 2003	Low	Low	Low	Low	Low	Low	Low	Low
Kane 2007b	Low	Low	Low	Low	Low	Low	Low	Low
Kane 2010a	Unclear	Unclear	Low	Low	Unclear	Low	Low	Low
Kane 2014	Low	Low	High	High	Low	Low	Low	High
Kane 2015	Low	Low	Low	Low	Low	Low	Low	Low
King 1998	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Kinon 2006c	Low	Low	Low	Low	Low	Low	Low	Low
Kinon 2011	Low	Low	Low	Low	High	Low	Low	Moderate
Kramer 2010	Low	Low	High	High	Low	Low	Low	High
Landbloom 2016	Low	Unclear	Low	Low	Low	Low	Low	Low
Lauriello 2008	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Lecrubier 2006	Low	Low	Low	Low	High	High	Low	High
Liebermann 2015	Low	Unclear	Low	Low	Low	Low	Low	Low
Lindenmayer 2008	Low	Low	Low	Low	Low	Low	Low	Low
Lindenmayer 2011	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Litman 2016	Low	Unclear	Low	Low	Low	Low	Low	Low
Litmann 2014	Low	Low	Low	Low	Low	Low	Low	Low
Loebel 2015a	Low	Low	Low	Low	Low	Low	Low	Low

Loo 1997	Low	Low	Low	Low	Low	High	High	High
Marder 1994	Low	Unclear	Low	Low	Low	Low	Low	Low
Marder 2007c	Low	Low	Low	Low	Low	Low	Low	Low
McEvoy 2007b	Low	Low	Low	Low	Low	Low	Low	Low
Meltzer 2004	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Meltzer 2007a	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Moderate
Meltzer 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Meltzer 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Low	Moderate
Meltzer 2015	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Meltzer 2020	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Nasrallah 2010	Low	Low	Low	Low	Low	Low	Low	Low
Nasser 2016	Low	Low	Low	Low	Low	Low	Low	Low
NCT00563706	Unclear	Unclear	Low	Low	Low	Low	Low	Low
NCT00711269	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
NCT00905307	Low	Low	Low	Low	Low	Low	Low	Low
NCT01098110	Low	Unclear	Low	Low	Low	Low	Low	Low
NCT01104766	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
NCT01614899	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
NCT02469155	Unclear	Unclear	Low	Low	Low	Low	Low	Low
NCT02876900	Low	Low	Low	Low	Low	Low	Low	Low
Pandina 2010	Low	Low	Low	Low	Unclear	Unclear	Low	Low
Patil 2007	Unclear	Unclear	Unclear	Unclear	Low	High	Low	Moderate
Peuskens 1995	Low	Low	Low	Low	Low	Low	Low	Low
Potkin 2003	Unclear	Unclear	Unclear	Unclear	Low	High	Low	Moderate
Potkin 2007c	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Protocol 128-301	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Moderate
Puech 1998	Low	Low	Low	Low	Low	Low	Low	Low

Schmidt 2014	Low	Low	Low	Low	Low	High	Low	Moderate
Shen 2014	Low	Low	Unclear	Unclear	High	High	Low	High
Simpson 1999	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Study 006	Low	Low	Low	Low	Low	Low	Low	Low
Study 049	Low	Low	Low	Low	Low	Low	Low	Low
Study 115 2000	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Moderate
Study 196	Low	Low	Low	Low	Low	Low	Low	Low
Study 229	Low	Low	Low	Low	Low	Low	Low	Low
Study 231	Low	Low	Low	Low	Low	Low	Low	Low
Study 233	Low	Low	Low	Low	Low	Low	Low	Low
Study 3000	Low	Low	Low	Low	Low	Low	Low	Low
Study 3004	Low	Low	Low	Low	Low	Low	Low	Low
Study 3005	Low	Low	Low	Low	Low	Low	Low	Low
Study 93202 2002	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Study 94202 2002	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Study RGH-MD-03	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low	Moderate
Study RGH-MD-05	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Moderate
Study RIS-USA-72 1996	Unclear	Unclear	Low	Low	Low	Low	Low	Low
Takahashi 2013	Unclear	Unclear	Low	Low	Low	Low	Low	Low
van Kammen 1996	Low	Unclear	Unclear	Unclear	Low	Low	Low	Low
Zborowski 1995	Low	Low	Low	Low	Low	Low	Low	Low
Zimbroff 1997	Low	Low	Unclear	Unclear	Low	High	Low	Moderate

Reference

1. Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. Chichester, UK: Wiley and Sons; 2011.

Summary of risk of bias of included studies used in the meta-analysis

Figure 1: Summary of risk of bias of included studies assessed by Cochrane risk of bias tool 1

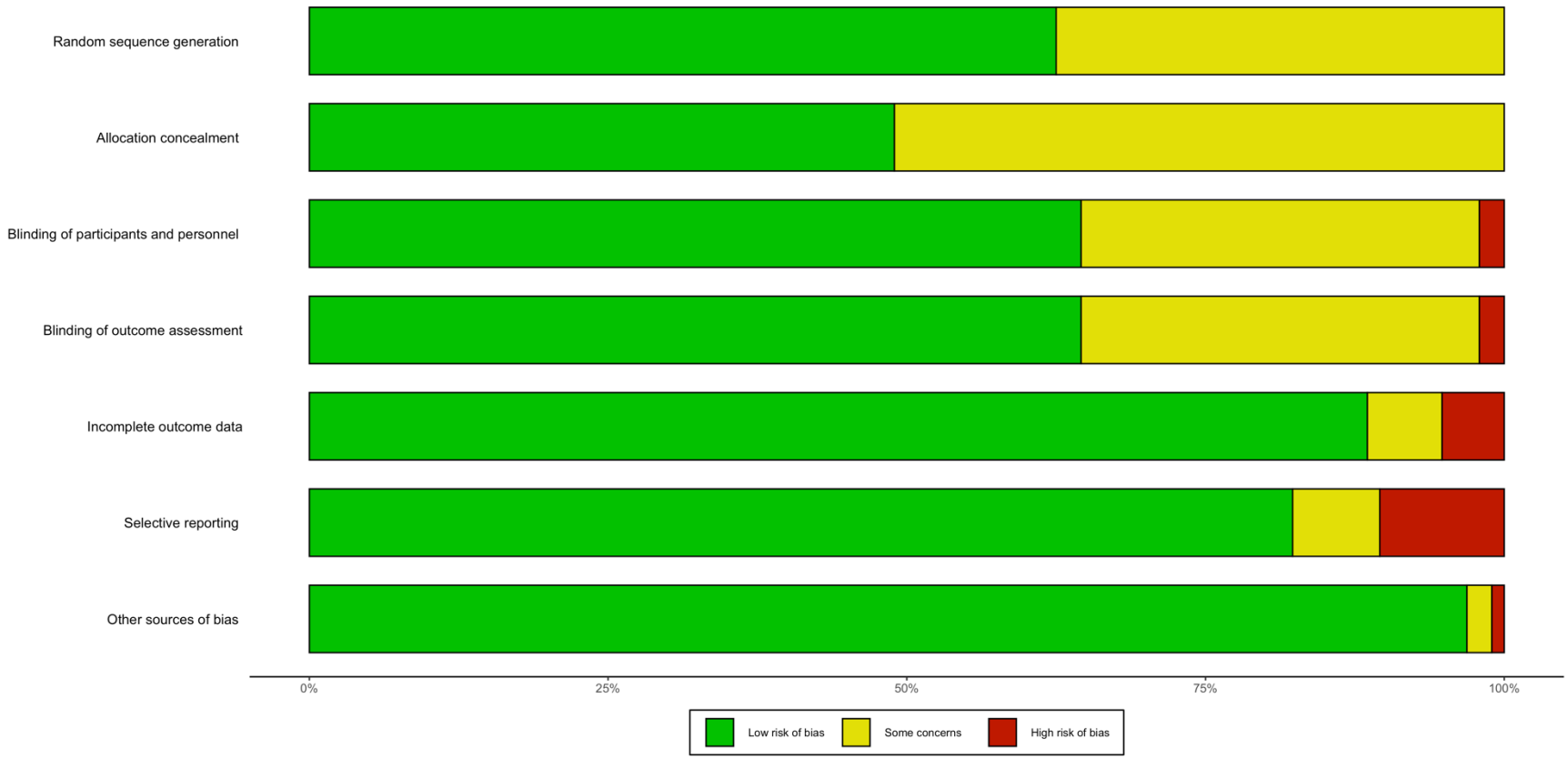


Figure 1: Summary of risk of bias of included studies

Appendix 8: Summary of the statistical results of the meta-analysis

Statistical summary of the primary outcome

Table 4A: Statistical summary of the primary outcome

Drug	N (studies)	N (participant)	Wald test (df=2)		Coefficient 1		Coefficient 2	
			X^2	p-value	Mean (95% CI)	p-value	Mean (95% CI)	p-value
Amisulpride	1	241	1.2921	0.5241	0.0003 (-0.0019 to 0.0025)	0.7908	-0.0007 (-0.0031 to 0.0016)	0.5400
Aripiprazole	10	2694	23.1758	0.0000	0.0624 (0.0031 to 0.1217)	0.0392	-0.0252 (-0.0769 to 0.0265)	0.3389
Asenapine*	5	1775	21.2431	0.0000	0.1707 (0.0953 to 0.2460)	0.0000	-0.1366 (-0.1960 to -0.0772)	0.0000
Brexpiprazole	4	2069	40.4379	0.0000	0.7429 (0.4507 to 1.0351)	0.0000	-0.5538 (-0.8573 to -0.2502)	0.0003
Cariprazine	4	1874	12.6046	0.0018	0.2509 (0.0769 to 0.4249)	0.0047	-0.1910 (-0.4058 to 0.0237)	0.0813
Clozapine	1	43	2.7915	0.2476	0.0065 (-0.0137 to 0.0268)	0.5260	-0.0005 (-0.0271 to 0.0261)	0.9707
Haloperidol	12	2044	10.9051	0.0043	0.1414 (-0.0079 to 0.2908)	0.0634	-0.1078 (-0.2645 to 0.0490)	0.1777
Iloperidone	4	1905	161.6554	0.0000	0.2944 (0.2084 to 0.3805)	0.0000	-0.1836 (-0.2689 to -0.0982)	0.0000

Lumateperone	3	1093	2.5855	0.2745	0.0039 (-0.0136 to 0.0215)	0.6620	0.0010 (-0.0132 to 0.0153)	0.8866
Lurasidone	9	3124	21.6075	0.0000	0.0139 (0.0070 to 0.0209)	0.0001	-0.0106 (-0.0175 to -0.0037)	0.0027
Olanzapine	16	3575	95.4823	0.0000	0.2856 (0.2125 to 0.3587)	0.0000	-0.1233 (-0.1862 to -0.0603)	0.0001
Paliperidone	10	3577	79.8243	0.0000	0.2488 (0.1395 to 0.3581)	0.0000	-0.0913 (-0.1717 to -0.0109)	0.0260
Quetiapine	7	2336	41.6383	0.0000	0.0030 (0.0017 to 0.0043)	0.0000	-0.0021 (-0.0041 to -0.0002)	0.0305
Risperidone	17	5244	112.8530	0.0000	0.5084 (0.4048 to 0.6121)	0.0000	-0.2492 (-0.3170 to -0.1814)	0.0000
Sertindole*	3	712	104.9066	0.0000	0.2987 (0.2151 to 0.3823)	0.0000	-0.1863 (-0.2750 to -0.0975)	0.0000
Ziprasidone	2	599	8.1060	0.0174	0.0217 (0.0056 to 0.0378)	0.0083	-0.0253 (-0.0463 to -0.0044)	0.0179

Table 4B: Statistical summary of the primary outcomes for patients with predominant negative symptoms

Drug	**N (studies)**	**N (participant)**	**Wald test (df=2)**		**Coefficient 1**		**Coefficient 2**	
			X^2	**p-value**	**Mean (95% CI)**	**p-value**	**Mean (95% CI)**	**p-value**

Amisulpride	3	482	17.1569	0.0002	0.0078 (-0.0384 to 0.0540)	0.7402	0.0100 (-0.0395 to 0.0595)	0.6927
Olanzapine	1	173	16.9702	0.0002	0.9542 (0.4623 to 1.4462)	0.0001	-1.4795 (-2.3370 to -0.6219)	0.0007

*****Knot locations at the 10th, 50th, and 90th percentiles were used.

Statistical summary of the secondary outcome

Table 5A: Statistical summary of the secondary outcome

Drug	N (study)	N (participants)	Overall effect (df=2)		Coeffiicient 1		Coefficient 2	
			X^2	p-value	Mean (95% CI)	p-value	Mean (95% CI)	p-value
Amisulpride	1	255	1.9118	0.3845	0.0012 (-0.0012 to 0.0036)	0.3254	-0.0019 (-0.0047 to 0.0010)	0.2009
Aripiprazole	10	2820	17.8114	0.0001	0.0984 (0.0500 to 0.1468)	0.0001	-0.0705 (-0.1136 to -0.0274)	0.0014
Asenapine*	5	1928	23.1622	0.0000	0.1730 (0.0941 to 0.2518)	0.0000	-0.1390 (-0.2310 to -0.0469)	0.0031
Brexpiprazole	4	2088	13.6052	0.0011	0.6429 (0.2591 to 1.0267)	0.0010	-0.4853 (-0.8386 to -0.1320)	0.0071
Cariprazine	4	1892	7.0269	0.0298	0.2242 (-0.0037 to 0.4521)	0.0538	-0.1376 (-0.3439 to 0.0688)	0.1914
Clozapine	1	48	1.7583	0.4151	0.0032 (-0.0071 to 0.0134)	0.5472	-0.0012 (-0.0136 to 0.0113)	0.8551
Haloperidol	16	2745	11.2018	0.0037	0.1696 (0.0585 to 0.2806)	0.0028	-0.1151 (-0.2028 to -0.0275)	0.0100
Iloperidone	4	1964	10.3451	0.0057	0.1401 (0.0439 to 0.2363)	0.0043	-0.0857 (-0.1711 to -0.0002)	0.0495

Lumateperone	3	1225	0.3349	0.8458	0.0071 (-0.0171 to 0.0313)	0.5635	-0.0050 (-0.0305 to 0.0206)	0.7031
Lurasidone	11	3648	5.0582	0.0797	0.0160 (0.0020 to 0.0300)	0.0250	-0.0145 (-0.0275 to -0.0015)	0.0284
Olanzapine	17	3905	104.0654	0.0000	0.1878 (0.1383 to 0.2373)	0.0000	-0.0866 (-0.1253 to -0.0479)	0.0000
Paliperidone	11	4215	30.8891	0.0000	0.1918 (0.0473 to 0.3364)	0.0093	-0.0843 (-0.2020 to 0.0334)	0.1602
Quetiapine	8	3045	13.3295	0.0013	0.0024 (0.0010 to 0.0038)	0.0005	-0.0024 (-0.0041 to -0.0006)	0.0083
Risperidone	21	6443	73.7476	0.0000	0.3109 (0.2292 to 0.3925)	0.0000	-0.1561 (-0.2048 to -0.1074)	0.0000
Sertindole*	3	737	13.5372	0.0011	0.1320 (0.0567 to 0.2073)	0.0006	-0.0872 (-0.1523 to -0.0220)	0.0087
Ziprasidone	4	1298	1.5331	0.4646	0.4335 (-0.0120 to 0.0280)	0.0080	0.6345 (-0.0345 to 0.0210)	-0.0067

Table 5B: Statistical summary of the secondary outcome for patients with predominant negative symptoms

Drug	**N (study)**	**N (participants)**	**Overall effect (df=2)**		**Coefficient 1**		**Coefficient 2**	
			X^2	**p-value**	**Mean (95% CI)**	**p-value**	**Mean (95% CI)**	**p-value**

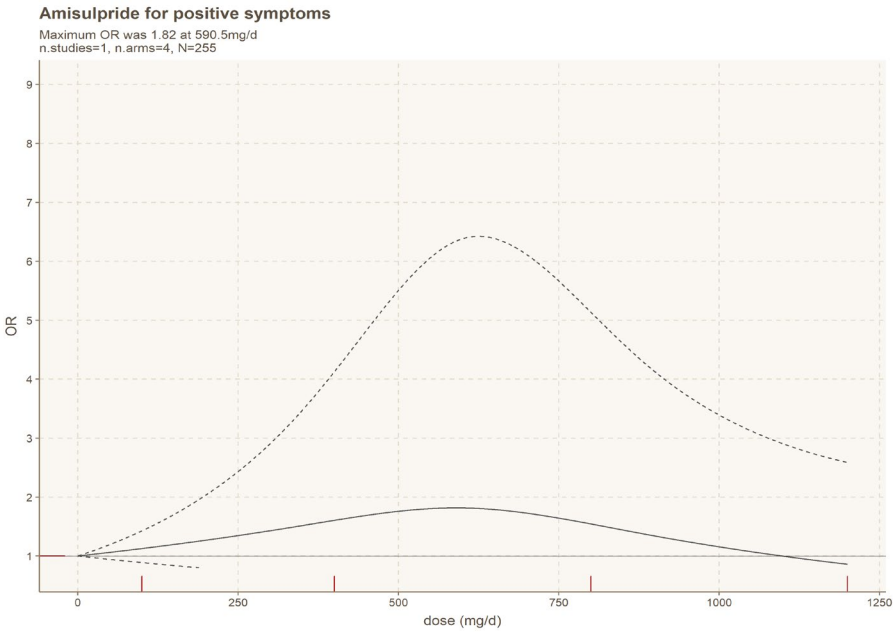
Amisulpride	3	482	4.3864	0.1116	0.0081 (-0.0315 to 0.0477)	0.6871	-0.0015 (-0.0481 to 0.0452)	0.9506
Olanzapine	1	173	4.4032	0.1106	0.3443 (0.0224 to 0.6661)	0.0360	-0.5499 (-1.0669 to -0.0330)	0.0371

*****Knot locations at the 10th, 50th, and 90th percentiles were used.

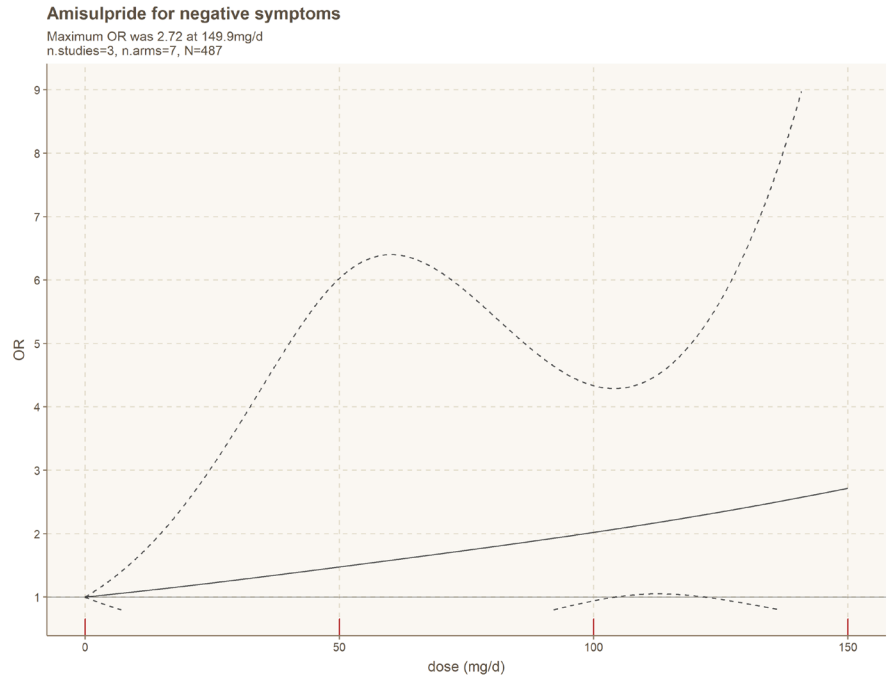
Appendix 9: Detailed description of the secondary outcome

Amisulpride

a. For positive symptoms: only one study with 255 participants was included and due to limited data, no overall dose-response relationship was detected.

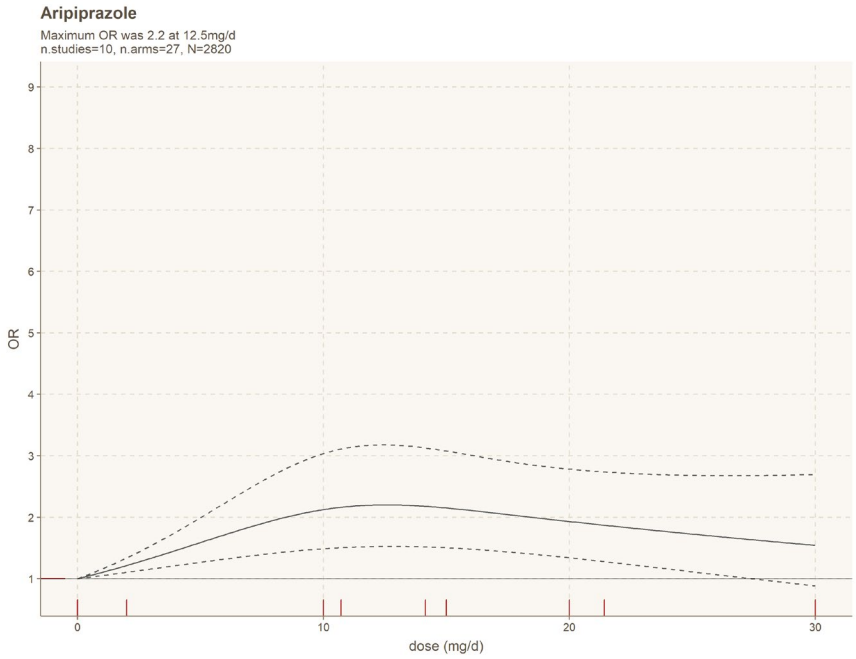


b. For negative symptoms: 3 studies with 487 participants were included in the analysis. The dose-response curve was monotonic as it is in the primary outcome. However, due to limited data, the confidence intervals were wide and no statistically significant result was detected.



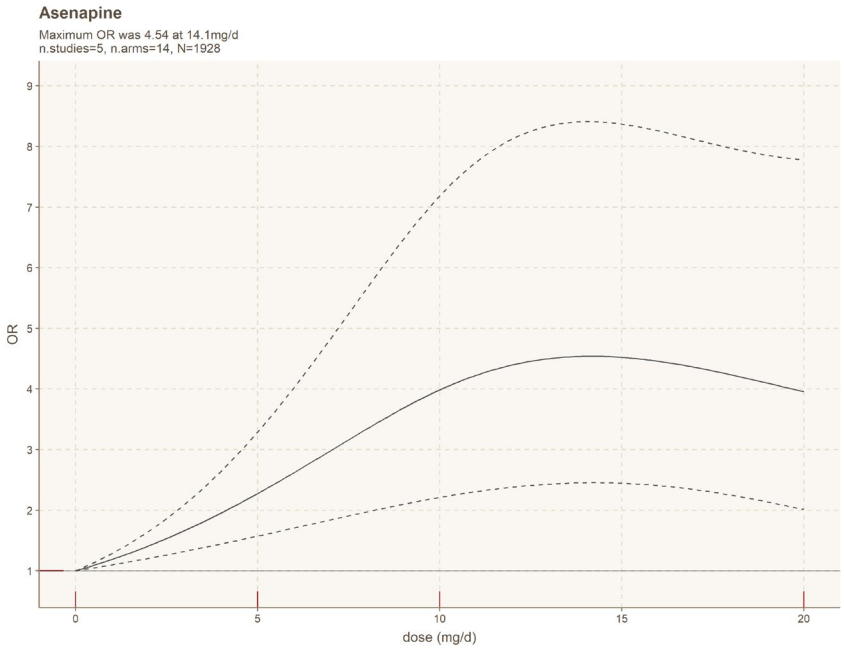
Aripiprazole

10 studies with 2820 participants were included. The dose response curve reached a plateau after 12.5mg/d.



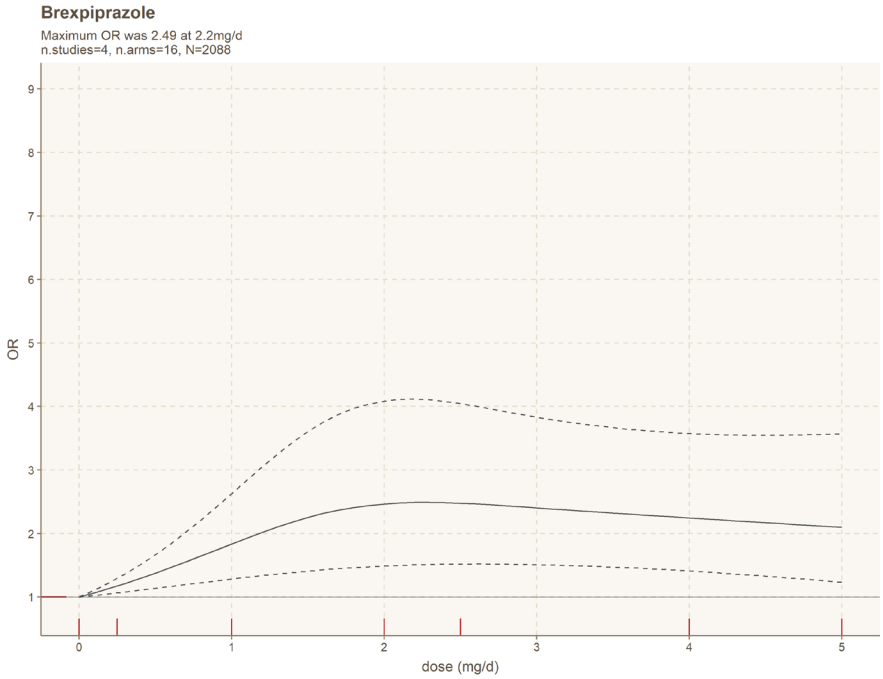
Asenapine

5 studies with 1928 participants were included. The dose response curve reached a plateau after 14mg/d.



