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This file is a(n) Appendix of:

Antipsychotics for negative and positive symptoms of schizophrenia: dose-response meta-analysis of randomized controlled acute phase trials

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Supplementary Information file

''Antipsychotics for negative and positive symptoms of schizophrenia: dose-response meta-analysis of randomized controlled acute phase trials''

Michel Sabe, Nan Zhao, Alessio Crippa, Stefan Kaiser.

This appendix formed part of the original submission.

We post it as supplied by the authors.

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Supplementary methods. PRISMA 2009 Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
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.	3-4
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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.	14 Supplementary notes
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.	16
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.	15-16
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	16. Supplementary notes
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).	15-16
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Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	15
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.	17
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	17

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.	17

Section/topic	#	Checklist item	Reported on page #
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).	17
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	17
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4 SM Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	SM Table 1
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).	Fig 1
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.	5-9. Fig 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-9. Fig 1
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10. Table S2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10. SM Fig 2 SM Fig 3
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).	10-13
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).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
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

Supplementary notes. Protocol and search strategy

1. **Review title**

Antipsychotics for negative and positive symptoms of schizophrenia: dose-response meta-analysis of randomized controlled acute phase trials

2. **Named contact**

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Named contact address and organisational affiliation of the review

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3. **Anticipated or actual start date / Anticipated completion date.**

01/01/2020 – 30/06/2020

4. **Review team members and their organizational affiliations**

Dr. Sabe Michel. Geneva University Hospitals.

Dr. Zhao Nan. Geneva University Hospitals.

Dr. Crippa Alessio. Karolinska Institutet.

Dr. Kaiser Stefan. Geneva University Hospitals.

5. **Funding sources/sponsors.**

Internal funding only. The senior author Stefan Kaiser assumes full responsibility for all parts of the review process.

6. **Conflicts of interest**

7. Review question

The primary aim of the present review is to examine the dose-response relationship between first- and second-generation antipsychotic drugs for negative and positive symptoms of schizophrenia in acute schizophrenia by applying a dose-response meta-analysis approach.

8. Search terms

The systematic review shall be conducted using the following databases: MEDLINE, EMBASE, PubMed, PsyARTICLES, PsyINFO, Cochrane Database of Systematic Reviews and different trail registries (ClinicalTrials.gov. and clinicaltrialsregister.eu).

We will use combinations of the following terms:

The full list of search term used for one database can be found below.

(benperidol OR chlorpromazine OR clopenthixol OR flupenthixol OR fluphenazine OR fluspirilene OR haloperidol OR levomepromazine OR methotrimeprazine OR molindone OR penfluridol OR perazine OR perphenazine OR pimozide OR thioridazine OR thiothixene OR trifluoperazine OR zuclopenthixol OR amisulpride OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR clozapine OR iloperidone OR lurasidone OR loxapine OR olanzapine OR paliperidone OR quetiapine OR risperidone OR sertindole OR ziprasidone OR zotepine) AND (schizo* OR psychosis OR psychotic).

The following search limits were applied: English language, human studies, adult population (aged 18- 65-year-old). Search results will be limited to clinical trials and randomized controlled trials.

Excluded studies: studies from mainland China were excluded to avoid a systematic bias.

We will inspect titles, abstracts, and methods of all papers or clinical trials identified in the electronic searches.

We will search previous reviews investigating antipsychotics in general schizophrenia to identify additional studies.

In order to reduce the exclusion of unpublished papers, additional sources including Food and Drug administration website, from data from Cochrane reviews, and previous published meta-analysis on the use on antipsychotics for acute schizophrenia will be screened for additional studies.

9. **Condition or domain being studied**

Negative symptoms of schizophrenia contribute heavily to functional disability and burden of the disease and are still an unmet clinical need.

The treatment of the negative symptoms during an acute schizophrenia episode is still rarely addressed and remain a considerable clinical challenge.