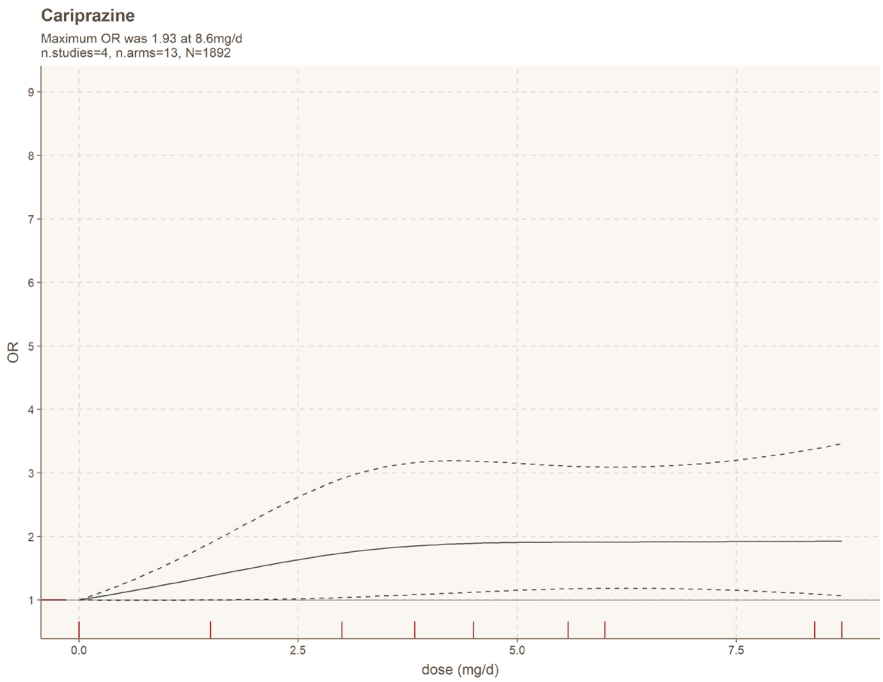
Brexpiprazole

4 studies with 2088 participants were included. The dose response curve reached a plateau after 2.2mg/d.



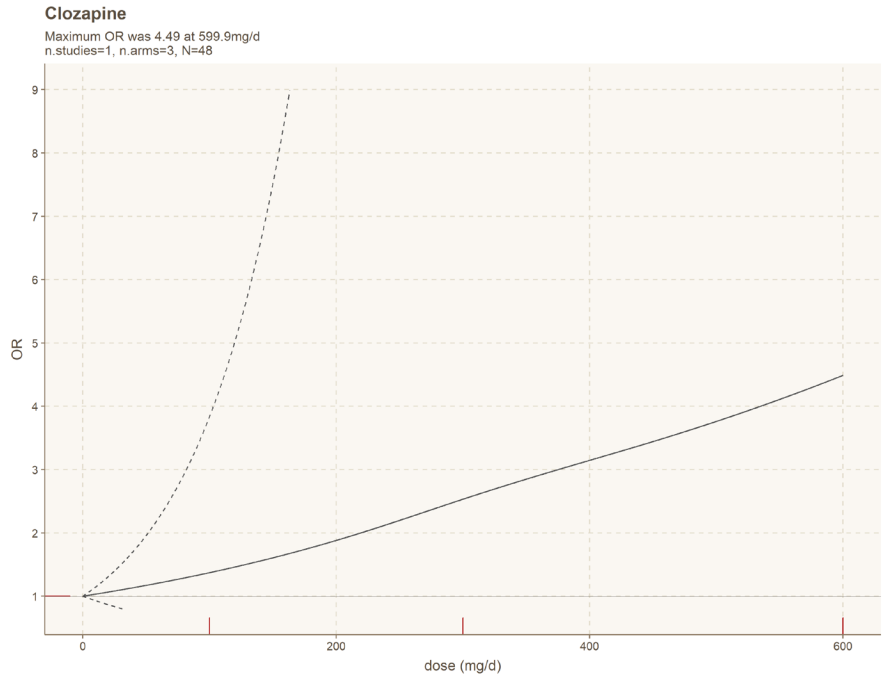
Cariprazine

4 studies with 1892 participants were included. The dose response curve reached a plateau after around 4.5mg/d.



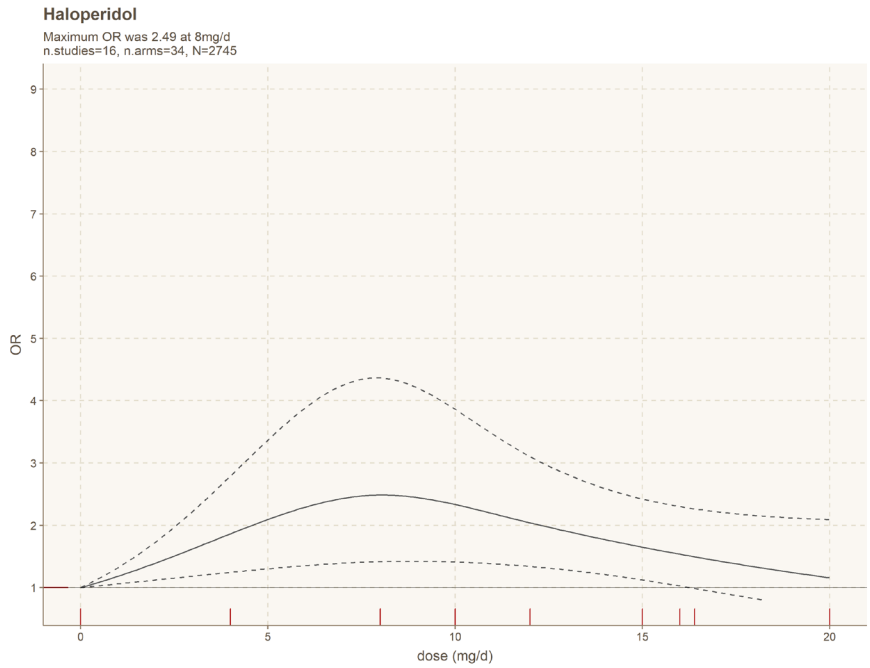
Clozapine

one study with 48 participants were included. The dose-response curve with monotonic with extremely wide confident intervals. Thus no overall dose-response relationship was detected due to limited data.



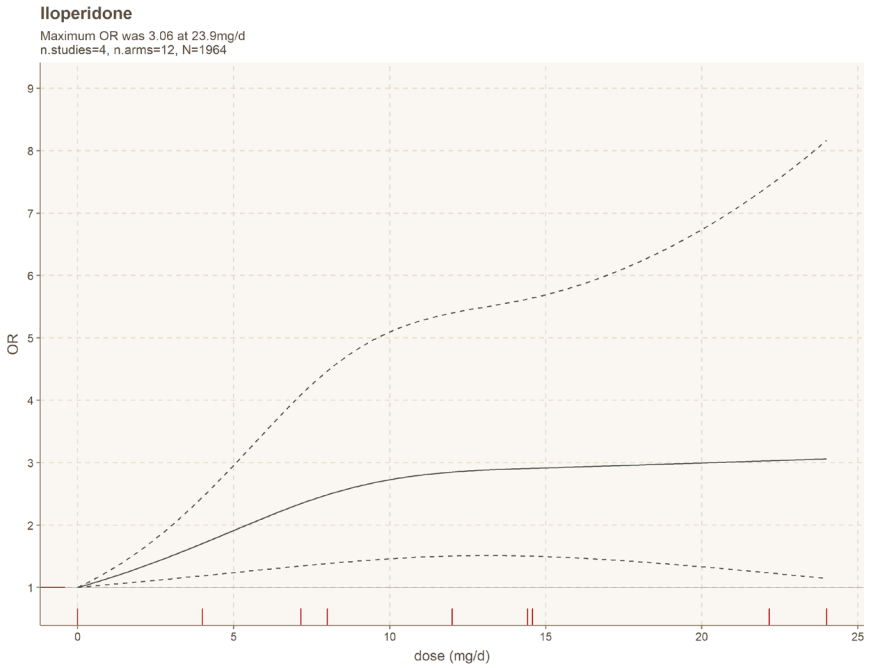
Haloperidol

16 studies with 2745 participants were included. The dose response curve was bell-shaped, and most number of participants with weight gain was achieved at 8mg/d.



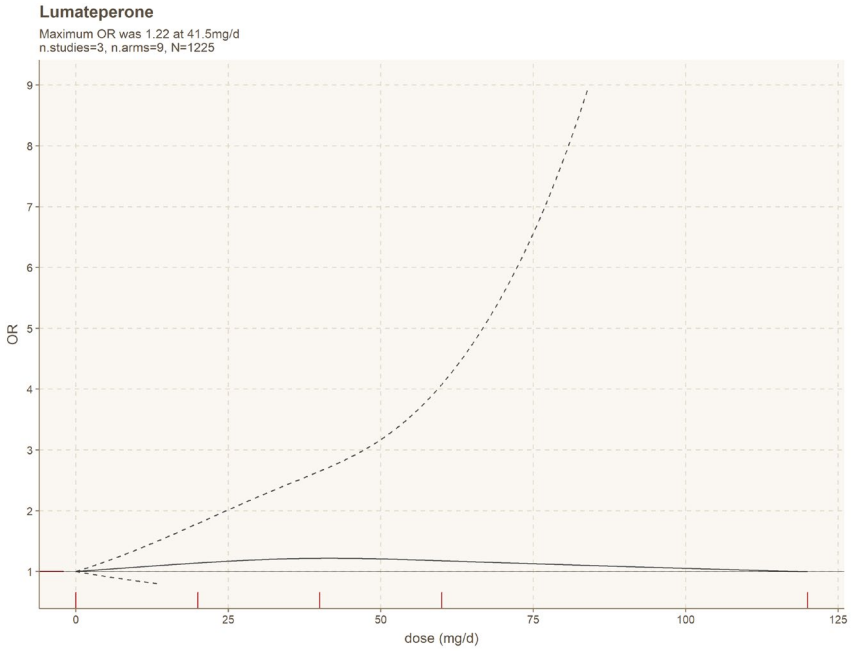
Iloperidone

4 studies with 1964 participants were included. The dose response curve reached a plateau after around 12mg/d.



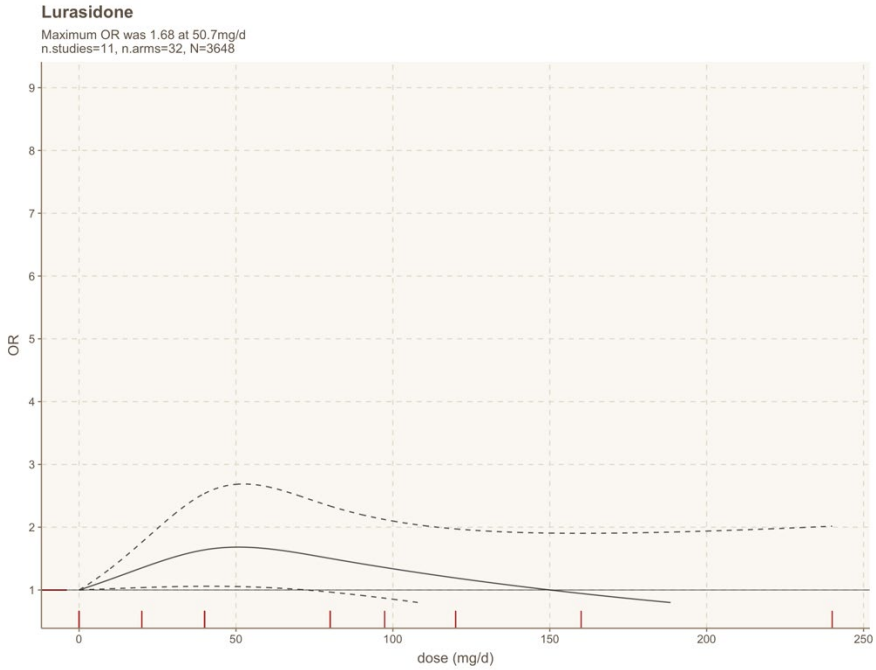
Lumateperone

3 studies with 1225 participants were included. No overall dose-response relationship was detected.



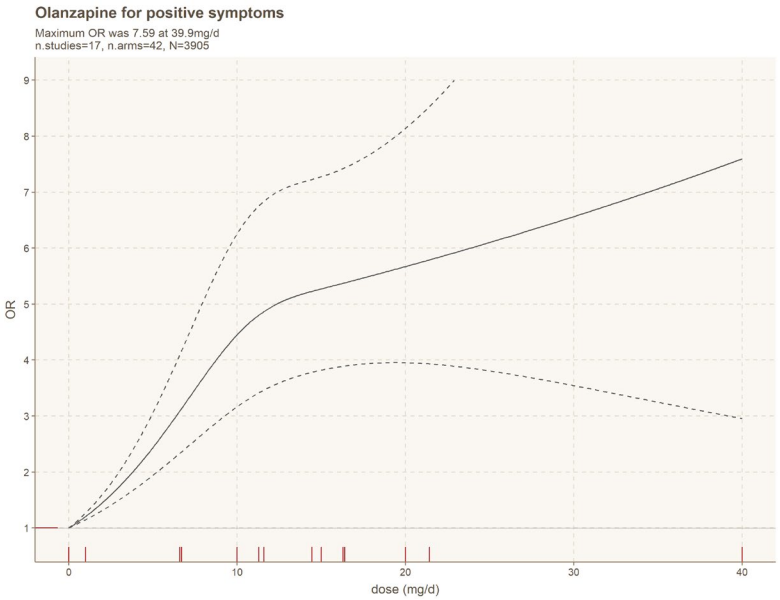
Lurasidone

11 studies with 3648 participants were included. No overall dose-response relationship was detected.

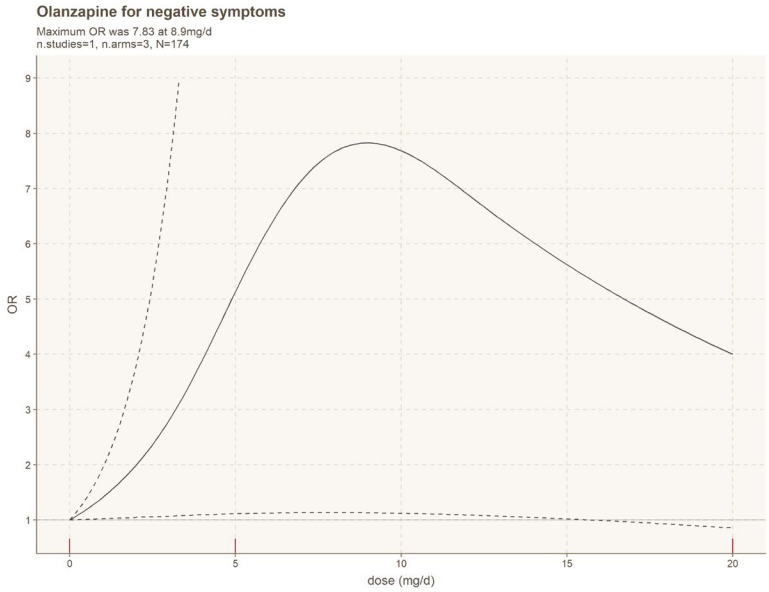


Olanzapine

a. For positive symptoms: 17 studies with 3905 participants were included. The number of participants with weight gain continuously increased with the rising doses, and the dose-response curve showed no sign of plateau at 40mg/d.

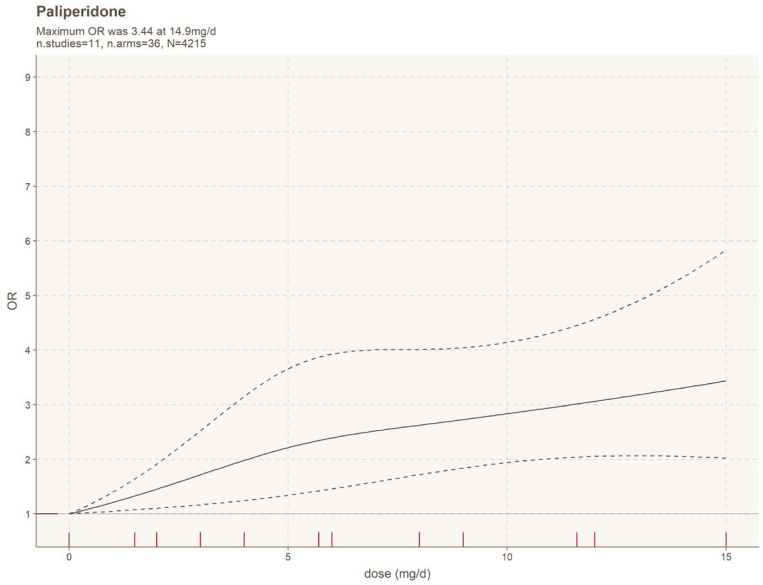


b. For negative symptoms: one study with 174 participants were included. No overall dose-response relationship was detected.



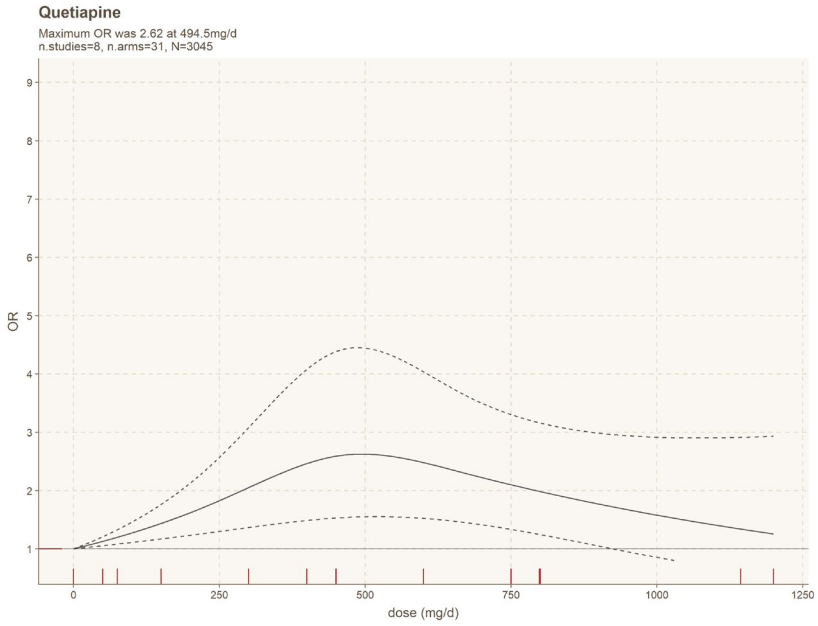
Paliperidone

11 studies with 4215 participants were included. The dose response curve was almost linear and didn't reach a plateau before 15mg/d.



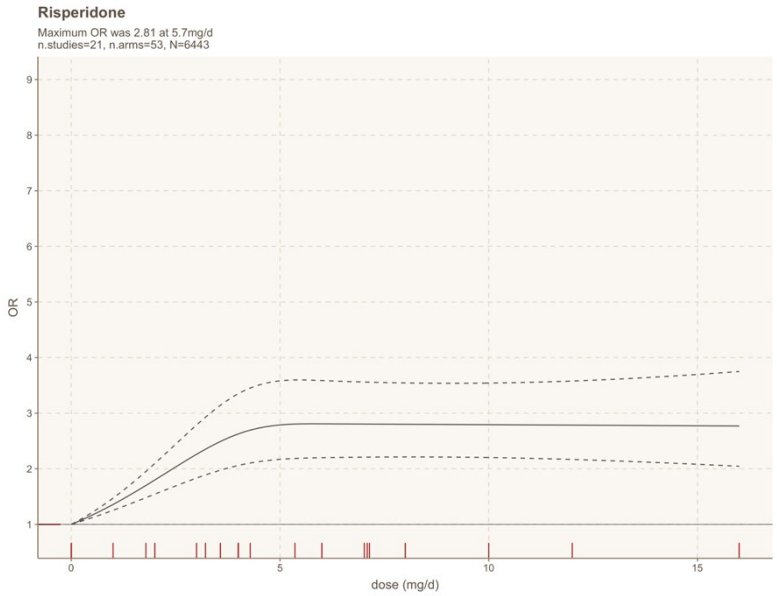
Quetiapine

8 studies with 3045 participants were included. The dose response curve was bell-shaped, and the most number of participants with weight gain was achieved at 494.5mg/d.



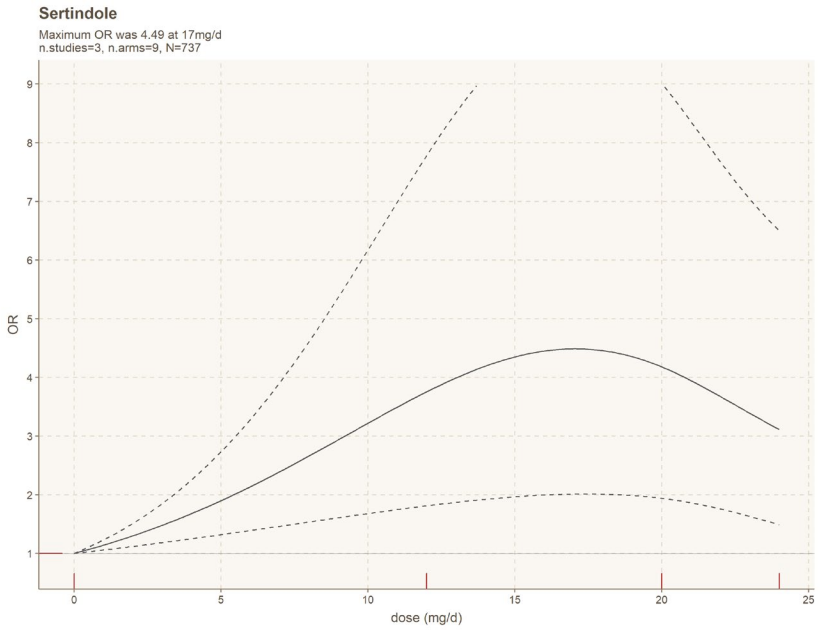
Risperidone

21 studies with 6443 participants were included. The dose response curve reached a plateaued after around 5mg/d.



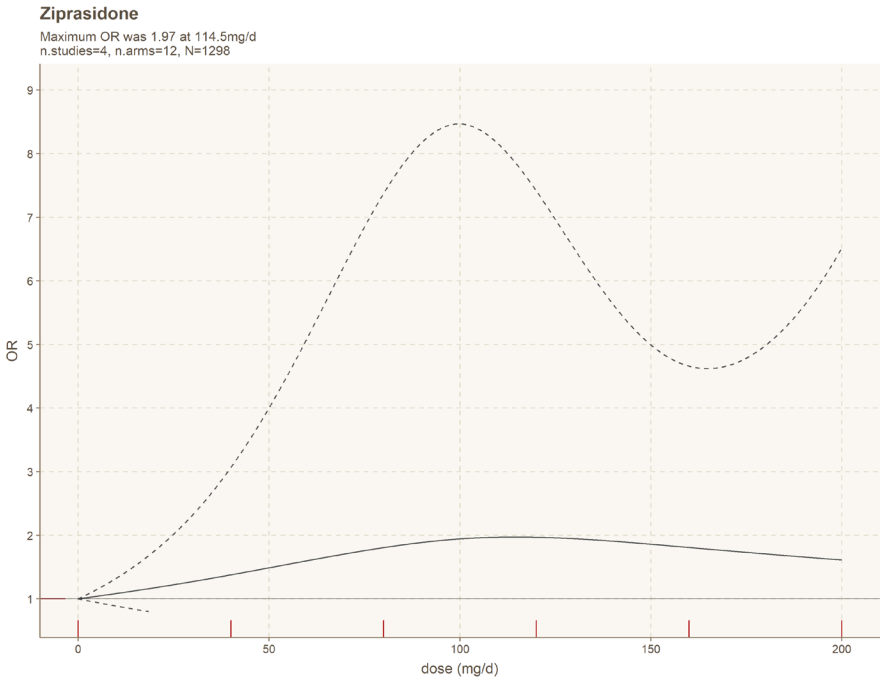
Sertindole

3 studies with 737 participants were included. The dose response curve reached a plateaued after 17mg/d.



Ziprasidone

4 studies with 1298 participants were included. The dose response curve reached a plateau after 114.5mg/d.



Zotepine

Only one placebo-controlled study with one dose arm provided usable data. However, no dose-response curve can be plotted for one antipsychotic dose arm.

Appendix 10: Sensitivity analyses

All sensitivity analyses for both primary and secondary outcomes are presented here. Red curves represent the main analyses, black ones showing sensitivity analyses.

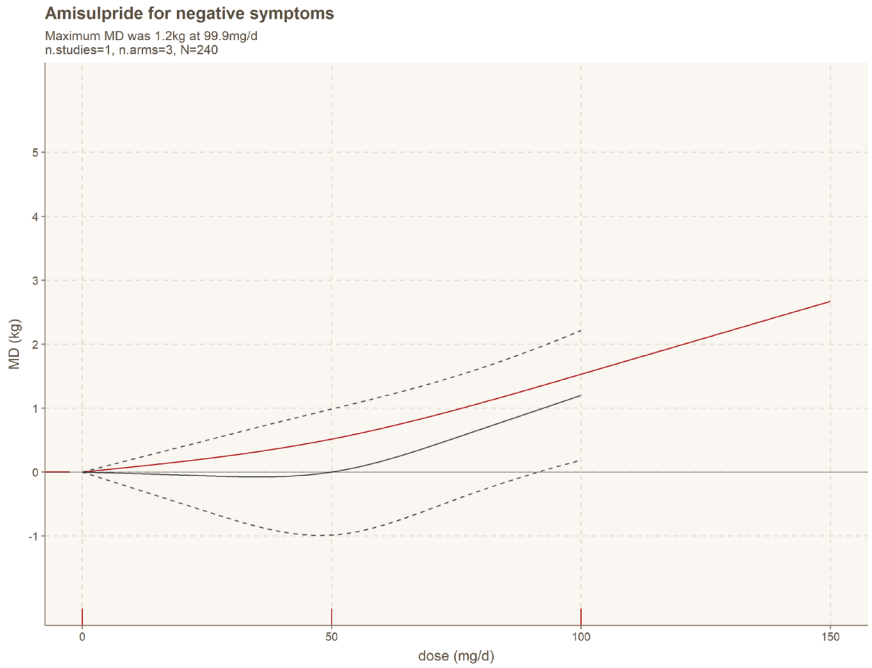
Sensitivity analyses for the primary outcome

Exclusion of studies that compared only one single dose of an antipsychotic with placebo

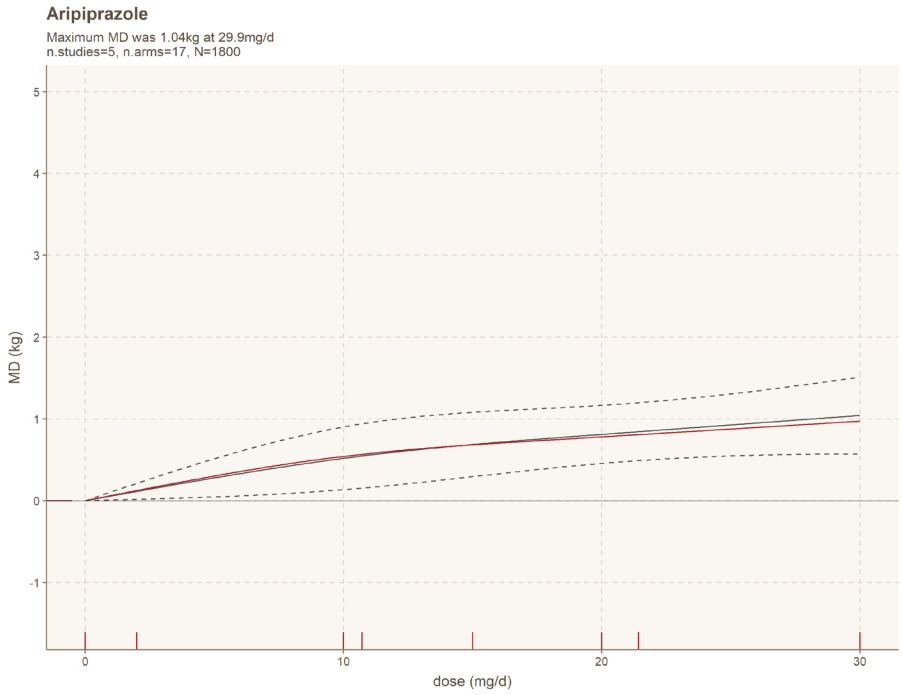
No study was removed from studies for amisulpride (patients with positive symptoms), brexipiprazole, cariprazine, clozapine, lumateperone and olanzapine (patients with negative symptoms).

For other individual antipsychotic drugs:

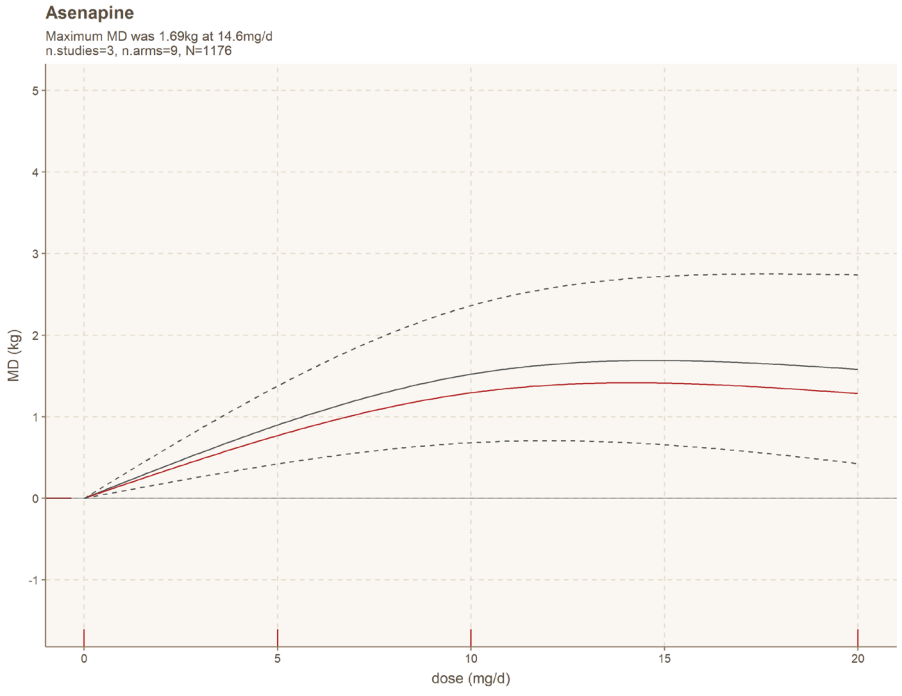
Amisulpride for negative symptoms: one study with 240 participants were analyzed. No substantial difference was noticed.



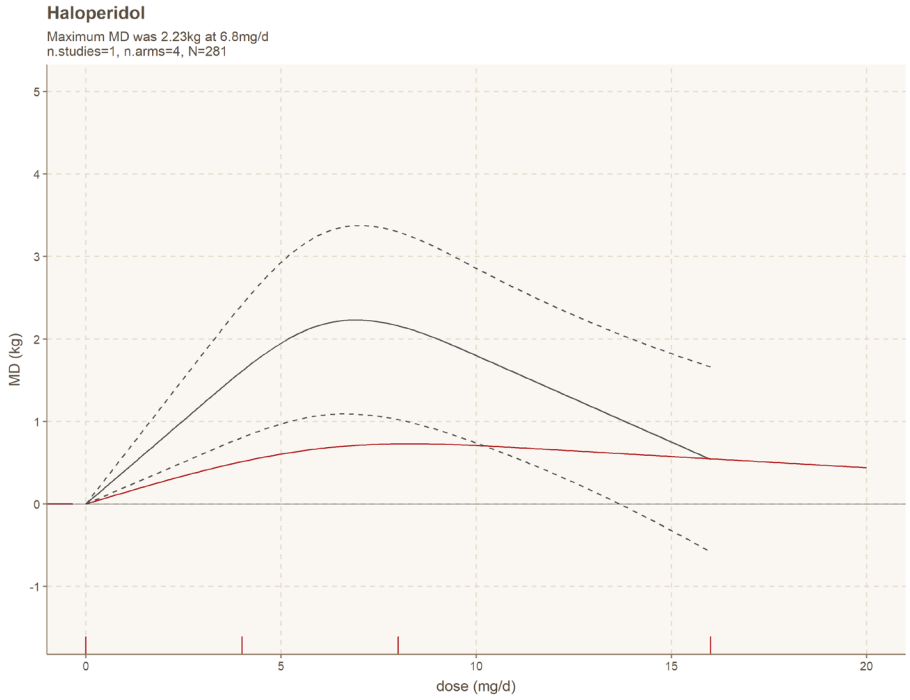
Aripiprazole: 5 studies with 1800 participants were analyzed. No substantial difference was noticed.



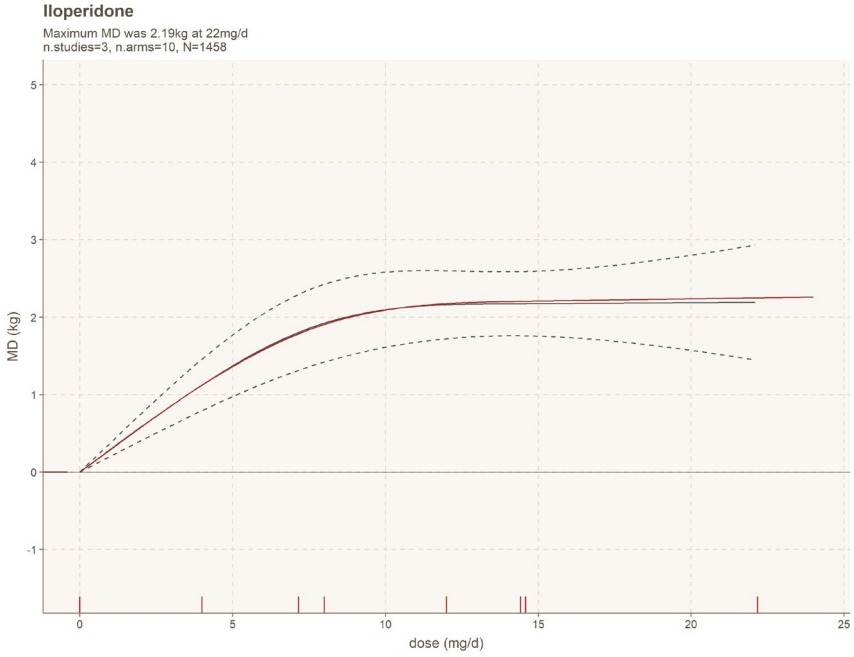
Asenapine: 3 studies with 1176 participants were analyzed. No substantial difference was noticed.



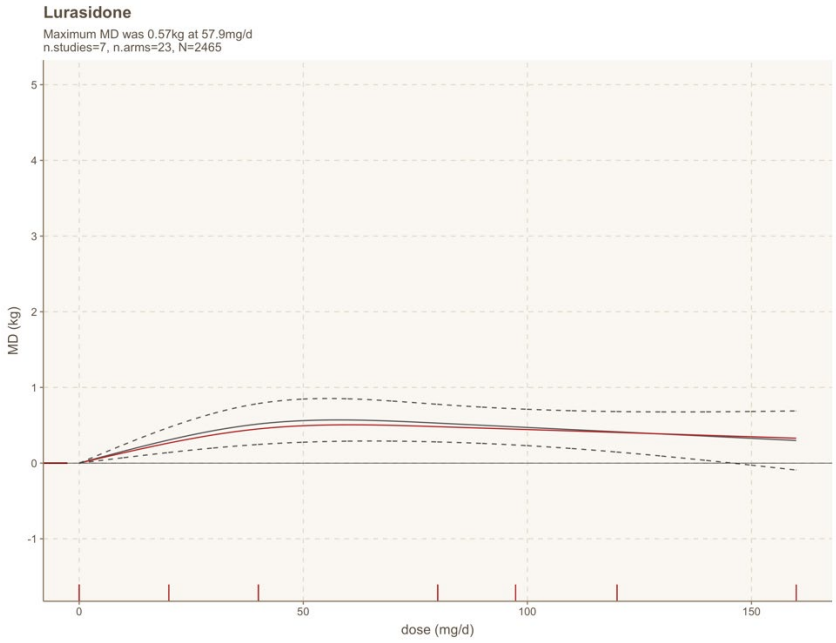
Haloperidol: 1 study with 281 participants were analyzed. The placebo-controlled study investigated doses at 4mg/d, 8mg/d and 16mg/d for 8 weeks, which was the only study in our search provided data under 8mg/d. The dose-response curve was bell-shaped, peaking at 2.23kg with the dose at 6.8mg/d.



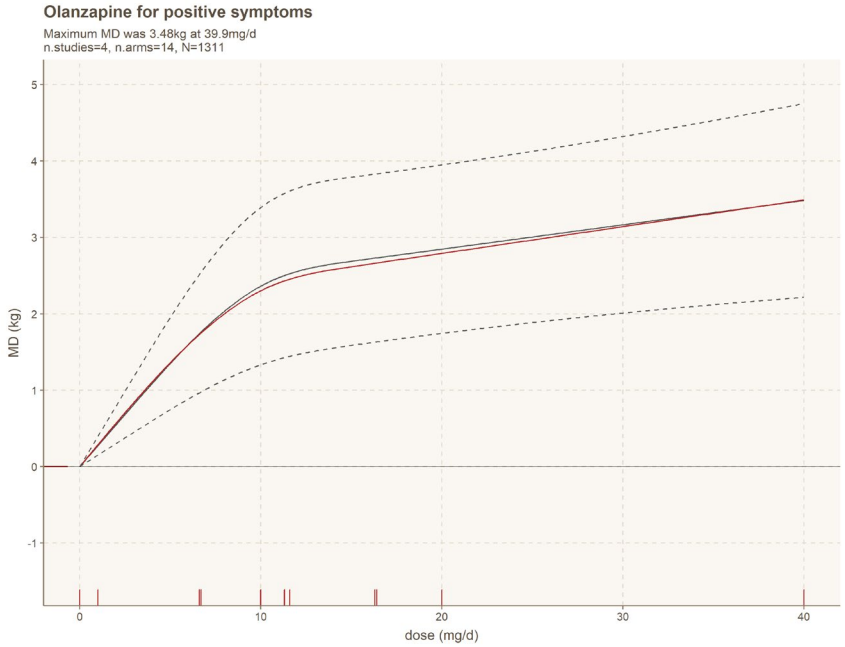
Iloperidone: 3 studies with 1458 participants were analyzed. No substantial difference was noticed.



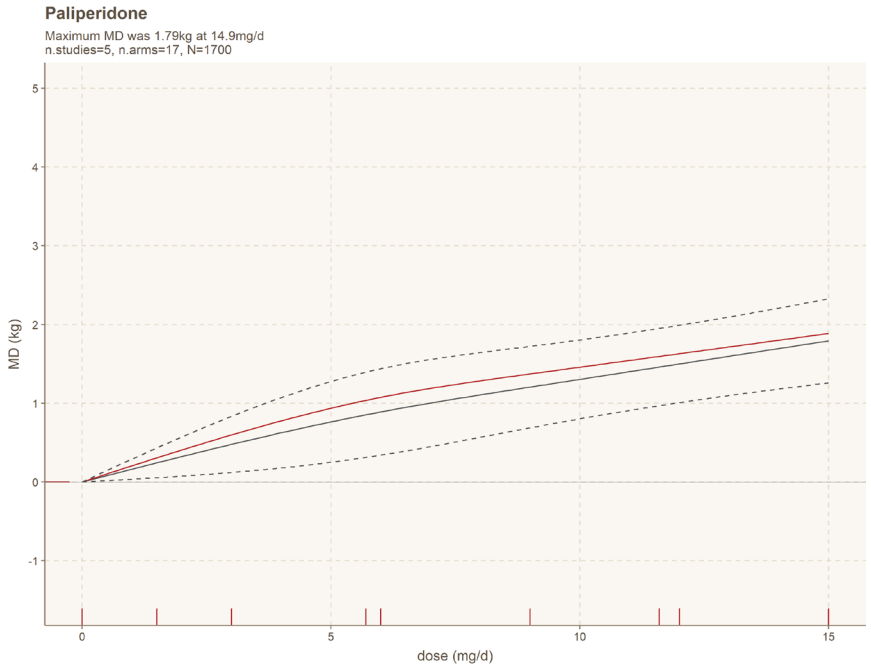
Lurasidone: 7 studies with 2465 participants were analyzed. No substantial difference was noticed.



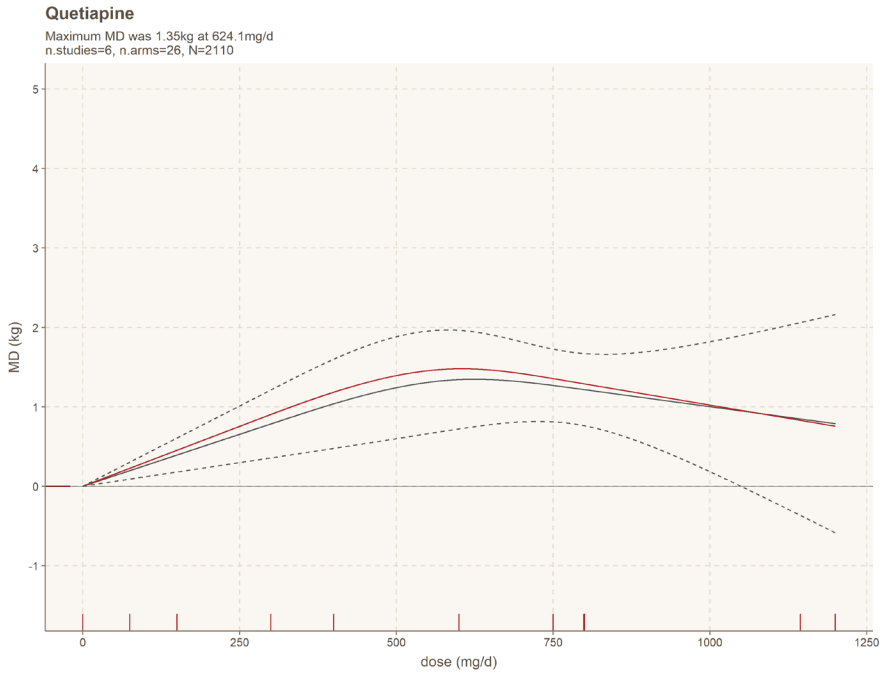
Olanzapine for positive symptoms: 4 studies with 1311 participants were analyzed. No substantial difference was noticed.



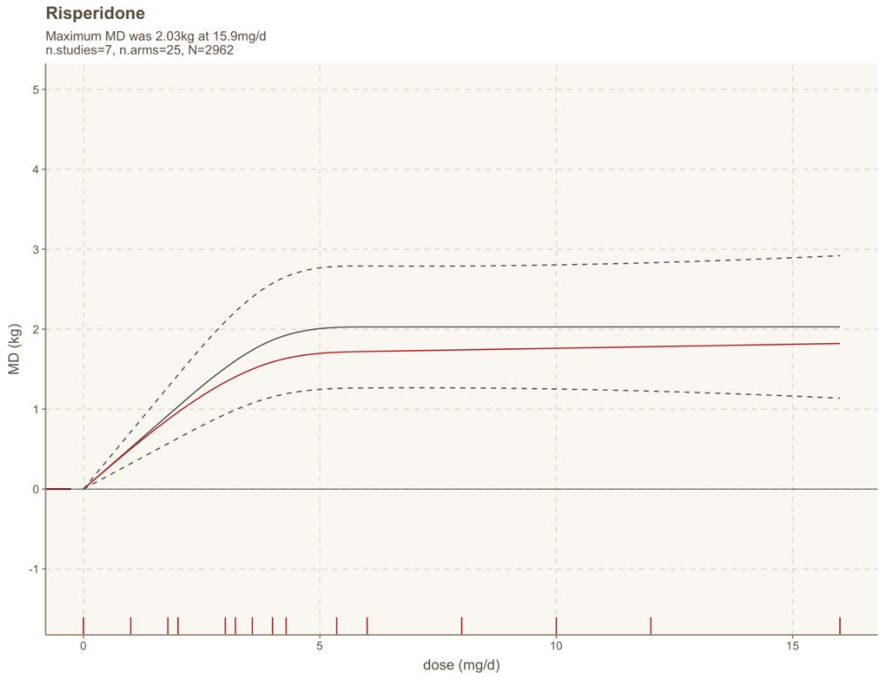
Paliperidone: 5 studies with 1700 participants were analyzed. No substantial difference was noticed.



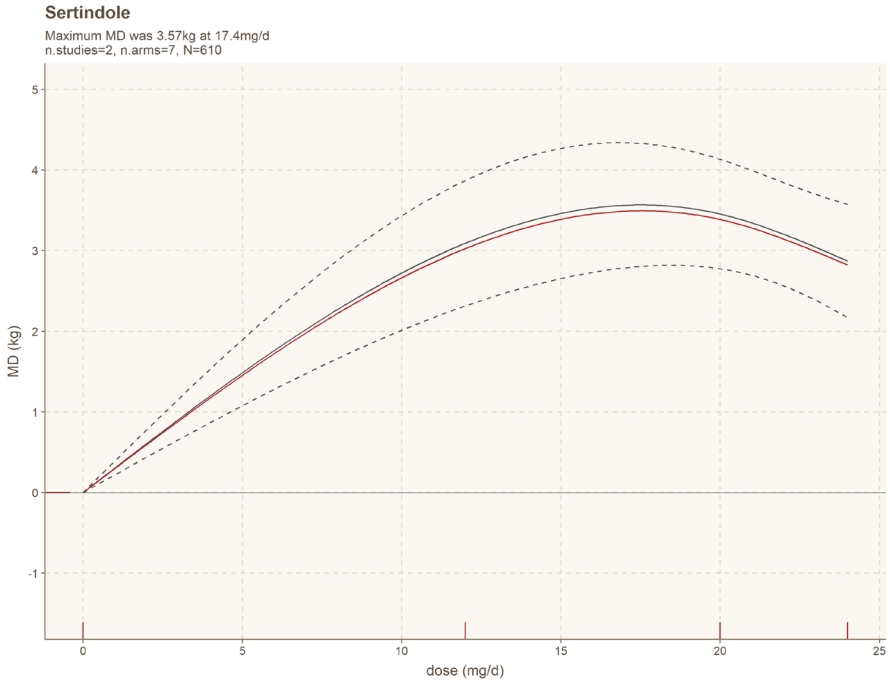
Quetiapine: 6 studies with 2110 participants were analyzed. No substantial difference was noticed.



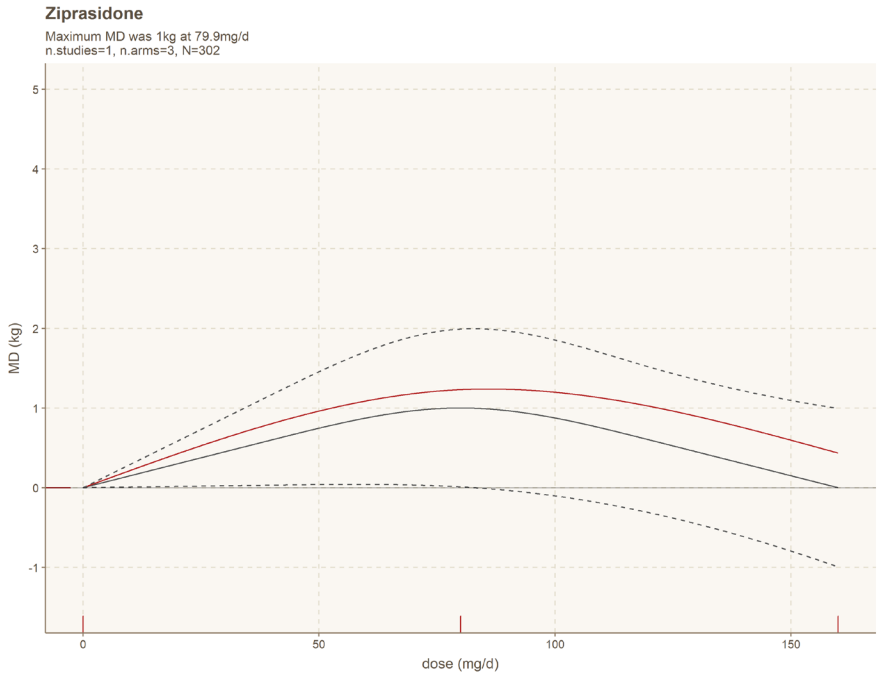
Risperidone: 7 studies with 2962 participants were analyzed. No substantial difference was noticed.



Sertindole: 2 studies with 610 participants were analyzed. No substantial difference was noticed.



Ziprasidone: 1 studies with 302 participants were analyzed. No substantial difference was noticed.