The issue of prescribing the best antipsychotics medications for patients with schizophrenia presenting predominant negative symptoms have been addresses in a recent meta-analysis by Krause and colleagues (Krause et al., 2018). In addition, Leucht and colleagues have focused on the dose-response profile of antipsychotics medication from all published randomized controlled trials (RCTs) for patients with schizophrenia (Leucht et al., 2020). Considering the small number of trials available, the authors have focused on acute exacerbation. However, these authors have mostly focused on the score change from baseline on the Positive and Negative Syndrome Scale (PANSS) and only optimal doses for treatment with amisulpride in a specific population of patients affected by predominant negative symptoms.

To the best of our knowledge, when considering all antipsychotics, uncertainty persists about the dose dependency and optimal target dose for negative symptoms antipsychotic medications. Hence, there is a clear need to identify with available studies the near-maximum effective doses for the treatment of negative symptoms of schizophrenia. This information would be important for decision making by clinicians. Therefore, we decided to conduct a systematic review and dose-response meta-analysis of double-blind RCTs that used fixed doses (or fixed doses ranges) of antipsychotic drugs for the treatment of negative symptoms in acute schizophrenia.

References

Krause, M., Zhu, Y., Huhn, M., Schneider-Thoma, J., Bighelli, I., Nikolakopoulou, A., & Leucht, S. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*, 268(7), 625-639. doi:10.1007/s00406-018-0869-3(2018)

Leucht, S., Crippa, A., Siafis, S., Patel, M. X., Orsini, N., & Davis, J. M. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. *Am J Psychiatry*, 177(4), 342-353. doi:10.1176/appi.ajp.2019.19010034 (2020).

10. Participants/ population

We will include adult people (18-65 years, no restriction in setting, gender, ethnicity) with schizophrenia or related disorders (such as schizophreniform, or

schizoaffective disorders).

We will include studies in which a small proportion of the participants presents other psychiatric disorders than schizophrenia (<20%).

We will not include patients presenting a first episode of schizophrenia.

11. Intervention/ exposure

Use of first-generation (''typical'') and second generation (''atypical'') antipsychotic drugs (any form of administration) compared to placebo drug.

List of first-generation antipsychotic drugs:

benperidol, chlopromazine, clopenthixol, flupenthixol, fluphenazine, fluspirilene, haloperidol, levomepromazine, methotrimeprazine, molindone, penfluridol,

perazine, perphenazine, pimozide, thioridazine, thiothixene, trifluoperazine, zuclopenthixol

List of second-generation antipsychotic drugs:

amisulpride, aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, loxapine olanzapine, paliperidone, quetiapine, risperidone,

sertindole, ziprasidone, zotepine

12. Comparator(s)/control

In order to estimate a flexible dose-response model defined by 2 coefficients to compare at least three fixed dose levels of treatments (with consideration of the placebo dose of 0 mg) in order to estimate model parameters (Crippa & Orsini, 2016a). No restriction will be applied regarding dose of treatment.

References:

Crippa, A. & Orsini, N.,. Dose-response meta-analysis of differences in means. *BMC medical research methodology* 16, 91. (2016a)

13. Context

We will include adult people with schizophrenia, schizophreniform or schizoaffective disorders with an acute exacerbation of their primary disease.

We will include studies in which less than 20% of participants are suffering from other psychiatric disorders.

We will include outpatient and inpatient settings.

Included studies must be of at least 3-week duration trials.

Included studies must report at least three fixed dose (or fixed doses range) levels of treatments (with consideration of the placebo dose of 0 mg) in order to estimate model parameters according to the statistical model used (Crippa & Orsini, 2016a).

14. Main outcome

The main outcomes are the intention to treat score change from baseline (mean change) negative and positive symptoms.

These outcomes are measured with scales allowing specific assessment of negative symptoms (SANS, PANSS-negative, BPRS-withdrawal/retardation, CAINS, BNSS), or positive symptoms (PANSS-positive, the SAPS, the BPRS- thinking/disturbance and hostile/suspiciousness factors).