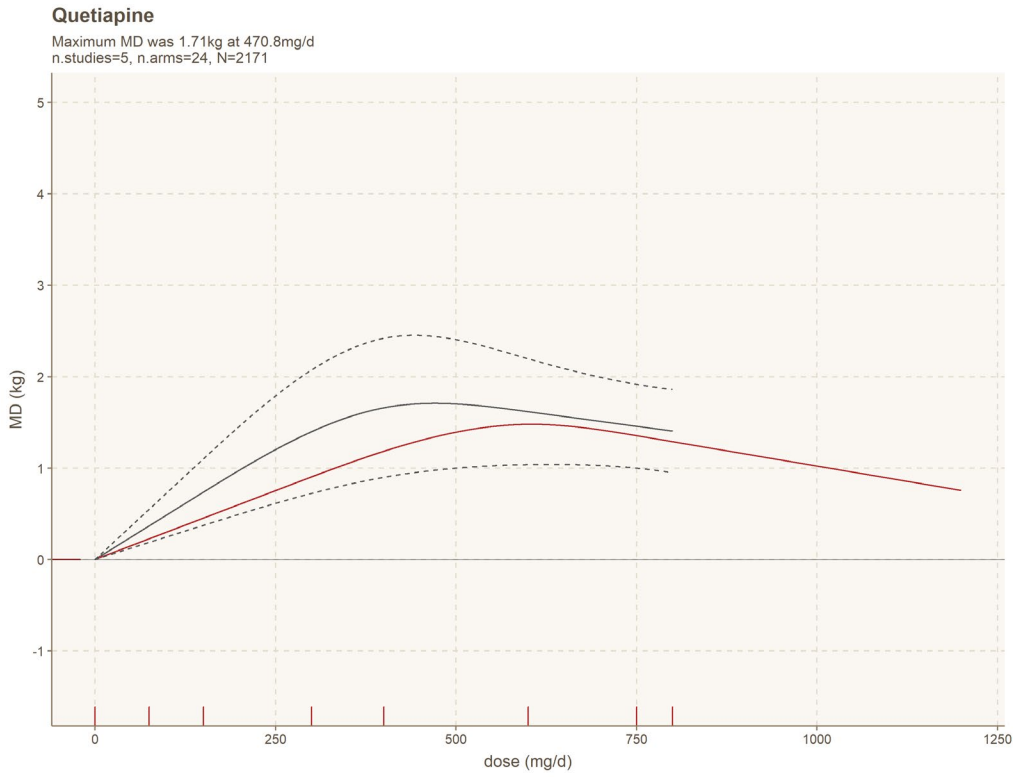


Exclusion of studies in treatment resistant patients.

Treatment resistant patients were recruited in 2 quetiapine studies (Honer 2010, Lindenmayer 2011), the only one clozapine study (Simpson 1999), 1 lurasidone study (Meltzer 2020) and 1 risperidone LAI study (Meltzer 2014). Two studies (Meltzer 2014, Meltzer 2020) were not included in the main analysis for primary outcome due to only BMI data reported.

So, we presented here the sensitivity analysis in quetiapine.

Quetiapine: 5 studies with 2171 participants were analysed. After removal of treatment resistant studies which contributed to the high doses, the curve plateaued at lower doses with comparable weight gain as primary analysis. The shape of the curve was not substantially changed.

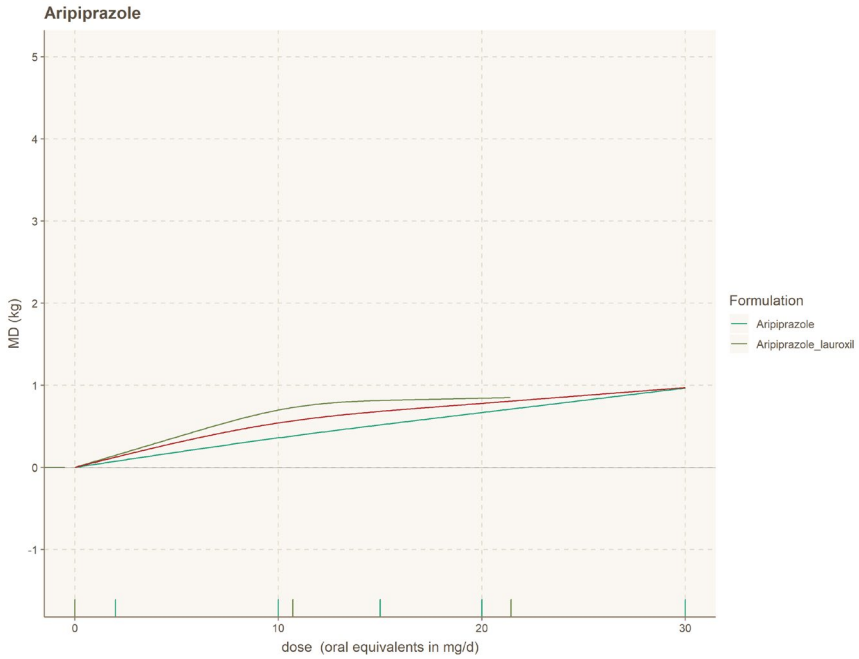


Separate analyses of different formulations of antipsychotics.

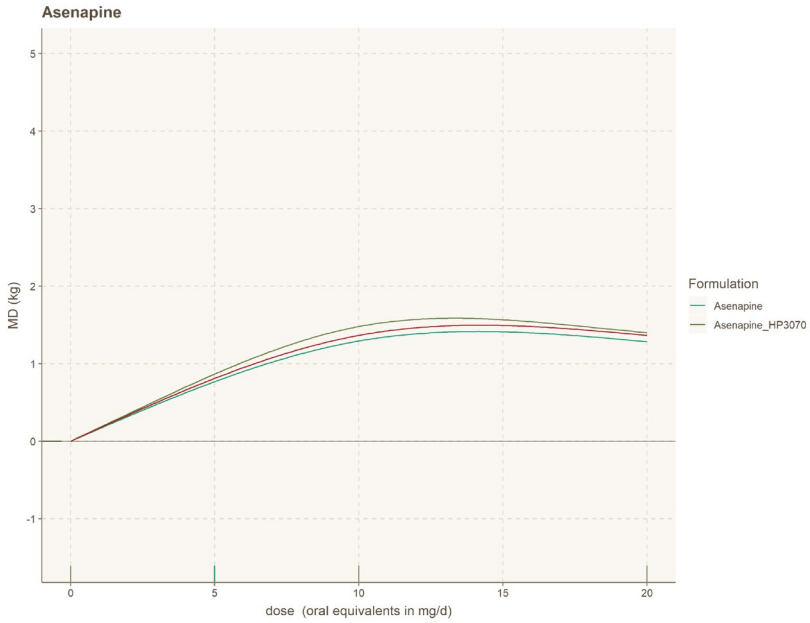
Aripiprazole (oral and lauroxil), asenapine (oral and transdermal patch (HP3070)), olanzapine (oral and LAI), paliperidone (oral and LAI), quetiapine (IR and XR), risperidone (oral, LAIs (consta, RBP-7000)) were analysed separately.

The red curves were the pooled curves in our main analyses. Other different coloured curves represented different formulations. Formulation information was provided on the right of the plots with corresponding colour identifiers.

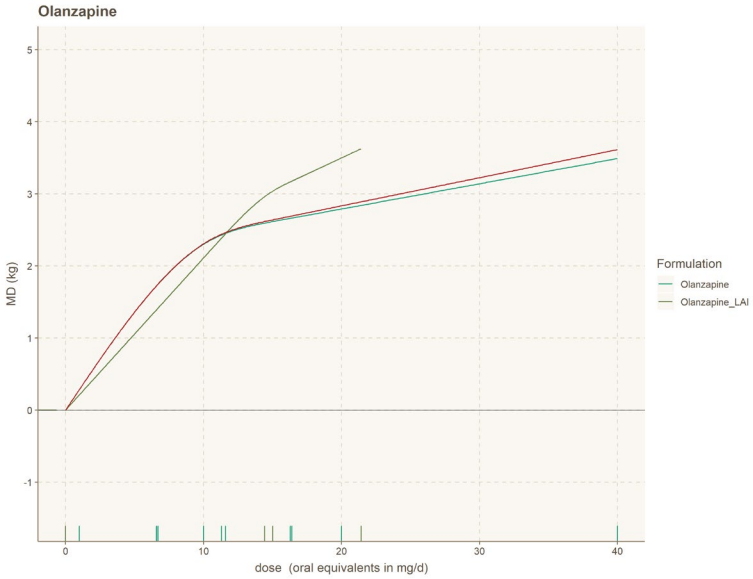
Aripiprazole: Eight studies (n=1733) examined aripiprazole oral doses between 2mg/day and 30mg/day. Two aripiprazole LAIs were available, lauroxil and maintena. One study (n=622) on aripiprazole lauroxil compared 441 mg four-weekly and 882mg four-weekly with placebo (1). One study (n=340) compared 400mg four-weekly aripiprazole maintena with placebo (2), thus no single curve for this formulation was drawn here. No substantial difference was noticed.



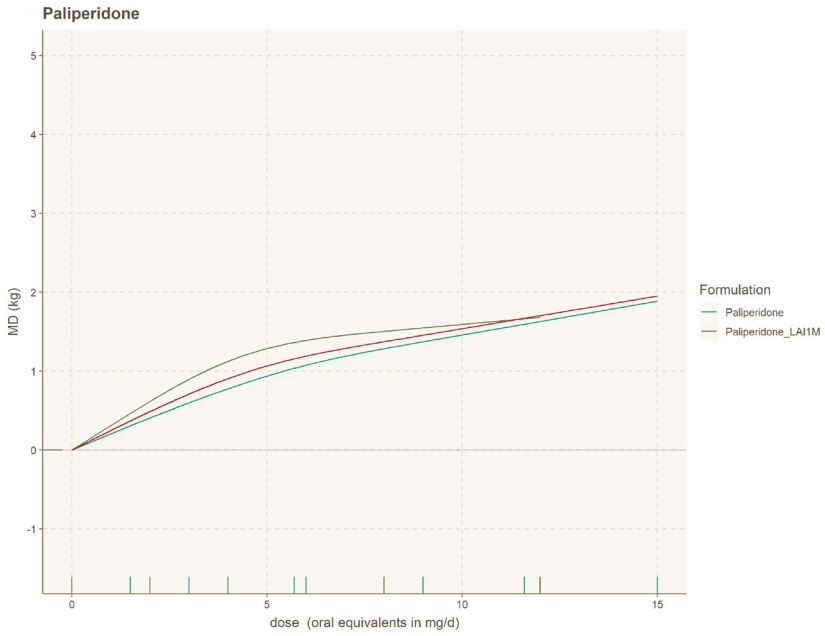
Asenapine: Four studies (n=1276) examined asenapine oral doses between 5mg/d and 20mg/d with placebo. One dosing-finding, placebo-controlled study (n=499) compared 3.8mg/d and 7.6mg/d asenapine maleate transdermal patch (HP3070). No substantial difference was noticed.



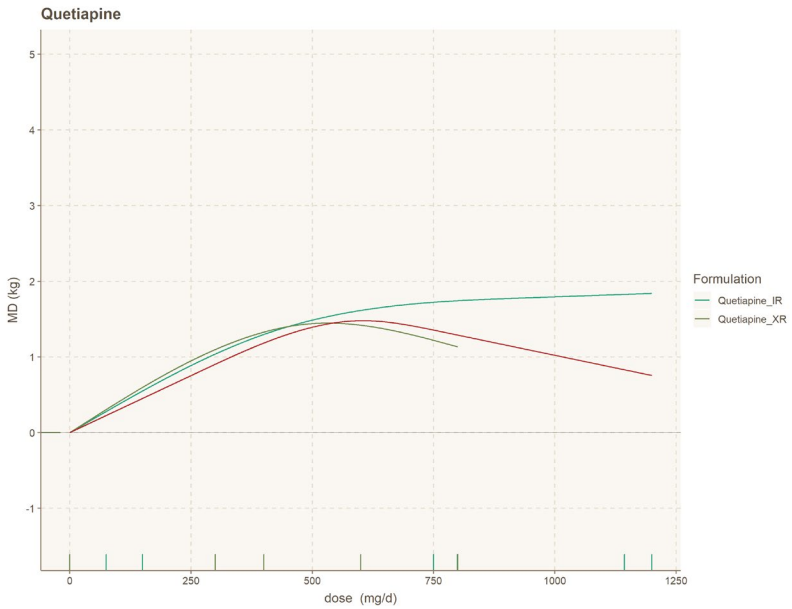
Olanzapine: For patients with acute exacerbations of positive symptoms, 15 studies (n=3171) examined olanzapine oral doses between 1mg/d and 40mg/d and one single study (n=404) compared olanzapine LAI 210mg fortnightly, 405mg four-weekly and 300mg fortnightly with placebo. 405mg four-weekly was converted to 202.25mg fortnightly for comparability. No substantial difference was noticed between the curve for olanzapine oral and the one for main analysis. The dose-response curve of olanzapine LAI also showed no sign of plateau in the examined dose range, however, due to limited data and no higher doses available, we avoided over interpretation.



Paliperidone: Six studies (n=1972) examined paliperidone oral doses between 1.5mg/d and 15mg/d. Four studies (n=1605) examined paliperidone LAI doses between 25 and 150 mg four-weekly. No substantial difference was noticed.



Quetiapine: Six studies (n=1179) examined quetiapine immediate release doses between 75 and 1200mg/d and four studies (n=1463) examined extended-release doses between 300 and 800mg/d.
The dose-response curve of quetiapine IR reached a plateau after 600mg/d.
The dose-response curve of quetiapine ER was similar with the main curve, however, data of doses higher than 800mg/d were not available.

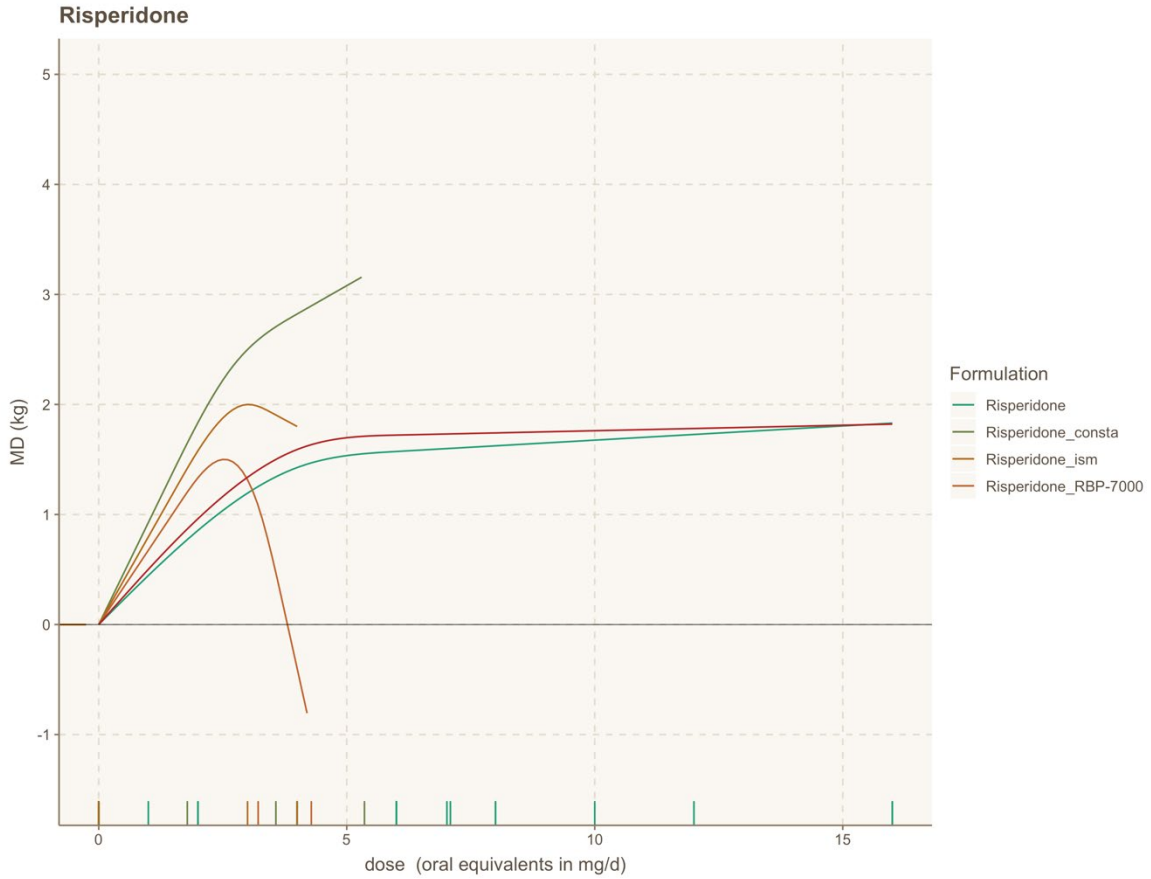


Risperidone: Fourteen studies (n=4144, Chouinard 1993 and Marder 1994 were combined as one study and Study 3004 and Study 3005 were summarized in one publication) compared *risperidone oral* doses between 2mg/d and 16mg/d. No substantial difference with the main analysis was noticed.

One dose-finding study (n=400) examined intramuscular injections of risperidone consta doses between 25mg and 100mg fornightly in acutely ill patients. More weight gain was reached and no higher doses were available. There was no sign of plateau within the examined dose range, however, the increase of the weight slowed down near the dose at which the curve plateaued in the main analysis.

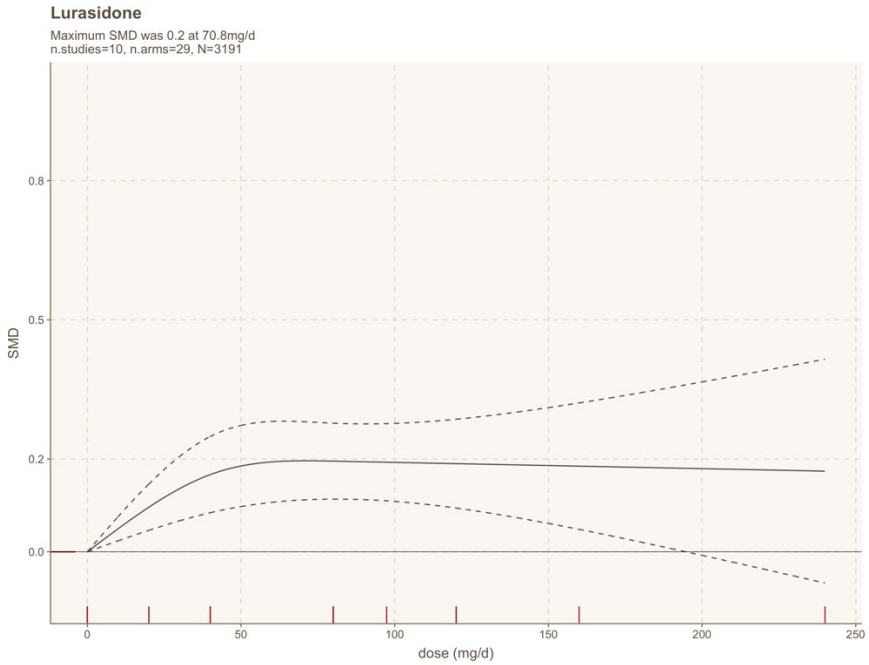
One dose-finding study (n=324) compared 90mg and 120mg once monthly RBP-7000, a sustained-release subcutaneous injection of risperidone with placebo. Data were limited and no overall dose-response relationship was detected (p-value = 0.7313).

One dose-finding study (n=376) compared 75mg and 100mg once monthly risperidone ISM, a new LAI intramuscular formulation of risperidone with placebo. A dose-response relationship was detected (p-value < 0.01), however, with limited data.

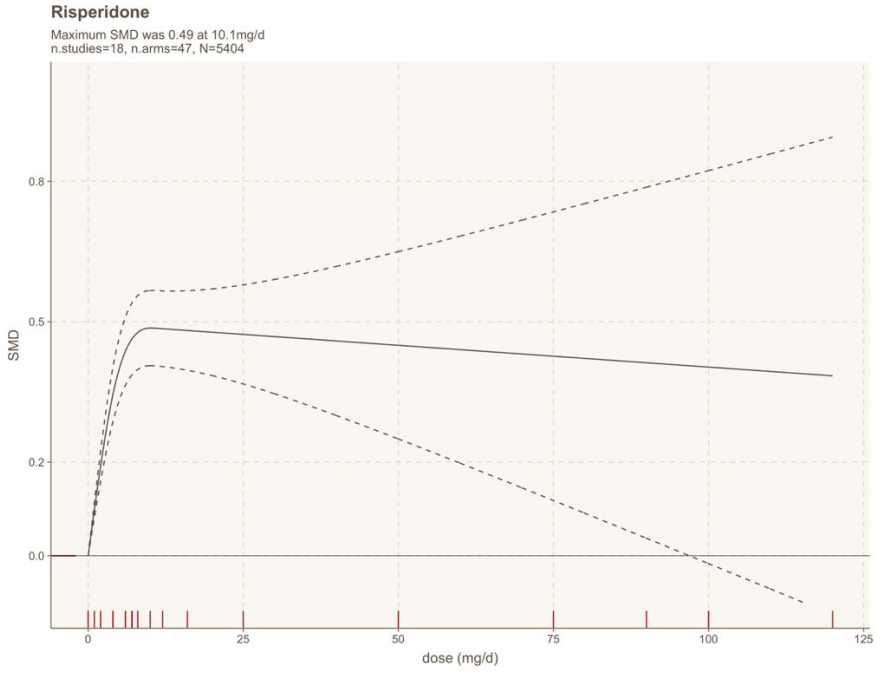


Standardized mean difference (SMD) as effect size measure in lurasidone and risperidone studies

Lurasidone: 10 studies with 3191 participants were analysed. The dose-response curve plateaued after around 50mg/d, which was similar to the primary analysis.

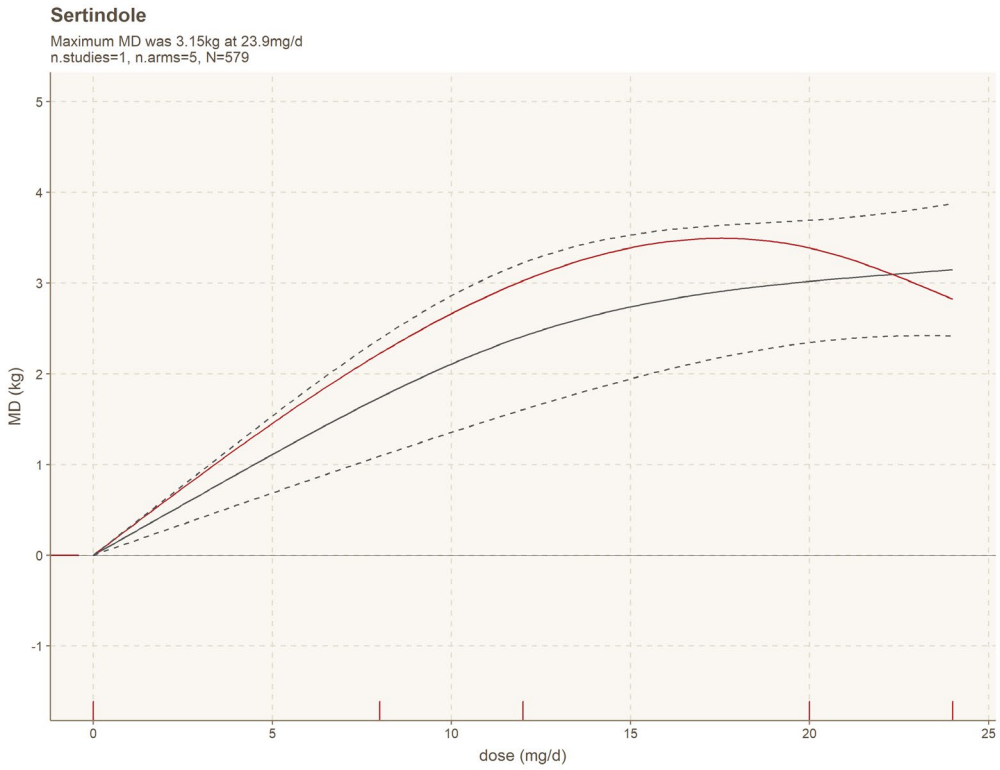


Risperidone: 18 studies with 5404 participants were analysed. The dose-response curve plateaued after around 5mg/d, which was similar to the primary analysis.



Analysis of the pooled data summarized in the 2009 FDA sertindole clinical review

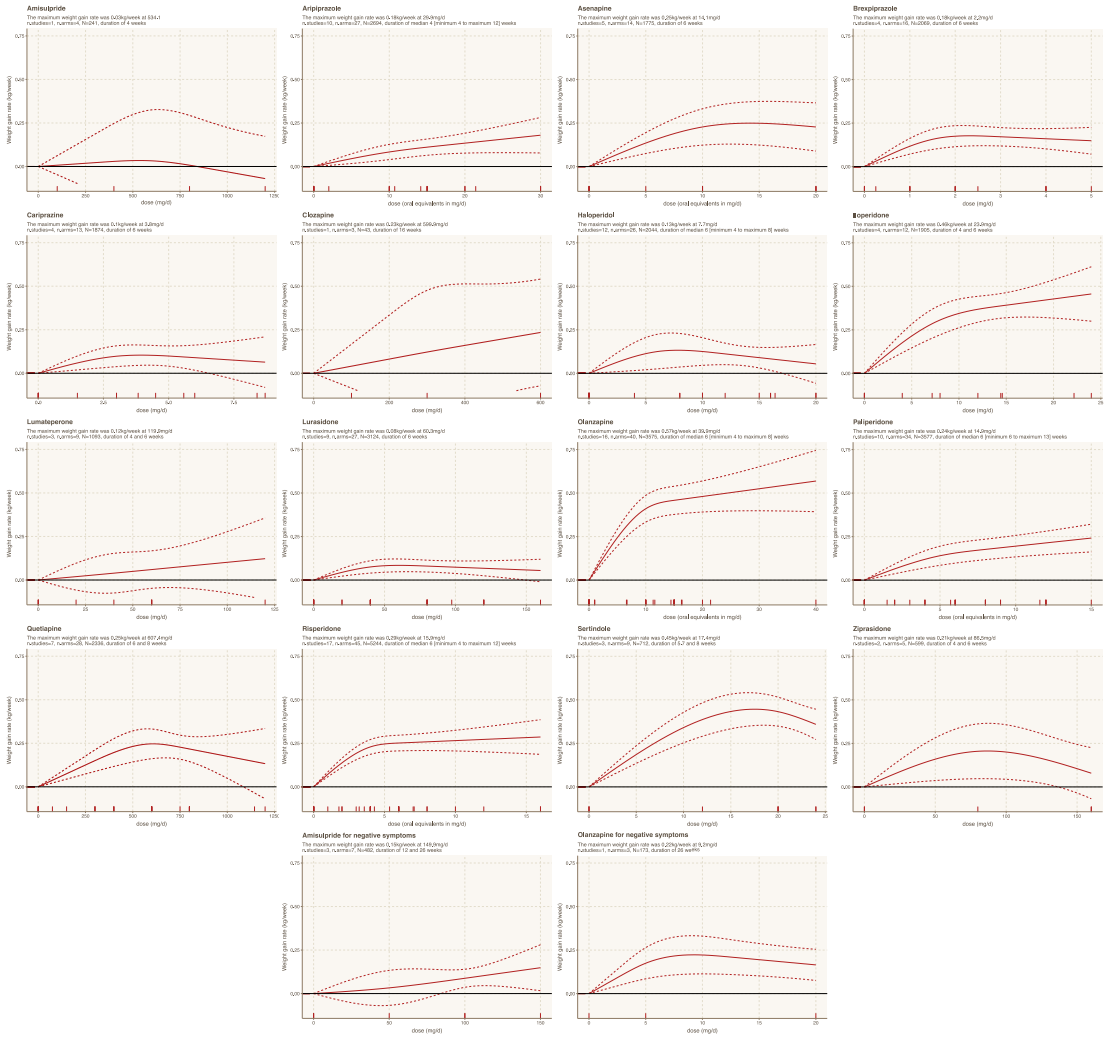
Sertindole: the separate data from the three individual studies had a total sample size of 712 participants while the pooled data from FDA clinical review had 579 participants. In the pooled data, data of 8mg/d were provided. The dose-response curve plateaued and not substantially differed from the main analysis.



Dose-response curves of individual antipsychotics with weight gain rate (kg/week)

Since we pooled studies with different durations (median duration of 6 weeks, ranging 4 to 26 weeks), we investigated dose-response curves of weight gain rate (weight gain divided by study duration, kg/week), assuming there was a linear temporal relationship between weight gain and dosing duration.

The shapes of dose-response curves and doses of maximum weight gain rates were basically same as the shapes and doses of maximum weight gain in the primary outcomes.



Sensitivity analyses for the secondary outcome

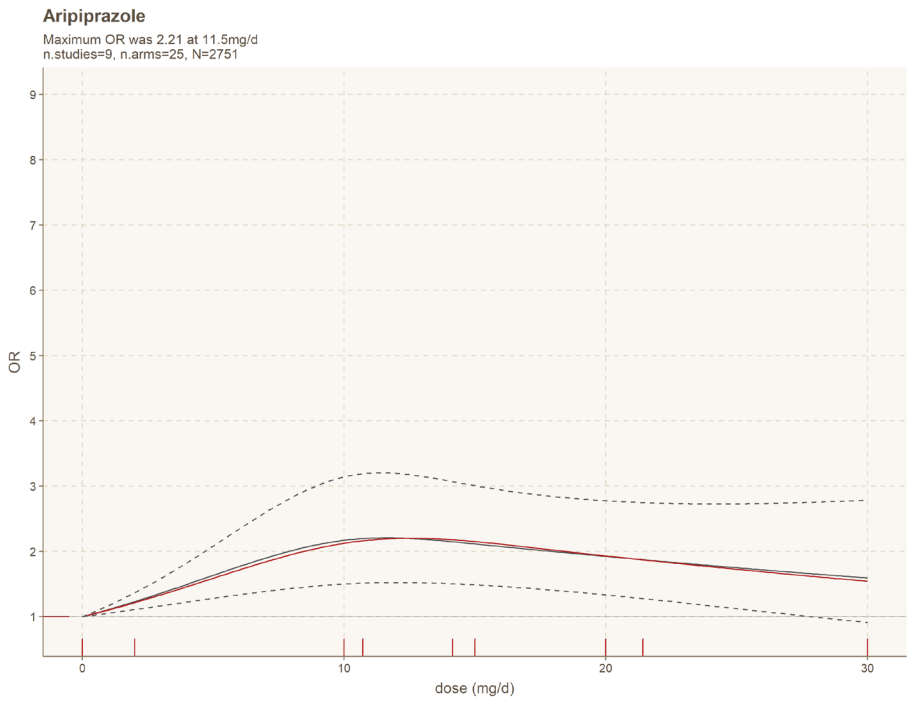
Exclusion studies with imputed number of patients with weight gain

No study was removed from studies for amisulpride, asenapine, brexpiprazole, clozapine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, ziprasidone.

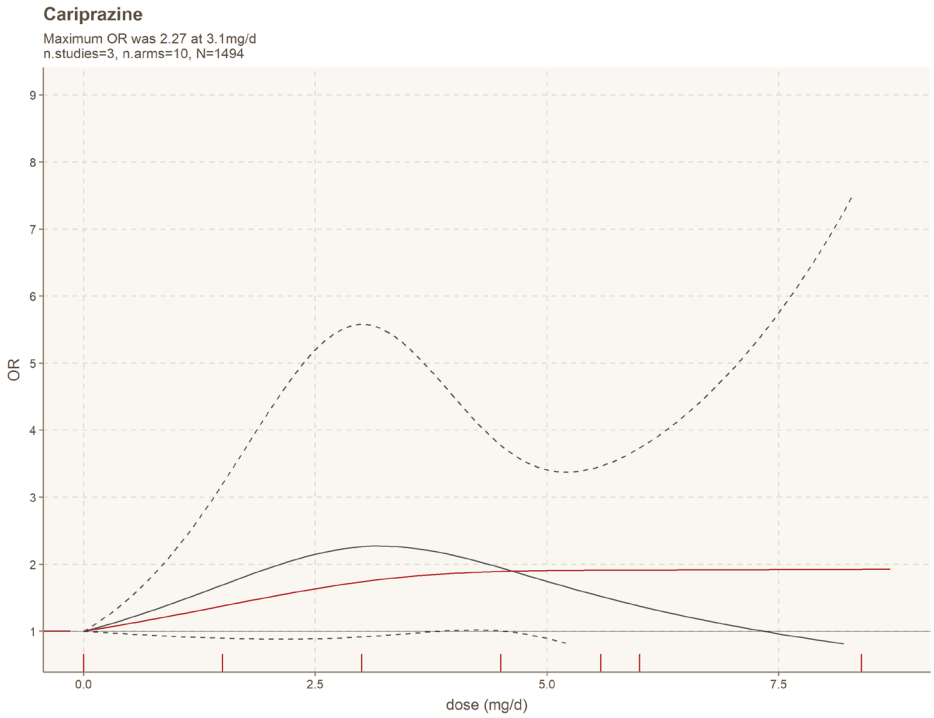
For sertindole studies numbers of patients with weight gain were all imputed.

For other individual antipsychotic drugs:

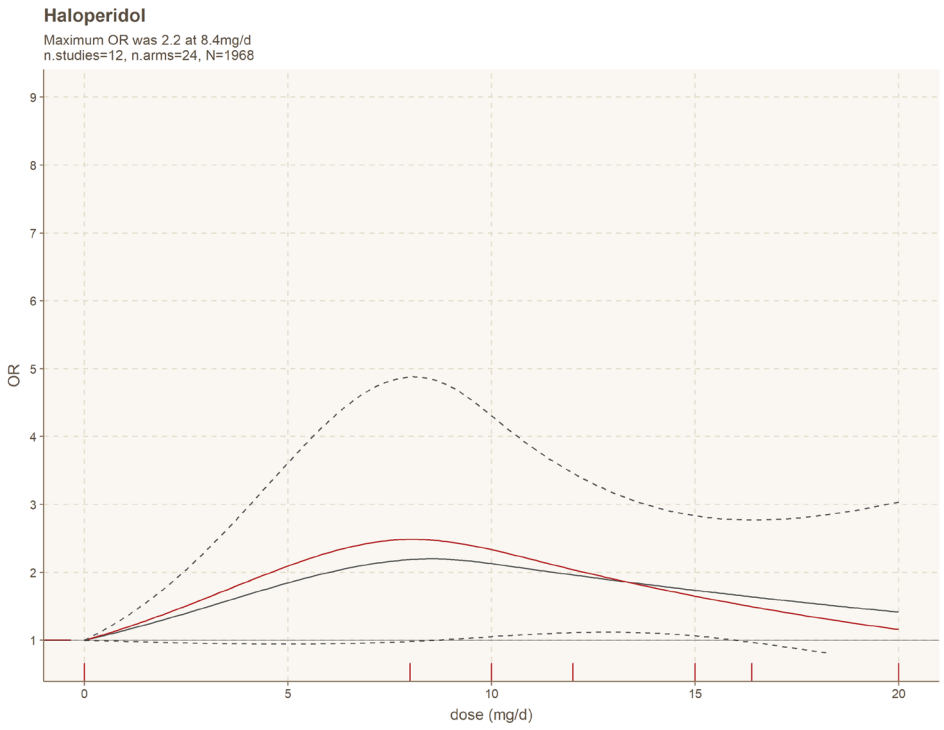
Aripoprazole: 9 studies with 2751 participants were analyzed. No substantial difference was noticed.



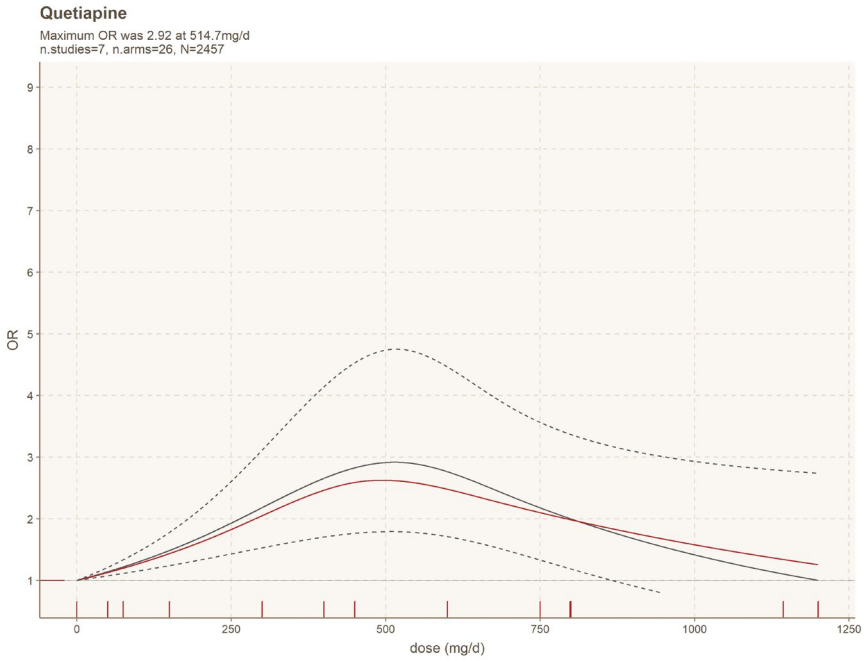
Cariprazine: 3 studies with 1494 participants were analyzed. No overall dose-response relationship was detected (p-value = 0.1316).



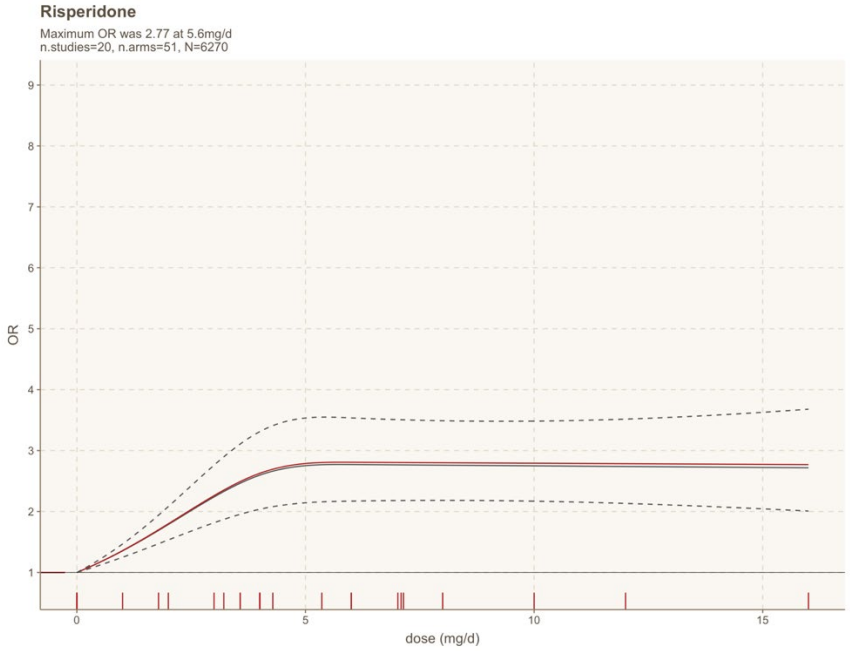
Haloperidol: 12 studies with 1968 participants were analyzed. No substantial difference was noticed.



Quetiapine: 7 studies with 2457 participants were analyzed. No substantial difference was noticed.



Risperidone: 20 studies with 6270 participants were analyzed. No substantial difference was noticed.



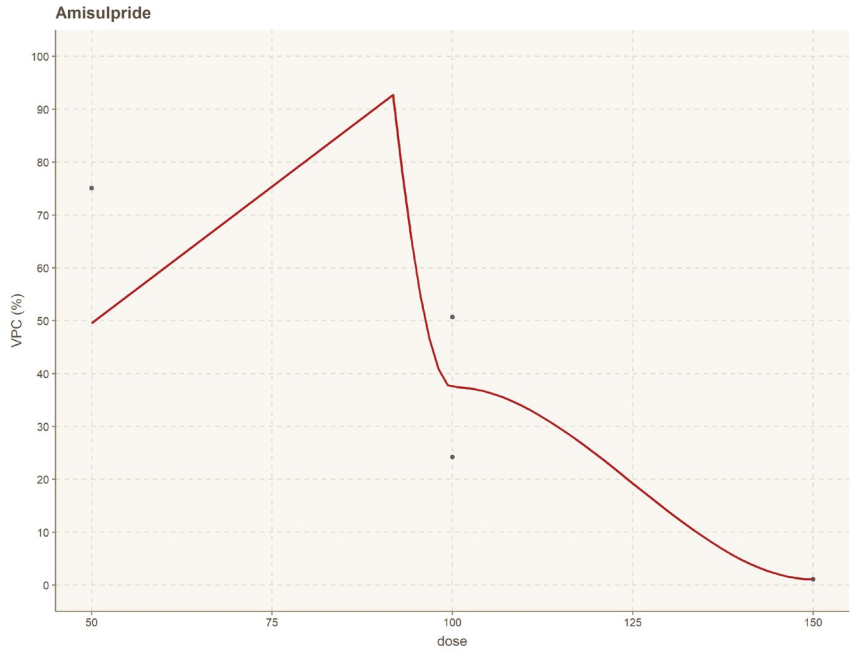
References

1. Meltzer HY, Risinger R, Nasrallah HA, Du Y, Zummo J, Corey L, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. The Journal of clinical psychiatry. 2015;76(8):1085-90.
2. Kane JM, Peters-Strickland T, Baker RA, Hertel P, Eramo A, Jin N, et al. Aripiprazole once-monthly in the acute treatment of schizophrenia: findings from a 12-week, randomized, double-blind, placebo-controlled study. The Journal of clinical psychiatry. 2014;75(11):1254-60.

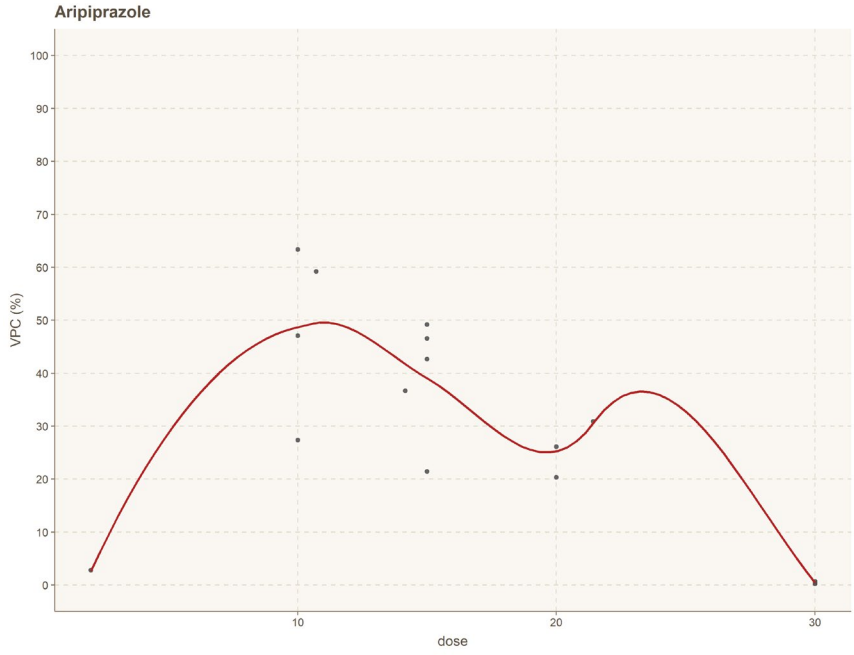
Appendix 11: Heterogeneity assessments

Heterogeneity assessments with the variance-partition-coefficient (VPC) for the primary outcome

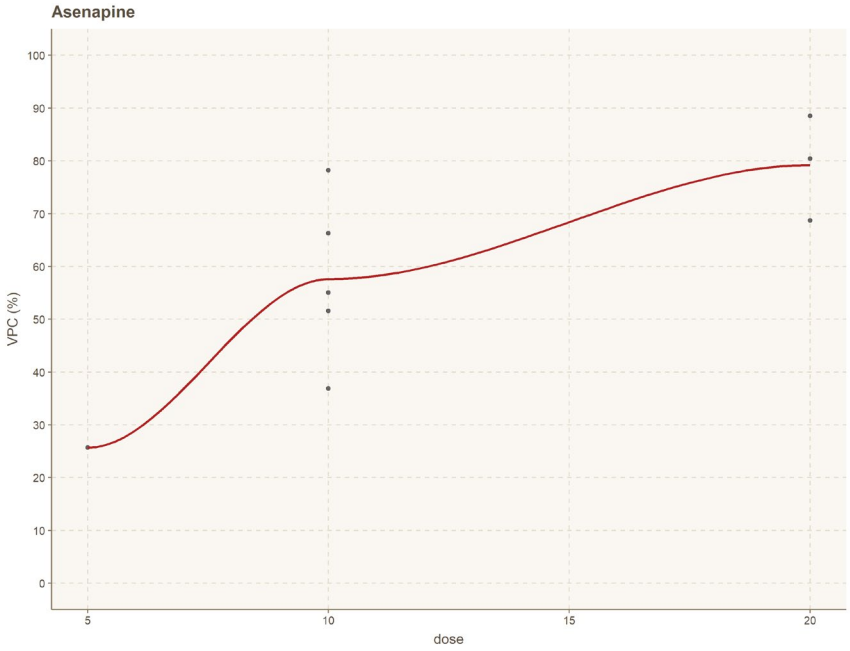
1. Amisulpride
    a) Amisulpride for positive symptoms: only one study was included, thus no heterogeneity was assessed.
    b) Amisulpride for negative symptoms: there was considerable level of heterogeneity with VPCs up to 90%.



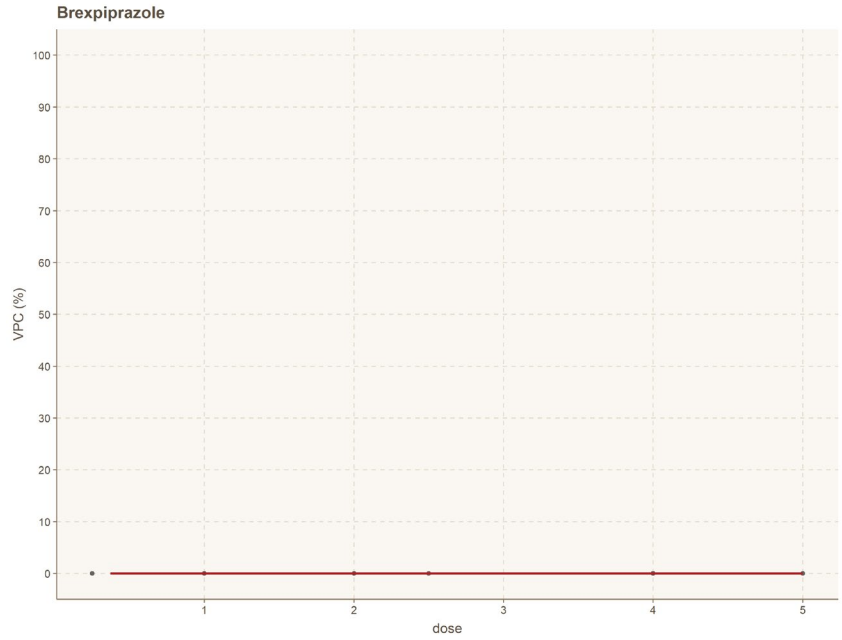
2. Aripiprazole: VPCs were under 50%, indicating moderate level of heterogeneity.



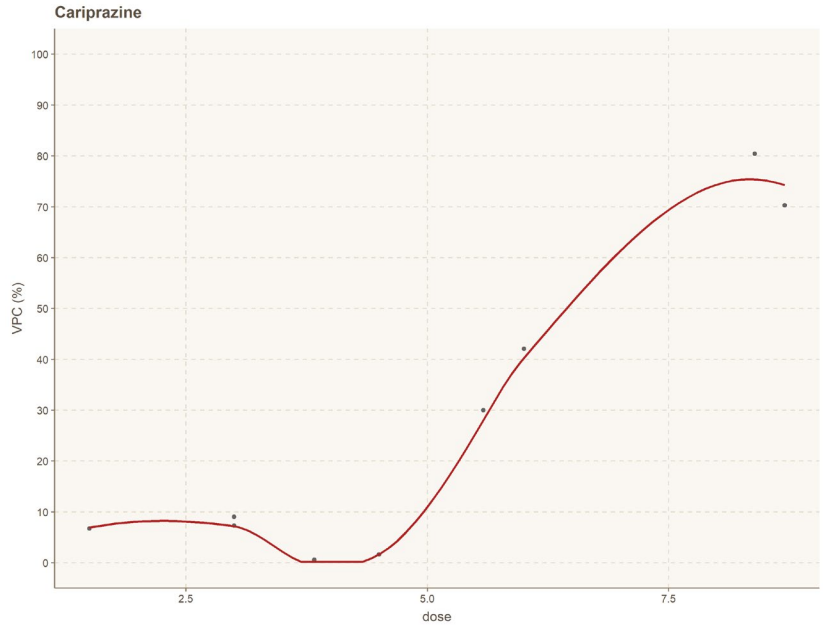
3. Asenapine: there was considerable level of heterogeneity with VPCs up to 80%.