Additional outcomes

-Estimation of effective doses

We will estimate for each drug the 50% (ED50) and 95%(ED95) effective doses, as it is commonly performed in dose-response analysis (Pinheiro et al. 2016).

The ED50 is the mean dose that produces half of the maximum reduction of the patient's symptoms.

-Estimation of dose equivalence

The ED95 of each drug will be used to obtain the risperidone dose equivalence ratios.

References:

Pinheiro, J. C., Bretz, F. & Branson, M. Analysis of dose-response studies: modeling approaches, in Dose Finding in Drug Development. Edited by Ting N. New York, Springer, pp 146–171. (2016)

15. Data extraction

Two review authors (MS and NZ) will independently screen the titles and abstracts yielded by the search against the inclusion criteria. We will obtain full reports

for all titles that appear to meet the inclusion criteria or for which there is any uncertainty. Both review authors will then screen the full-text reports and decide

whether these meet the inclusion criteria.

We will seek additional information from study authors where necessary to resolve questions about eligibility. We will resolve disagreement through discussion.

We will record the reasons for excluding trials.

16. Risk of bias assessment

Two reviewers (MS and SK) will independently assess the risk of bias employing the Cochrane Collaboration bias assessment tool:

1) Random sequence generation; was the allocation sequence adequately generated?

2) Allocation concealment; was the allocated treatment adequately concealed from the study participants and clinicians and other healthcare or research staff at

the enrollment stage?

3) Blinding of participants and personnel; were the personnel assessing outcomes and analyzing data sufficiently blinded to the intervention allocation throughout the trial?

4) Blinding of outcome assessment; were all measures used, if any, to blind outcome assessors from the knowledge of which intervention a participant received, was there a report on the intended blinding effectiveness?

5) Incomplete outcome data; were participant exclusions, attrition, and incomplete outcome data adequately addressed in the published report?

6) Selective reporting; is there evidence of selective outcome reporting and might this have affected the study results?

Unpublished studies will be searched by checking pre-registration of trials.

If possible, publication bias will be assessed using a funnel plot. Disagreements between the reviews authors over the risk of bias in particular studies will be resolved by discussion.

17. Strategy for data synthesis

We plan to conduct a dose-response meta-analysis of aggregated data following the method proposed by Crippa and Orsini (Crippa & Orsini, 2016).

Our statistical approach is entirely based on the two-stage approach dose-response meta-analysis of differences in means described in the Crippa and Orsini paper (Crippa & Orsini, 2016).

We plan to pool dose-response relations from aggregated data where the changes in the distribution of the quantitative outcome are expressed in terms of differences in means.

The effect size was the standardized mean difference (cohen's d).

The Crippa and Orsini model is deployed using a two-stage approach:

First, a flexible dose-response model is estimated within each study taking into account the covariance of the data points (mean differences, standardized mean differences). Regression splines will be used to flexibly model the dose of interest. Splines represent a family of functions that describe a wide range of curves. These curves consist of piecewise polynomials over consecutive intervals defined by k knots. We will use knots located at the 25th, 50th and 75th percentiles. And second, parameters describing the study-specific curves are then combined using a multivariate random-effects model to address heterogeneity across studies. Dose-response curves will be estimated.

These dose-response curves characterize the relative efficacy of the dose under investigation using the placebo effect as referent.

References:

Crippa, A. & Orsini, N.,. Dose-response meta-analysis of differences in means. *BMC medical research methodology* 16, 91. (2016a).

18. **Analysis of subgroups or subsets**

Subgroup analyses will be conducted by restricting included studies to those defining change in negative symptoms as primary outcome. If appropriate, additional sensitivity analysis will be conducted.