4. Brexpiprazole: VPCs were 0%, indicating no heterogeneity.

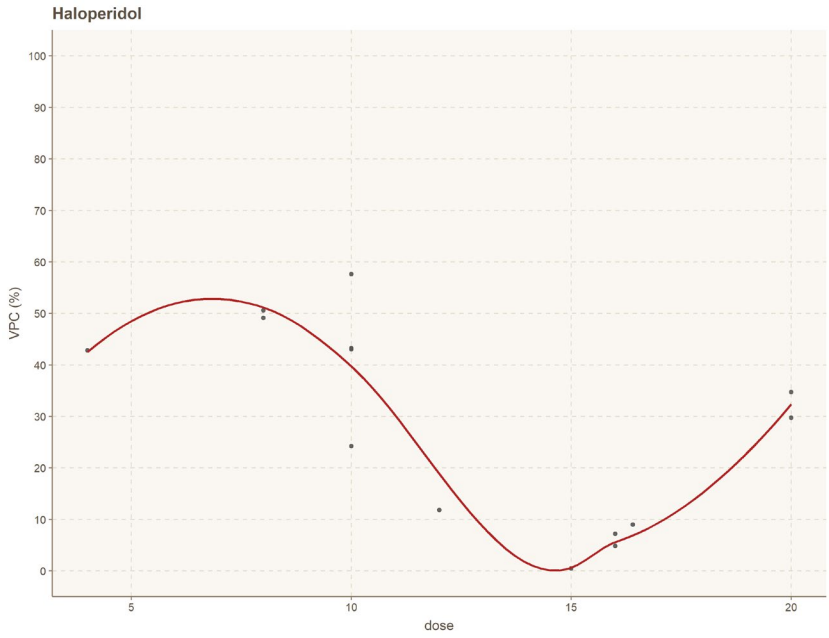


5. Cariprazine: there was considerable level of heterogeneity with VPCs up to 75%.

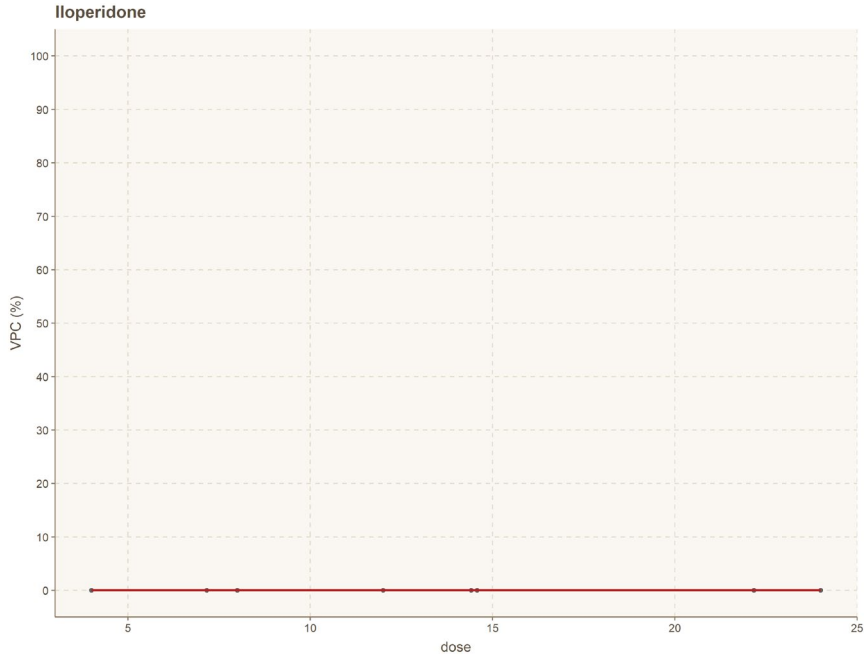


6. Clozapine: only one study was included, thus no heterogeneity was assessed.

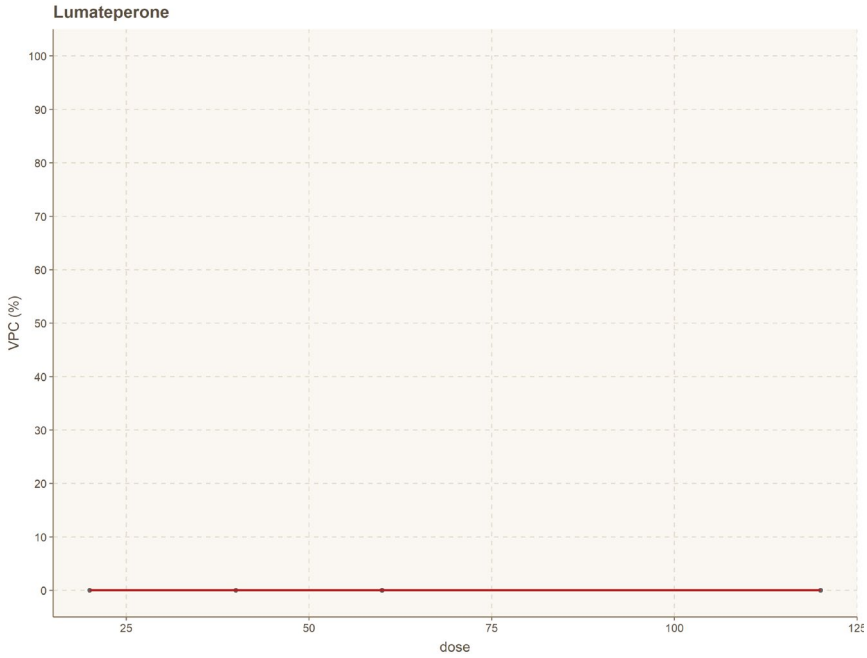
7. Haloperidol: VPCs were under around 50%, indicating moderate level of heterogeneity.



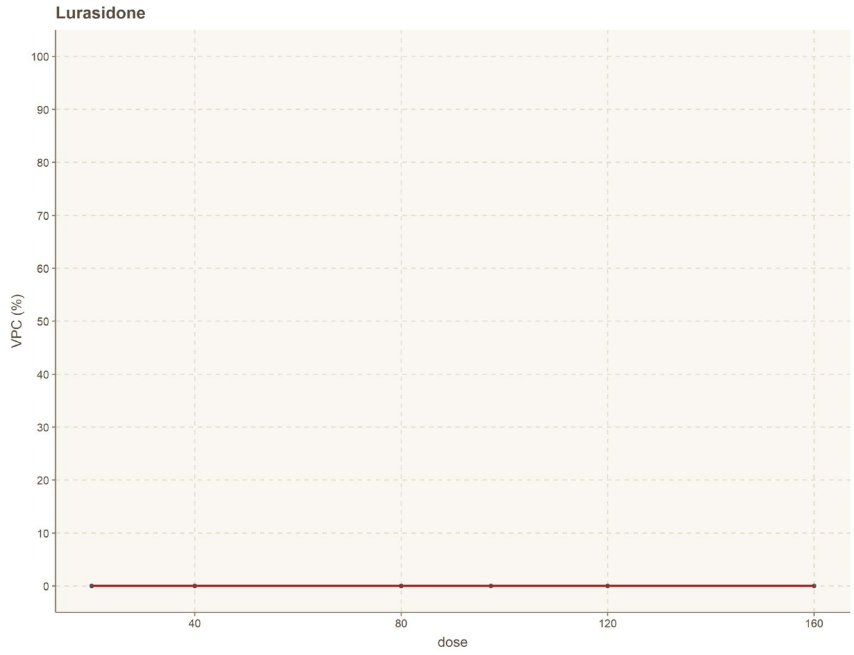
8. Iloperidone: VPCs were 0%, indicating no heterogeneity.



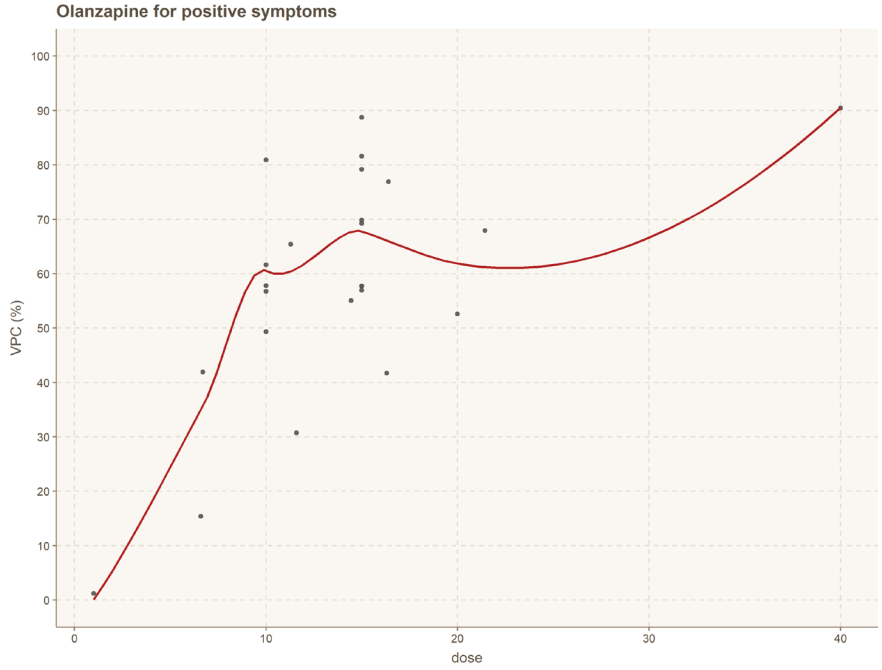
9. Lumateperone: VPCs were 0%, indicating no heterogeneity.



10. Lurasidone: VPCs were 0%, indicating no heterogeneity.

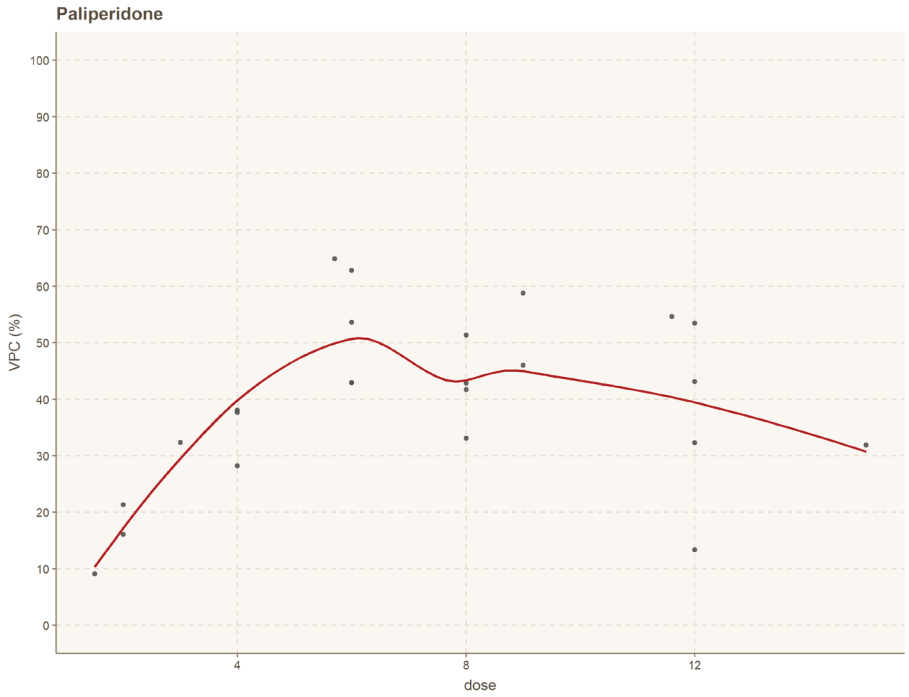


11. Olanzapine
    a) Olanzapine for positive symptoms: the majority of VPCs were under around 70%, indicating moderate level of heterogeneity.

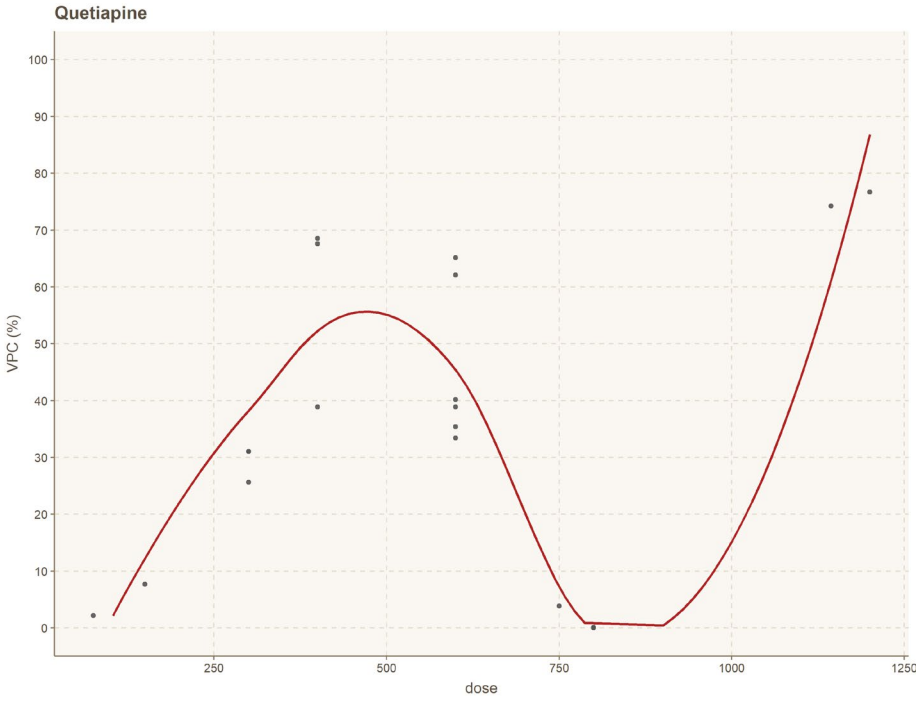


    b) Olanzapine for negative symptoms: only one study was included, thus no heterogeneity was assessed.

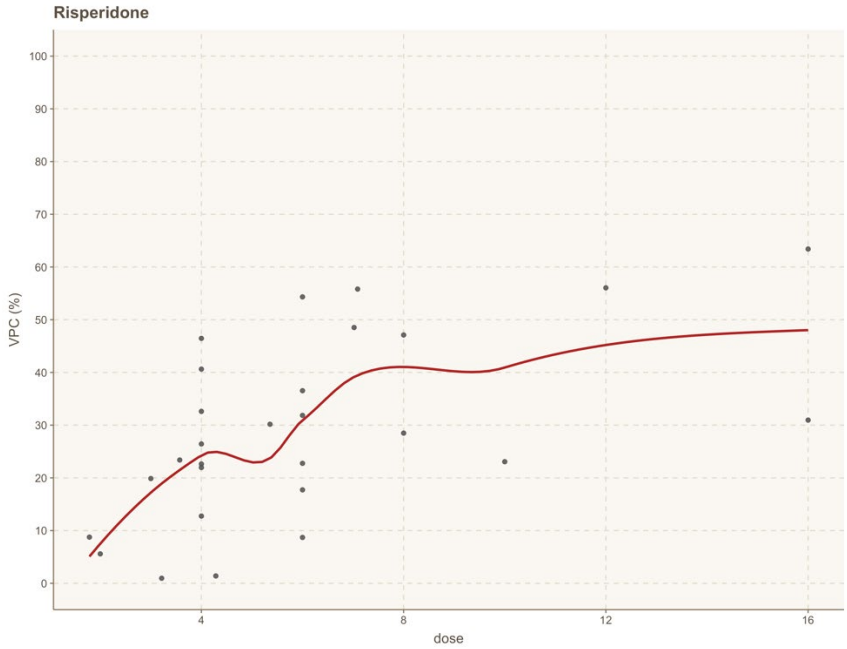
12. Paliperidone: VPCs were under 50%, indicating moderate level of heterogeneity.



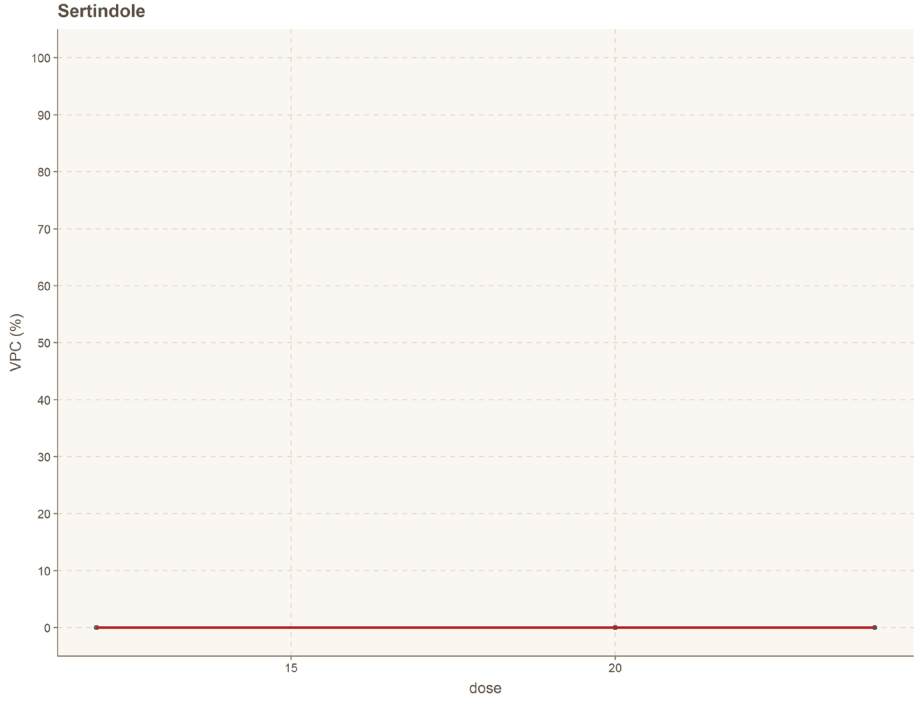
13. Quetiapine: there was considerable level of heterogeneity with VPCs up to 80%.



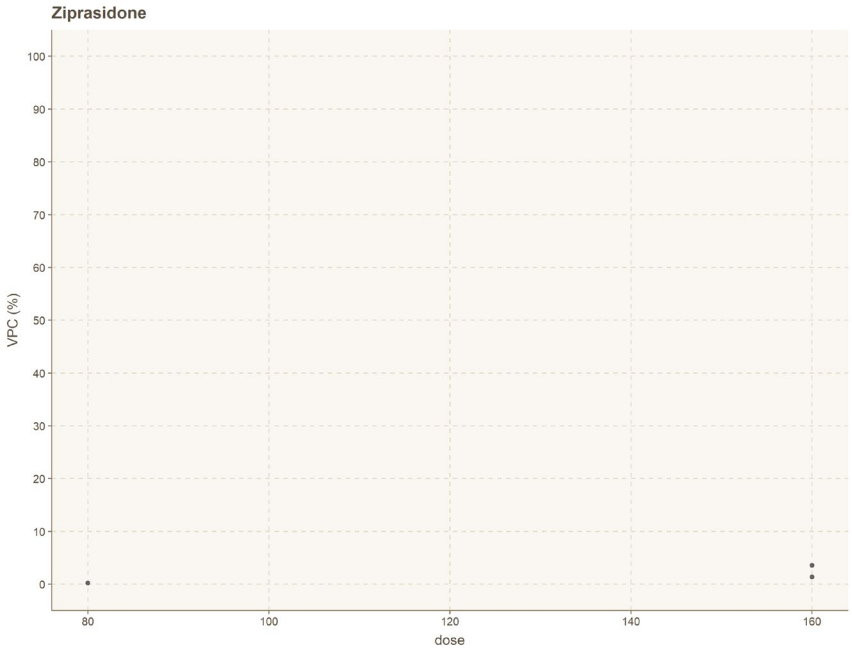
14. Risperidone: VPCs were under 50%, indicating moderate level of heterogeneity.



15. Sertindole: VPCs were 0%, indicating no heterogeneity.



16. Ziprasidone: there was no heterogeneity detected, however, only two doses were available.



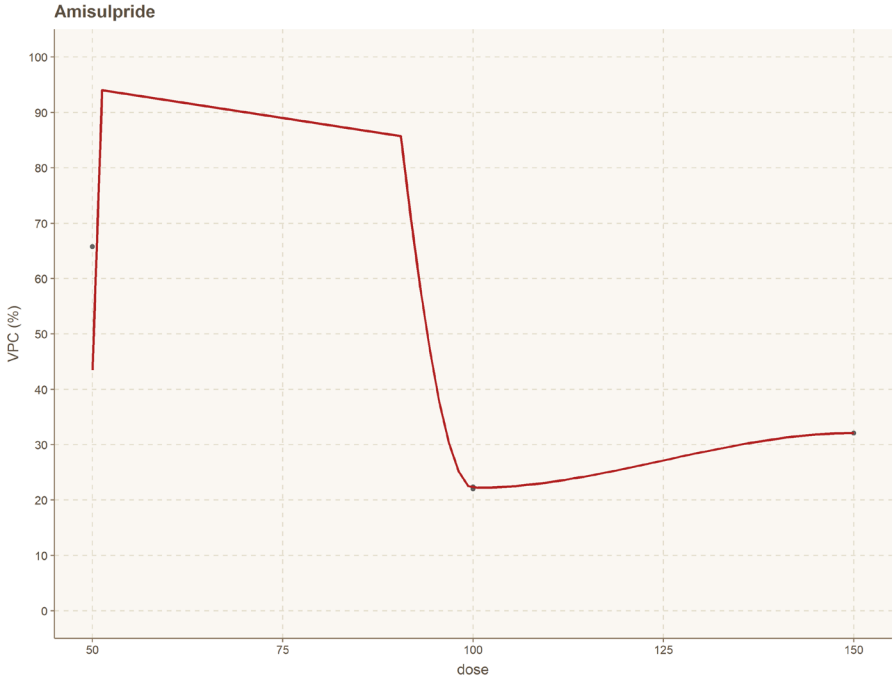
17. Zotepine: only one study was included, thus no heterogeneity was assessed.

Heterogeneity assessments with the variance-partition-coefficient (VPC) for the secondary outcome

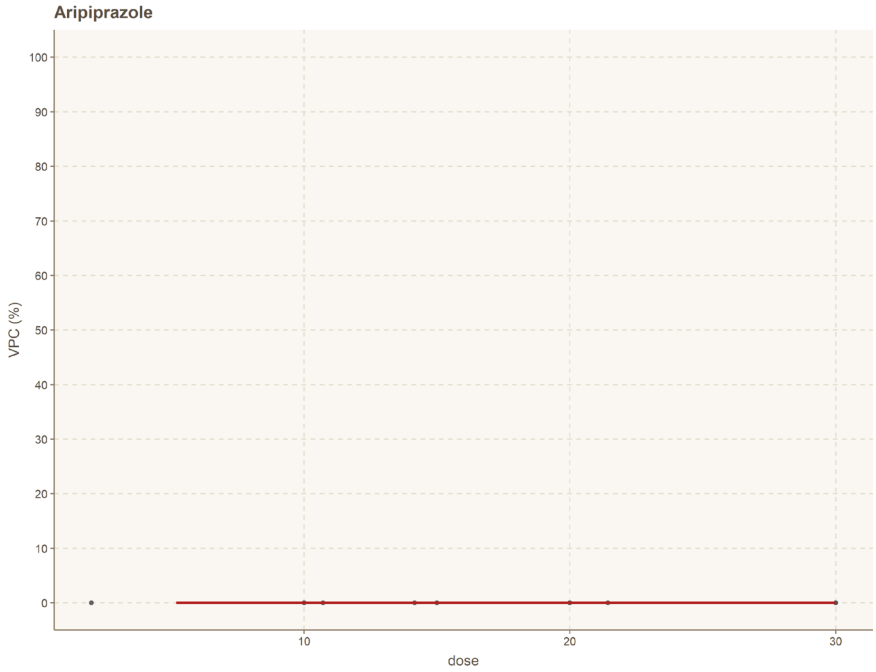
1. Amisulpride

a) Amisulpride for positive symptoms: only one study was included, thus no heterogeneity was assessed.

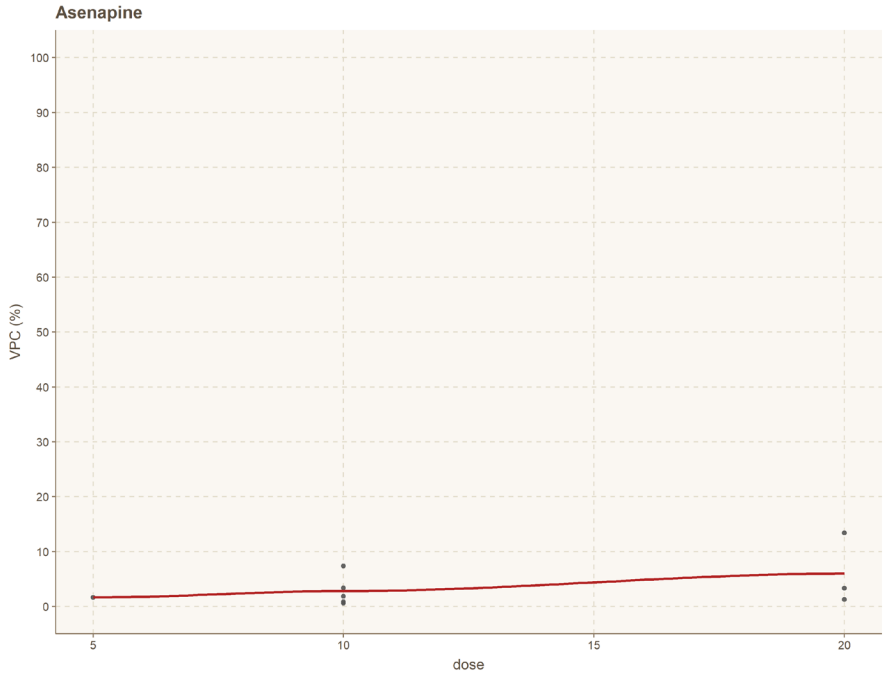
b) Amisulpride for negative symptoms: there was considerable level of heterogeneity with VPCs up to 90%.