Supplementary Table 1. Characteristics of included studies

Authors, year	Characteristics of patients	Scale used to report negative, positive symptoms and extrapyramidal side effects	Mean duration of illness in years	Duration of the trial	Number of patients included per group	Fixed doses considered
First generation antipsychotics						
Haloperidol						
(Zimbroff et al., 1997)[1]	All patients had a primary diagnosis of DSM-III-R or DSM-IV schizophrenia, with no other primary psychiatric diagnoses. A combined score of at least eight on any two of the positive symptoms of the BPRS[a] (hallucinatory behavior, conceptual disorganization, unusual thought content, or suspiciousness) was required in order to enroll patients with active psychosis of at least moderate severity. Scores of less than three on each item of the AIMS were also required to restrict individuals with tardive dyskinesia from entry, which ensured the exclusion of patients with even mild tardive dyskinesia. Inpatients were included (18 to 65-year-old).	SANS[b] PANSS[c] SAS[d]	16.2[e]	8 weeks	n= 71; 67; 70 n= 73	Haloperidol 4, 8, 16 mg/day Placebo
Second generation antipsychotics						
Amisulpride						
(Puech, Fleurot, & Rein, 1998)[2]	All patients had a primary diagnosis of chronic or subchronic schizophrenia, with acute exacerbation, according to DSM-III-R criteria; a minimum score of 4 (moderate) on at least two of four core positive symptoms on the BPRS; and a minimum total score of 12 for four core BPRS items. Inpatients only were included (18 to 60-year-old).	PANSS SAS	10.1	4 weeks	n= 61; 64; 65; 65 n= 64 n=61	Amisulpride 100, 400, 800, 1200 mg/day Haloperidol 15 mg/day No placebo arm, the 100 mg Amisulpride arm is considered as a sub-therapeutic arm [j].
Aripiprazole						
(Cutler et al., 2006)[3]	Patients had a diagnosis of schizophrenia, according to the DSM-IV criteria, in acute relapse. Patients required to present a PANSS Total score of >60 and a score of at least 4 on >2 of the PANSS items of delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness. Inpatients were included (≥18-year-old).	PANSS SAS	16.3[e]	6 weeks	n= 93; 92; 94 n= 88	Aripiprazole 2, 5, 10 mg/day Placebo
(McEvoy, Daniel, Carson, McQuade, & Marcus, 2007)[4]	Patients had a diagnosis of schizophrenia DSM-IV and were experiencing an acute exacerbation of symptoms that required inpatient hospitalization. In addition, patients were required to have PANSS Total score of 60 or more (1–7 scale) and a score of at least 4 on two or more of the following PANSS items at the baseline assessment: delusions, hallucinatory behavior, conceptual disorganization or suspiciousness/persecution. Inpatients were included (≥18-year-old).	PANSS SAS	16.4[e]	6 weeks	n= 106; 106; 100 n= 108	Aripiprazole 10, 15, 20 mg/day Placebo
(Potkin et al., 2003)[5]	Patients had a primary diagnosis of schizophrenia or schizoaffective disorders (DSM-IV), who were hospitalized due to an acute relapse. For inclusion, patients had to present a PANSS total score of at least 60, and a minimum score of 4 on at least 2 items of the psychotic item subscale: delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness. Inpatients were included (18 to 65-year-old).	PANSS SAS	n.a.	4 weeks	n= 101; 101; 103 n= 99 n= 103	Aripiprazole 20, 30 mg/day Risperidone 6 mg/day Placebo