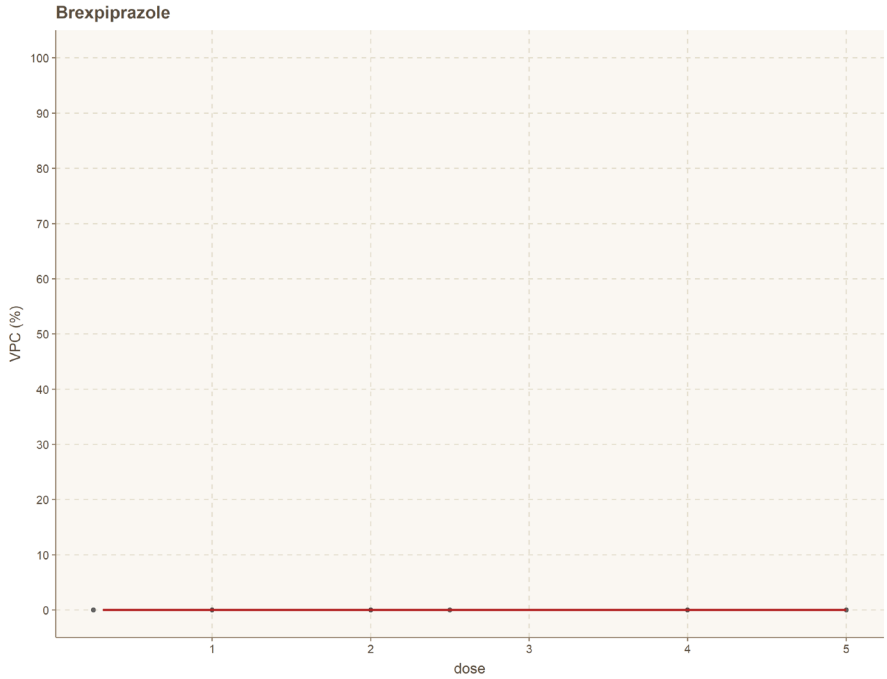
2. Aripiprozole: VPCs were 0%, indicating no heterogeneity.



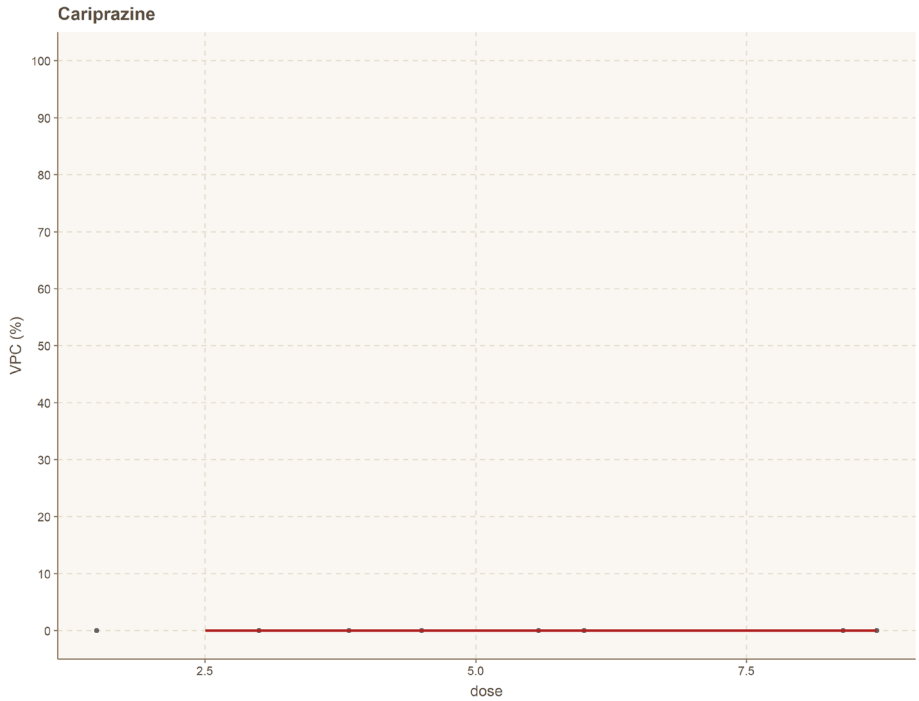
3. Asenapine: VPCs were under 10%, indicating low level of heterogeneity.



4. Brexpiprazole: VPCs were 0%, indicating no heterogeneity.

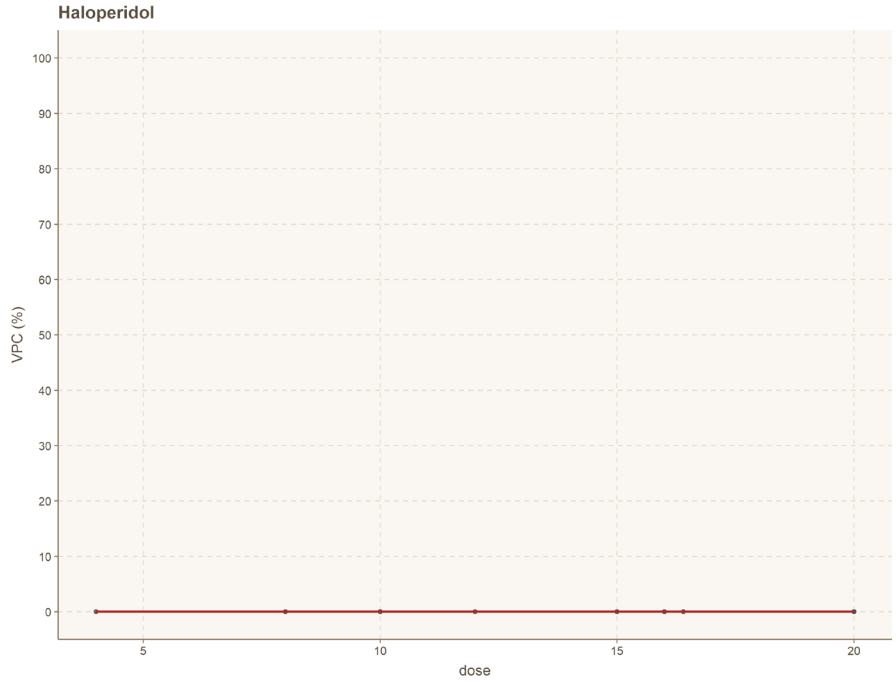


5. Cariprazine: VPCs were 0%, indicating no heterogeneity.

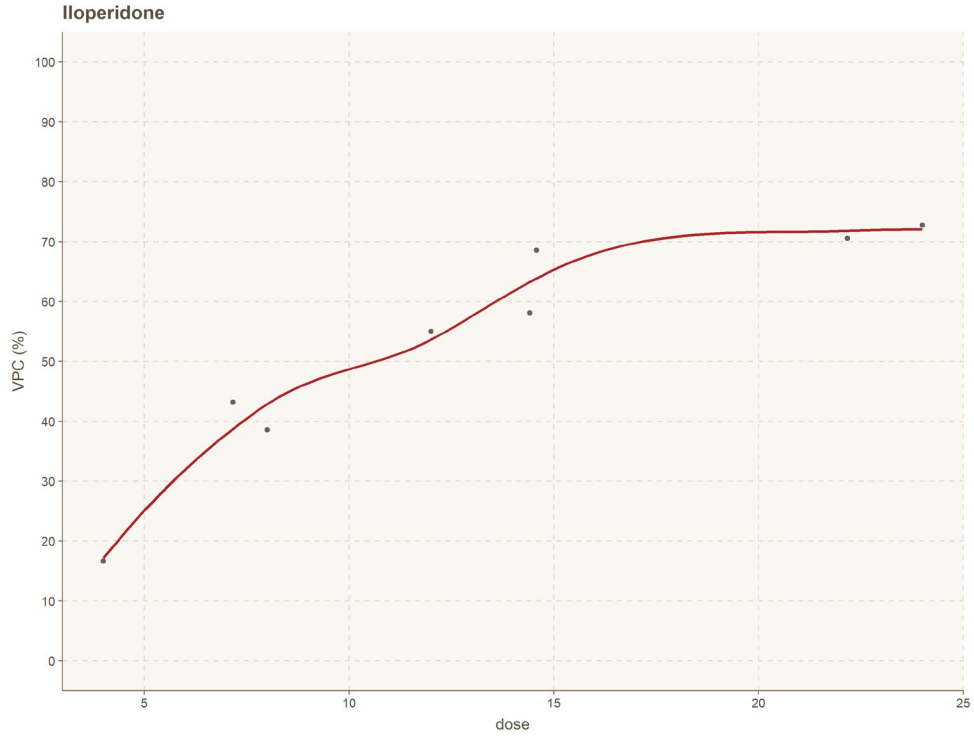


6. Clozapine: only one study was included, thus no heterogeneity was assessed.

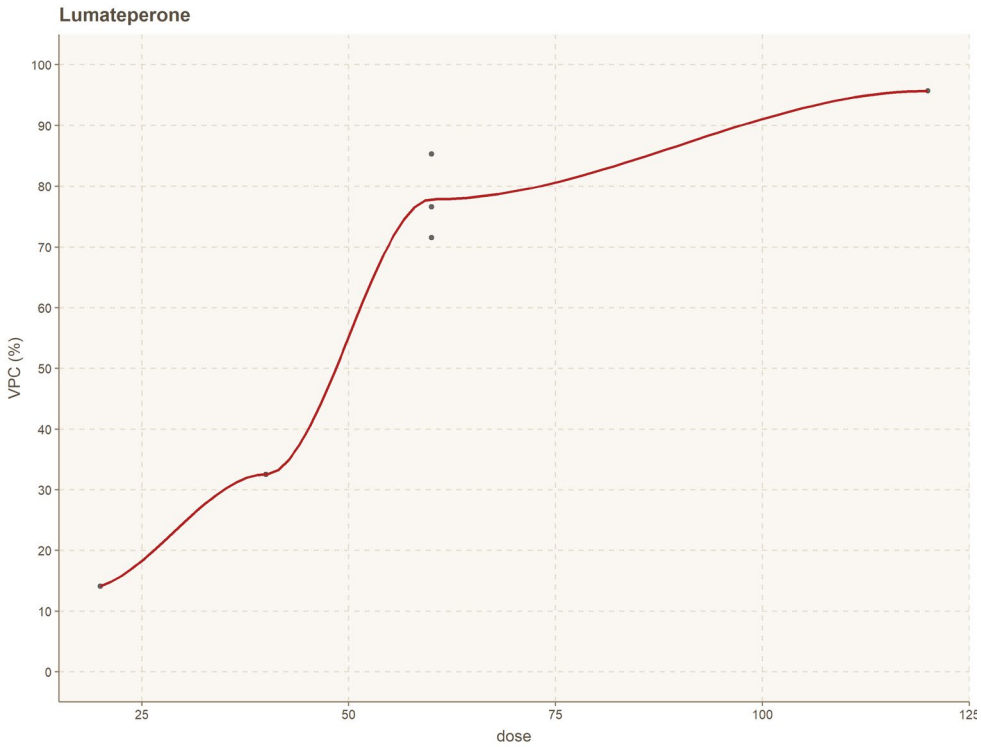
7. Haloperidol: VPCs were 0%, indicating no heterogeneity.



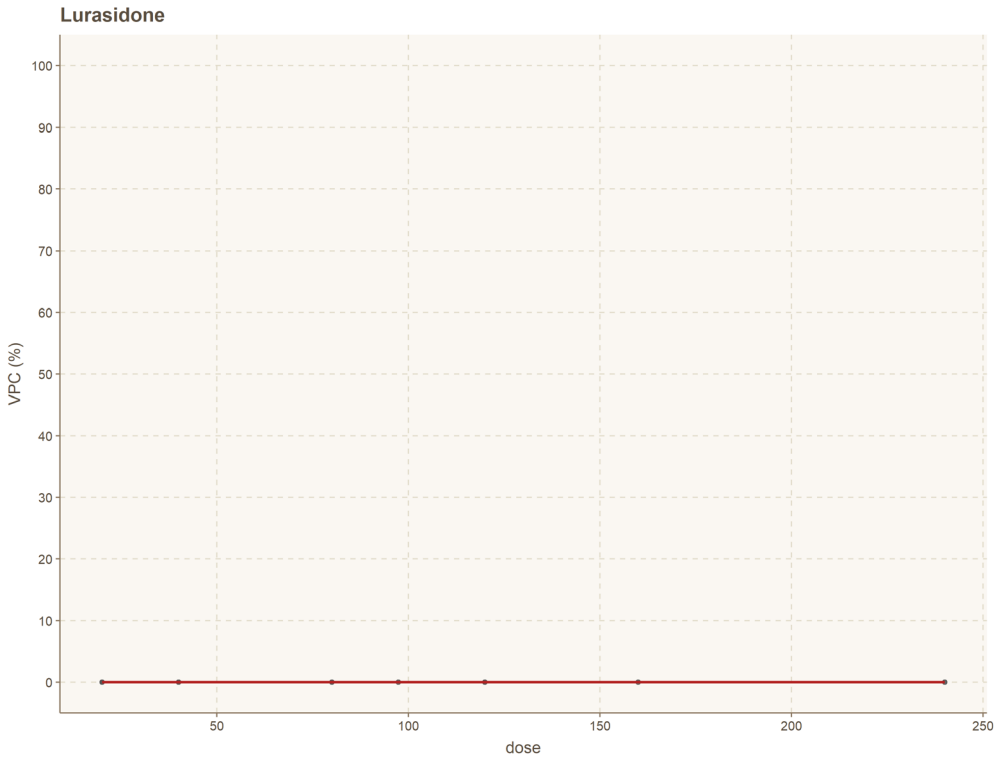
8. Iloperidone: there was considerable level of heterogeneity with VPCs up to 70%.



9. Lumateperone: there was considerable level of heterogeneity with VPCs up to over 90%.

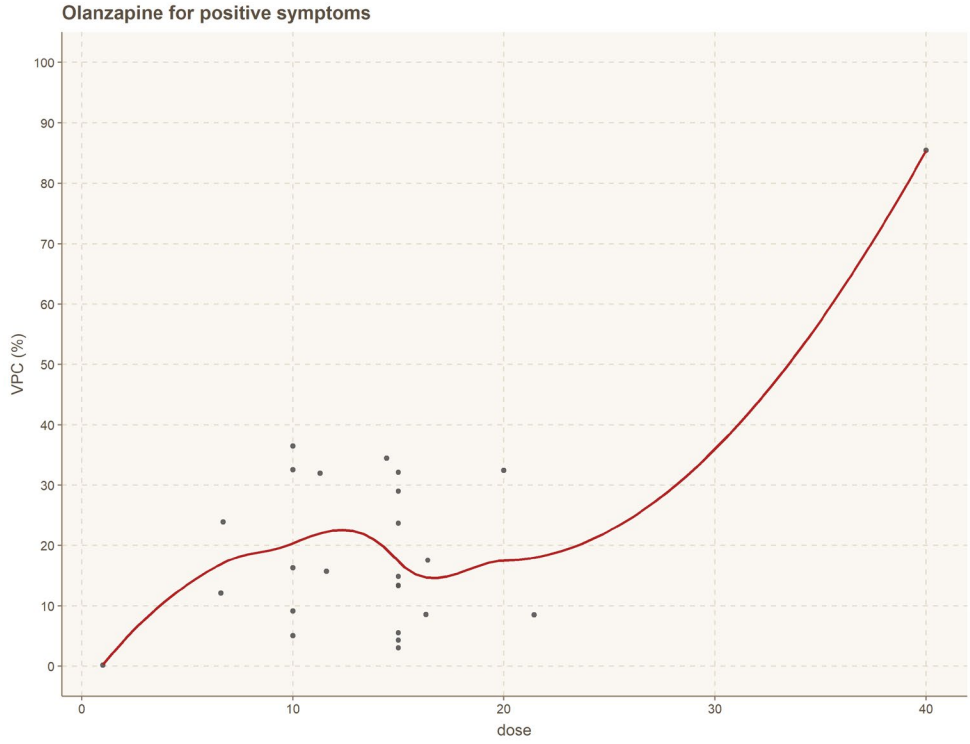


10. Lurasidone: VPCs were 0%, indicating no heterogeneity.



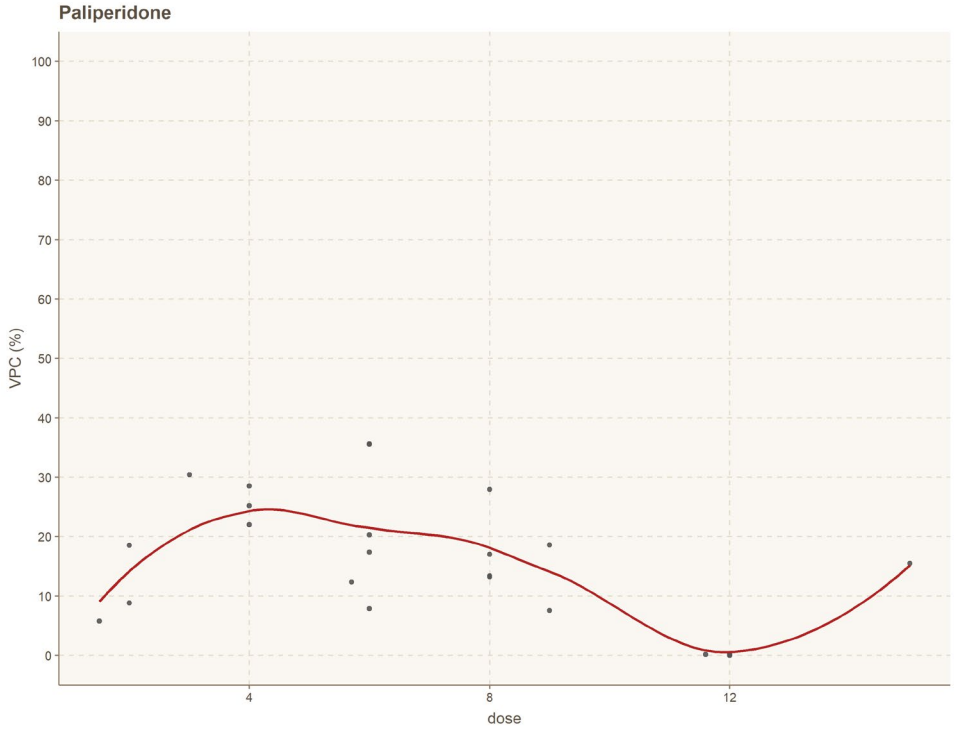
11. Olanzapine

a) Olanzapine for positive symptoms: the majority of VPCs were under around 20%, indicating low level of heterogeneity.

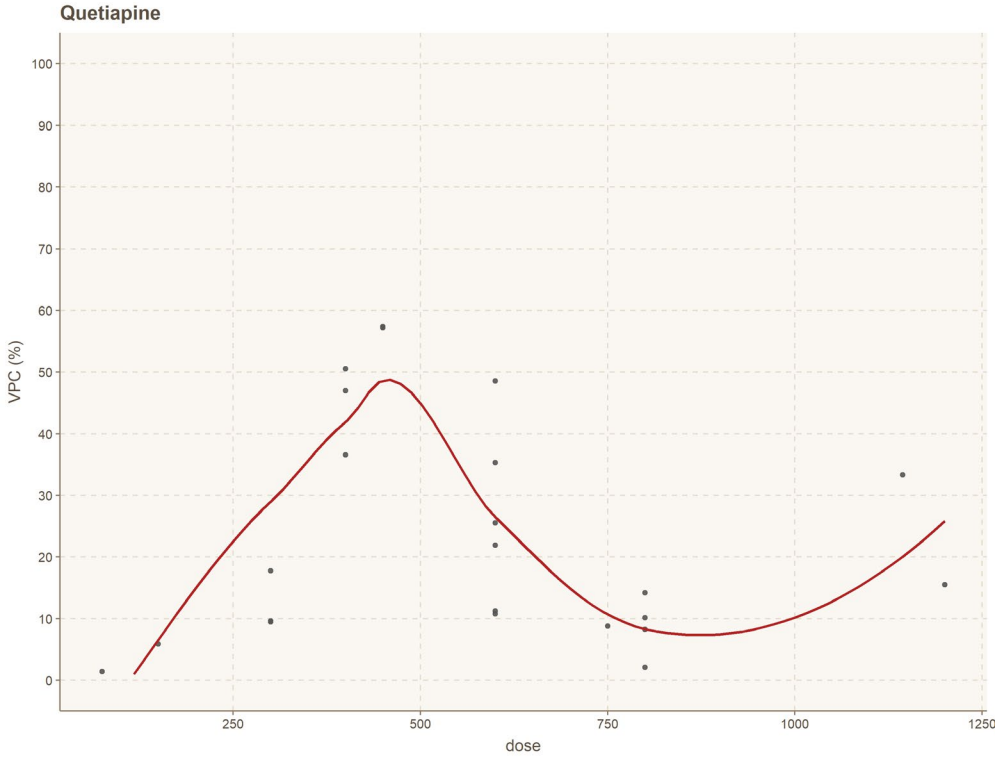


b) Olanzapine for negative symptoms: only one study was included, thus no heterogeneity was assessed.

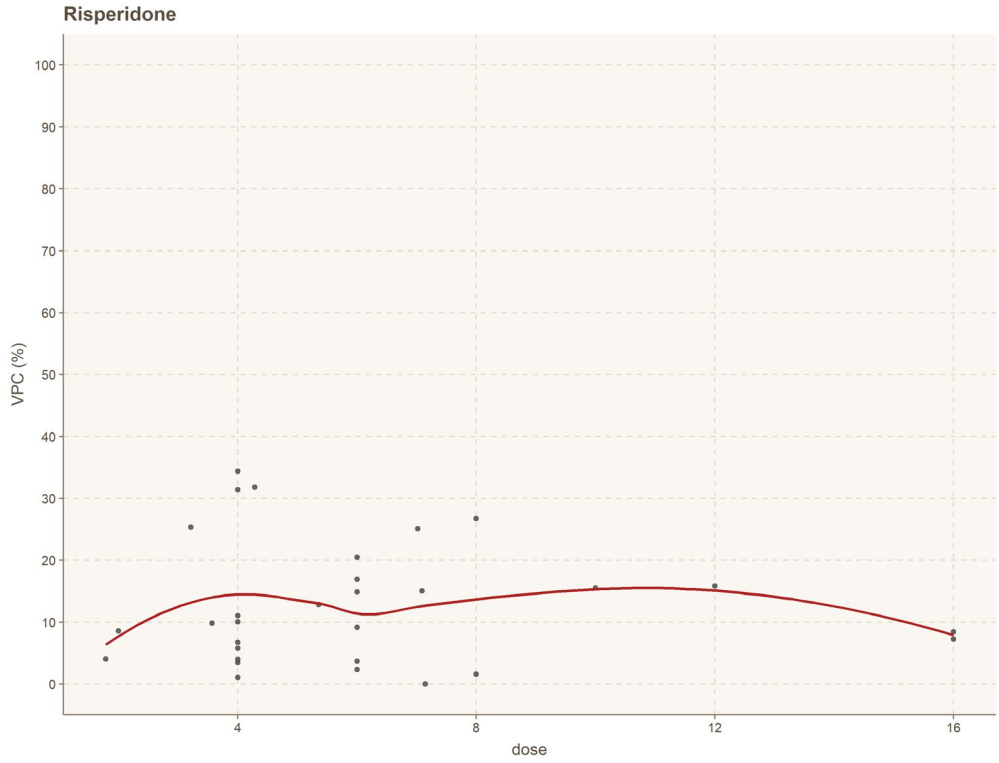
12. Paliperidone: VPCs were under 25%, indicating low level of heterogeneity.



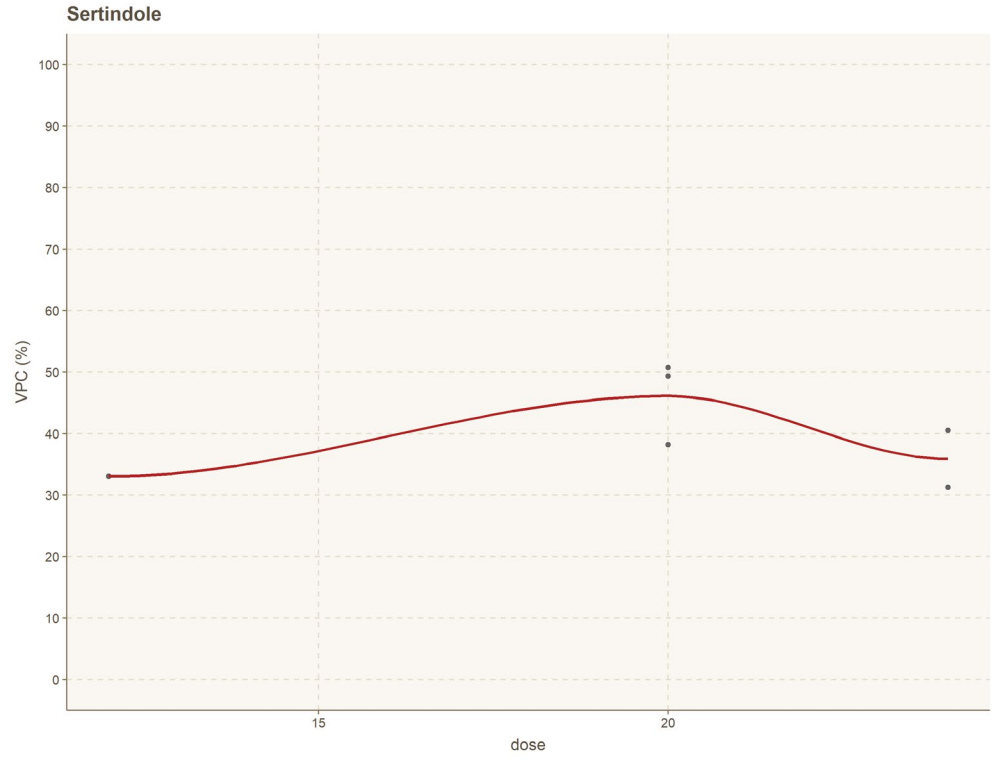
13. Quetiapine: VPCs were under 50%, indicating moderate level of heterogeneity.



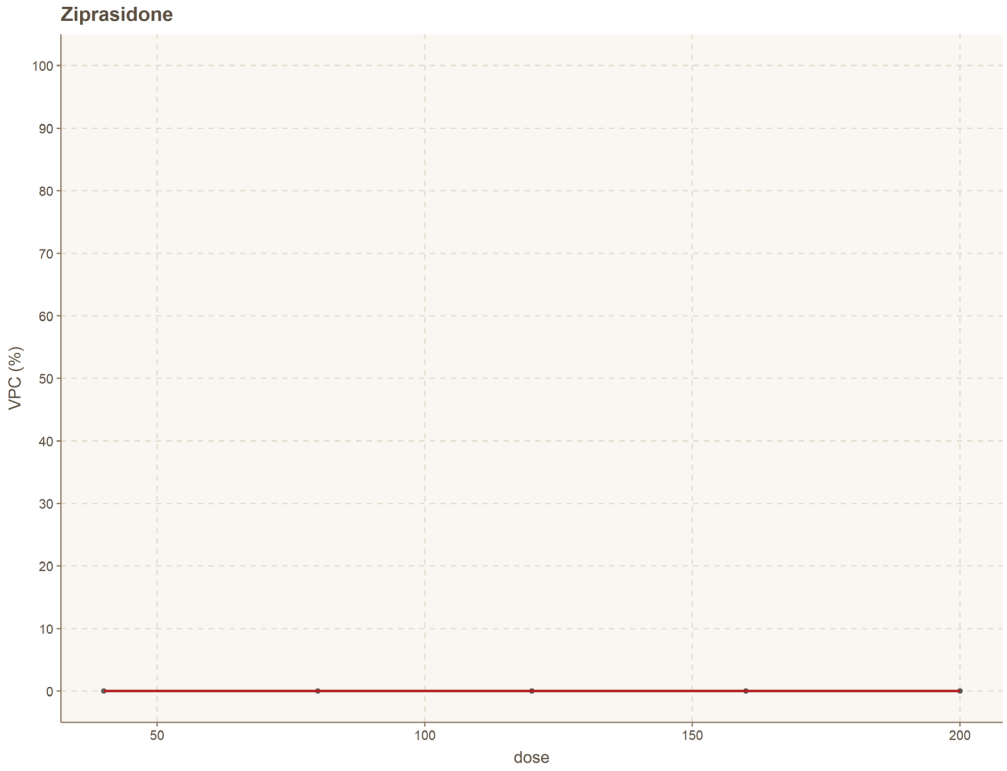
14. Risperidone: VPCs were under 20%, indicating low level of heterogeneity.



15. Sertindole: VPCs were under 50%, indicating moderate level of heterogeneity.



16. Ziprasidone: VPCs were 0%, indicating no heterogeneity.



17. Zotepine: only one study was included, thus no heterogeneity was assessed.

Reference

1. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res. 2019;28:1579-1596.

Appendix 12: Small-study effect and publication bias assessments

We have conducted pairwise meta-analyses comparing antipsychotic groups (all doses combined) with placebo groups in haloperidol (12 studies), olanzapine (13 studies) and risperidone (13 studies). Then funnel plots for each aforementioned drug were conducted for assessments. Forest and funnel plots are presented as below.

Figure 4A: Forest plot of haloperidol (all dose combined) comparing placebo

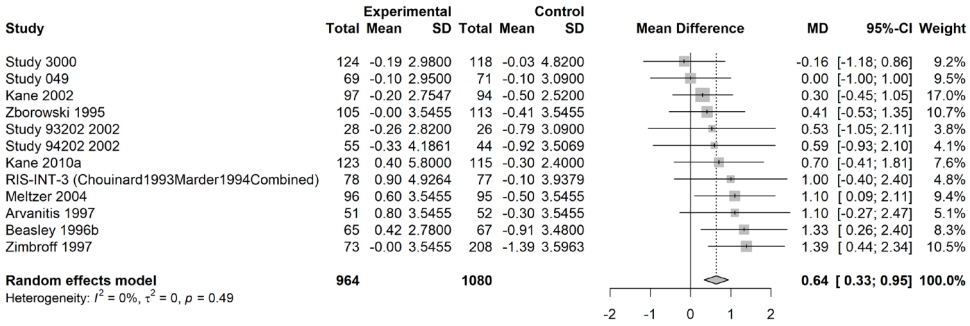


Figure 4a: Forest plot of haloperidol (all dose combined) comparing placebo

Figure 4B: Forest plot of olanzapine (all dose combined) comparing placebo

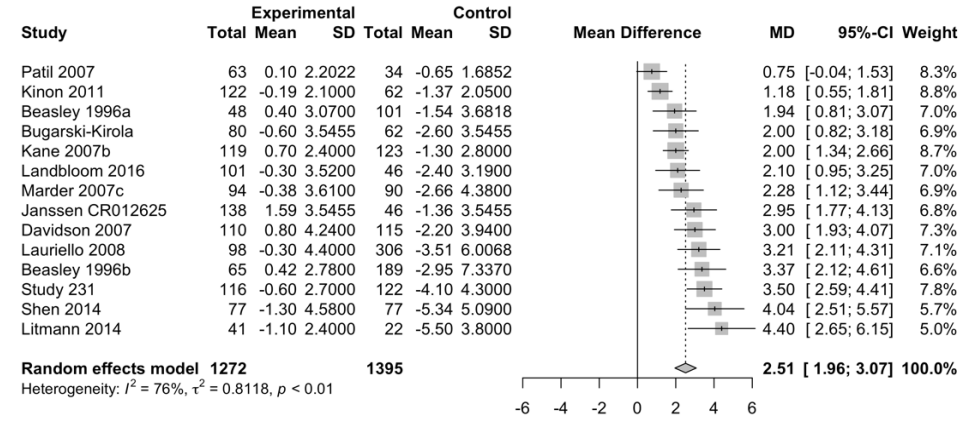


Figure 4b: Forest plot of olanzapine (all dose combined) comparing placebo

Figure 4C: Forest plot of risperidone (all dose combined) comparing placebo

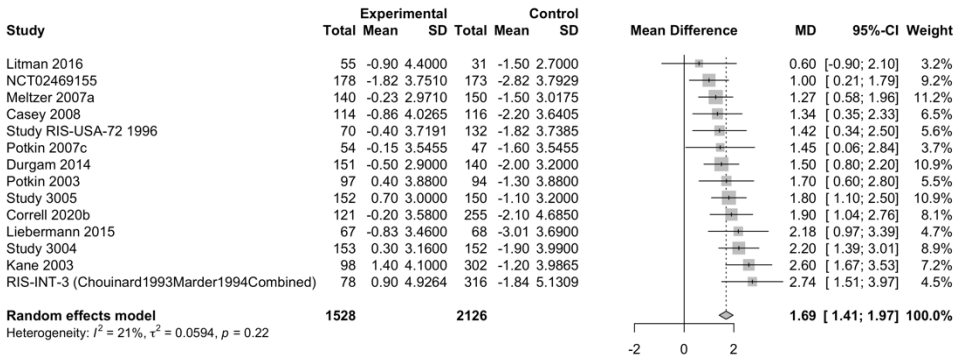


Figure 4c: Forest plot of risperidone (all dose combined) comparing placebo

Figure 4D: Forest plot of paliperidone (all dose combined) comparing placebo

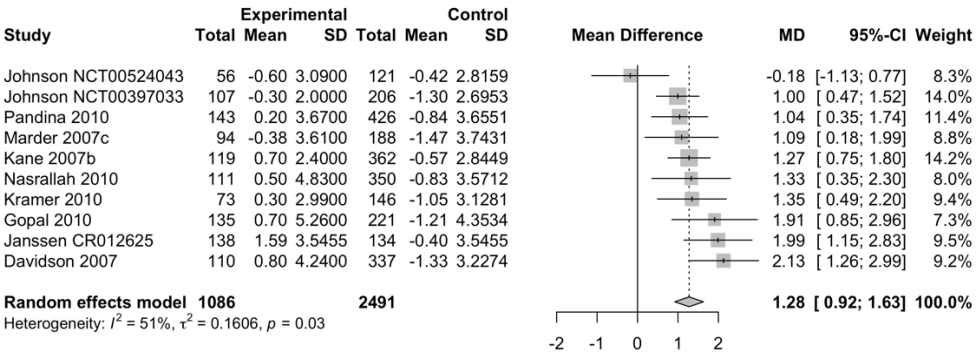


Figure 4d: Forest plot of paliperidone (all dose combined) comparing placebo

Figure 5A: Contour enhanced funnel plot for haloperidol studies

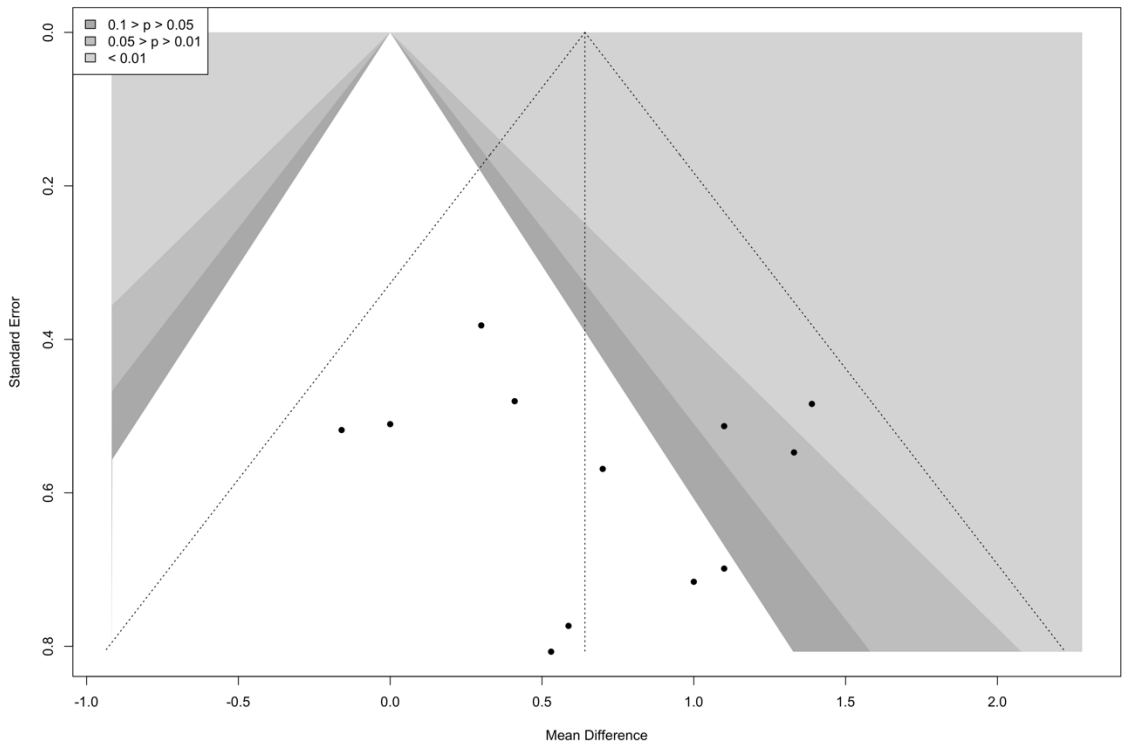


Figure 5a: Funnel plot for haloperidol studies

Egger's test:

Linear regression test of funnel plot asymmetry

data: meta_hal_pair

t = 0.79553, df = 10, p-value = 0.4448

alternative hypothesis: asymmetry in funnel plot

sample estimates:

bias	se.bias	intercept
1.094160	1.375388	0.058489

Egger's test for small study effects bias was not significant (p = 0.4448) and the contour-enhanced funnel plot was rather symmetrical. We detected no publication bias for haloperidol studies regarding weight gain in our analyses.

Figure 5B: Funnel plot for olanzapine studies

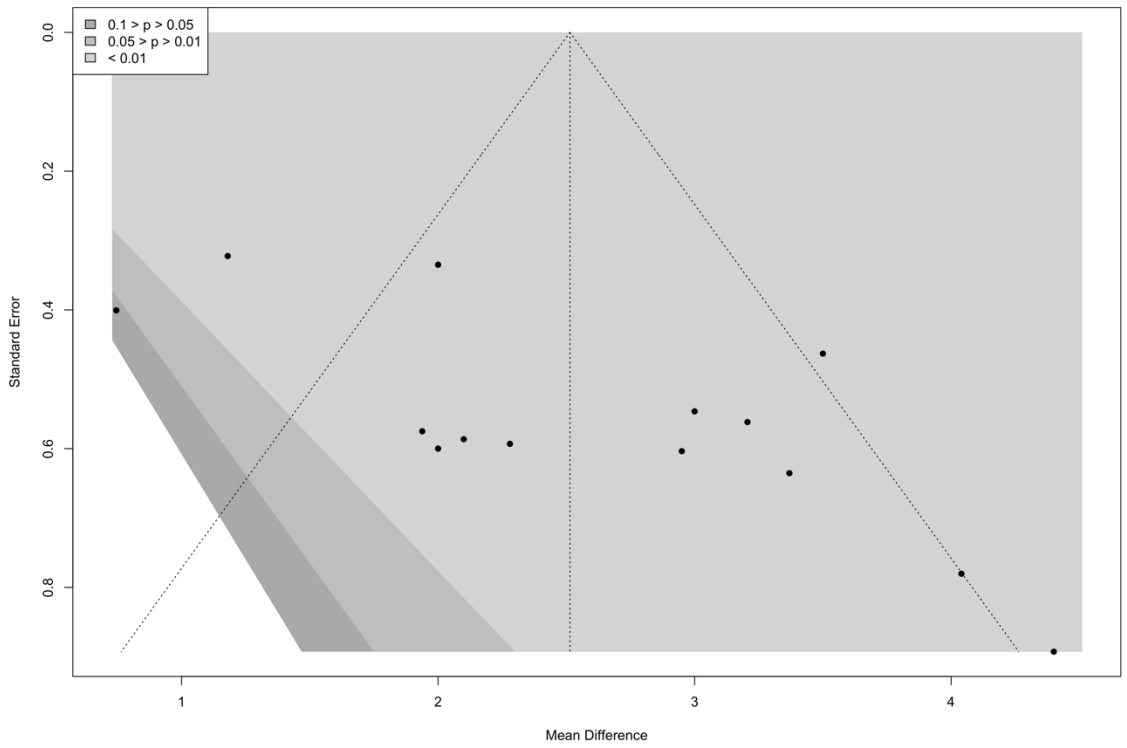


Figure 5b: Funnel plot for olanzapine studies

Linear regression test of funnel plot asymmetry

data: meta_ola_pair

t = 3.4905, df = 12, p-value = 0.004459

alternative hypothesis: asymmetry in funnel plot

sample estimates:

bias	se.bias	intercept
4.9520171	1.4187225	-0.1735919

Egger's test for small study effects bias was significant (p = 0.004459) and the contour-enhanced funnel plot was not symmetrical. Publication bias was detected in olanzapine studies.

Figure 5C: Funnel plot for risperidone studies

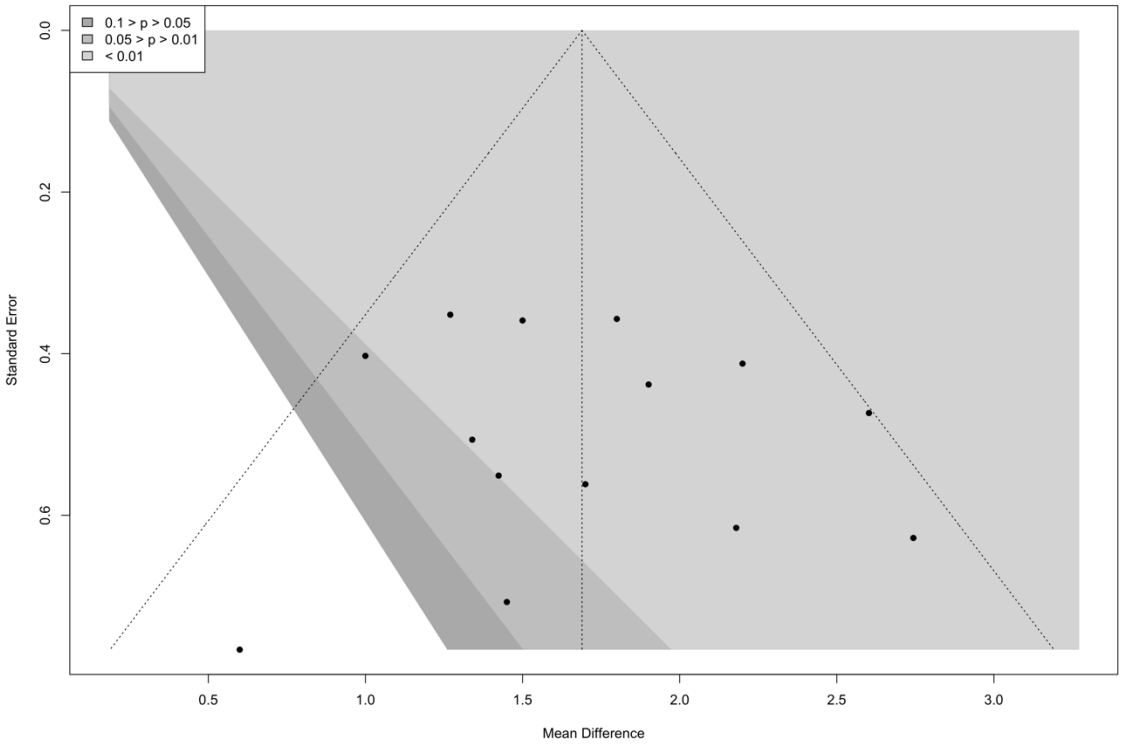


Figure 5d: Funnel plot for paliperidone studies

Linear regression test of funnel plot asymmetry

data: meta_ris_pair

t = 0.36665, df = 12, p-value = 0.7203

alternative hypothesis: asymmetry in funnel plot

sample estimates:

bias	se.bias	intercept
0.4854512	1.3240009	1.4600305

Egger's test for small study effects bias was not significant (p = 0.7203) and the contour-enhanced funnel plot was rather symmetrical. We detected no publication bias for risperidone studies regarding weight gain in our analyses.

Figure 5D: Funnel plot for paliperidone studies

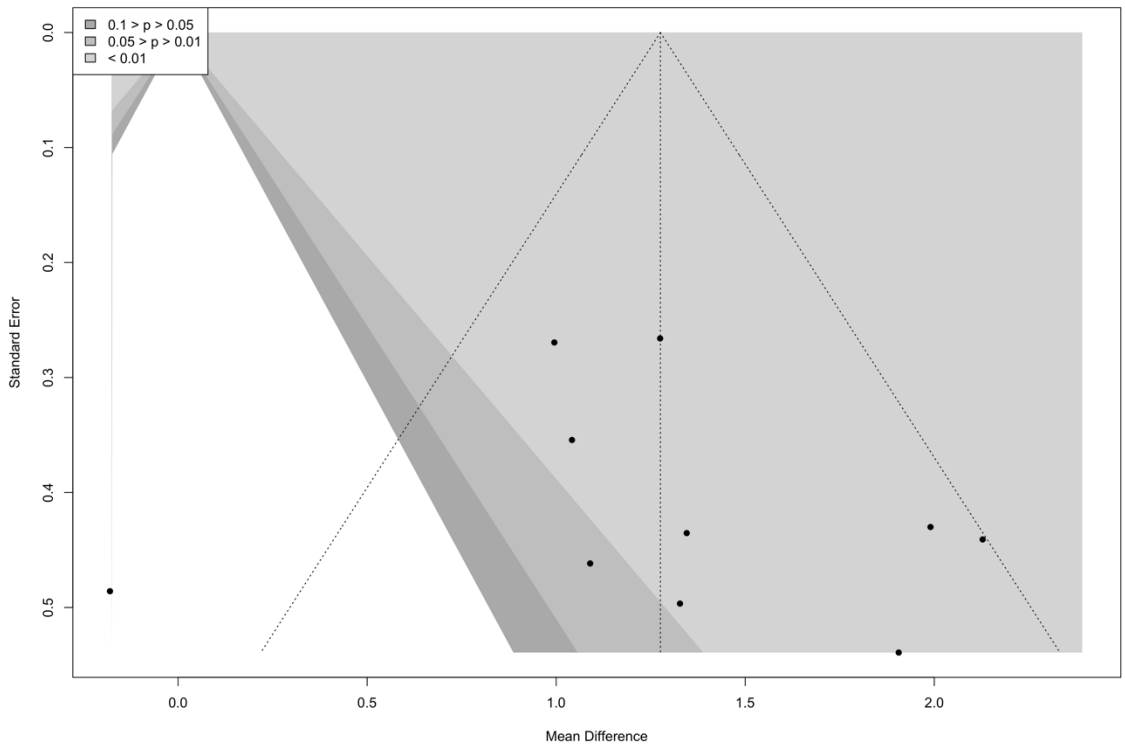


Figure 5d: Funnel plot for paliperidone studies

Linear regression test of funnel plot asymmetry

data: meta_pal_pair

t = 0.49591, df = 8, p-value = 0.6333

alternative hypothesis: asymmetry in funnel plot

sample estimates:

bias	se.bias	intercept
0.9427783	1.9010998	0.8996786

Egger's test for small study effects bias was not significant (p = 0.6333) and the contour-enhanced funnel plot was rather symmetrical. We detected no publication bias for paliperidone studies regarding weight gain in our analyses.

References

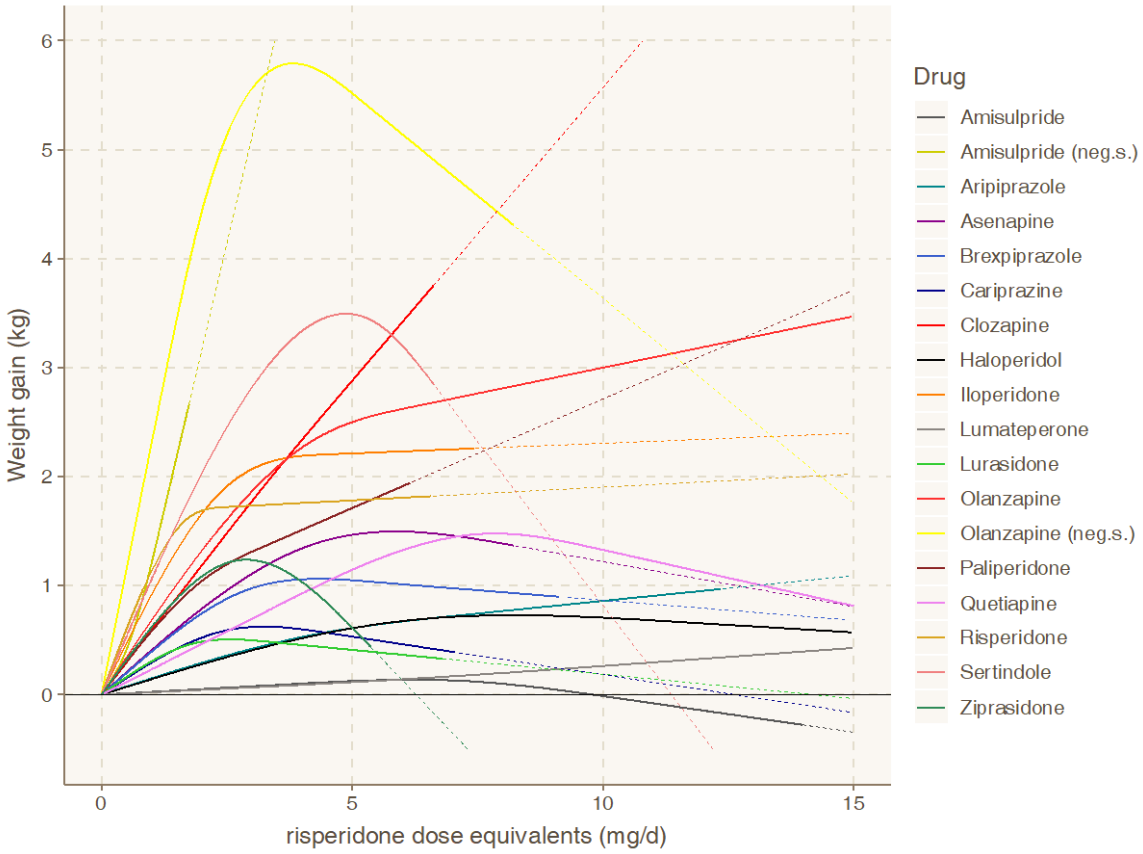
1. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34.

2. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008;61:991-996.

Appendix 13: overview of dose-response curves

Figure 6: dose-response curves of individual antipsychotics using risperidone dose equivalence

We calculated risperidone dose equivalents using the method reported in Leucht et al. 2020.(1) Dose-response curves of all individual antipsychotics were plotted in a single figure in order to allow an overview and comparability of the dose relationships among individual antipsychotics. It showed that antipsychotics differed in their propensity of weight gain and shape of the dose-response curve.



Reference:

1. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry. 2020;177(4):342-53.