Asenapine						
(Kane, Cohen, Zhao, Alphs, & Panagides, 2010)[6]	Patients had a DSM-IV-TR diagnosis of schizophrenia with an acute exacerbation of psychotic symptoms at study enrollment. For inclusion, patients had to present PANSS total score of 60 or higher, with scores of 4 or higher on at least 2 of 5 predefined PANSS positive subscale items (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution) at the initial screening assessment and at baseline for enrolled patients, and a CGI-S[f] score of 4 or higher (moderately ill) at baseline. Inpatients were included. These patients could continue the study as outpatients (≥18-year-old).	PANSS SAS	12.5[e]	6 weeks	n= 109; 105 n= 112 n= 122	Asenapine 5, 10 mg/day Haloperidol 4 mg/day Placebo
(Kinoshita, Bai, Kim, Miyake, & Oshima, 2016)[7]	Patients had a DSM-IV-TR diagnosis of schizophrenia with an acute exacerbation of psychotic symptoms at study enrollment. The current acute exacerbation of schizophrenia had to be of ≤2 months duration. Other key inclusion criteria were a PANSS total score ≥60, with scores of ≥4 in two or more of five items on the PANSS positive subscale (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution) at the initial screening assessment and at baseline, and a score of ≥4 on the CGI-S scale at baseline. Inpatients were included (20 to 64-year-old).	PANSS DIEPSS[g]	n.a.	6 weeks	n= 175; 181 n= 174	Asenapine 5, 10 mg/day Placebo
Brexpiprazole						
(Correll et al., 2015)[8][h]	Patients had a DSM-IV-TR diagnosis of schizophrenia confirmed by the Mini International Neuropsychiatric Interview. Included patients experienced an acute exacerbation of schizophrenia and were hospitalized. Inpatients were included (18 to 65-year-old).	PANSS SAS	12.8[e]	6 weeks	n= 87; 180; 178 n= 178	Brexipiprazole 0.25, 2, or 4 mg/day Placebo
(Ishigooka, Iwashita, & Tadori, 2018)[9]	Patients were diagnosed with DSM-IV-TR for schizophrenia and confirmed by the Mini International Neuropsychiatric Interview assessment for experiencing acute exacerbation of psychotic symptoms, psychotic disorders, and marked deterioration of normal function by meeting the following criteria at screening and baseline: CGI-S score of ≥4, BPRS score of ≥40, and score of ≥4 for two or more of the BPRS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content). Inpatients were included (18 to 65-year-old).	PANSS DIEPSS	16.4[e]	6 weeks	n= 115; 115; 113 n= 116	Brexipiprazole 1, 2, 4 mg/day Placebo
(Kane et al., 2015)[10]	Patients were affected with a current diagnosis of schizophrenia (DSM-IV-TR) confirmed by the Mini International Neuropsychiatric Interview. Included patients were experiencing an acute exacerbation of psychotic symptoms and marked deterioration of usual function, as demonstrated by meeting all of the following criteria at screening and baseline visits: BPRS score ≥40; score of ≥4 on two or more BPRS items (hallucinatory behavior, unusual thought content, conceptual disorganization or suspiciousness); and CGI-S score ≥4. Inpatients were included (18 to 65-year-old).	PANSS SAS	12.8[e]	6 weeks	n= 120; 186; 184 n= 184	Brexipiprazole 1, 2, 4 mg/day Placebo
Cariprazine						
(Durgam et al., 2014)[11]	Included patients met the DSM-IV-TR criteria for schizophrenia. Patients had the diagnosis for at least one year, a current exacerbation less than 2 weeks' duration, and at least one psychotic episode requiring hospitalization/antipsychotic medication change/intervention during the preceding year. PANSS total score between 80 and 120, a score≥4 (moderate) on at least 2 of 4 PANSS positive symptoms (delusions, hallucinatory behavior, conceptual disorganization, suspiciousness/persecution), and CGI-S rating ≥4 were required. Body mass index between 18 and 35 was also required.	PANSS SAS	11.3	6 weeks	n= 145; 146; 147 n= 151	Cariprazine 1.5, 3, 4.5 mg/day Placebo

	Inpatients were included (18 to 60-year-old).					
(Durgam et al., 2015)[12]	Included patients had a DSM-IV-TR criteria for schizophrenia, present for more than one year and with at least one psychotic episode that required hospitalization or change of antipsychotic medication during the past year. To ensure that participants' current psychotic episode was acute, duration of the current episode must be inferior to two weeks. A CGI-S score ≥4, a PANSS total score ≥80 and ≤120, and a score ≥4 on at least 2 of the PANSS positive symptoms of delusions, hallucinatory behavior, conceptual disorganization or suspiciousness/persecution was also required. Inpatients were included. These patients could continue the study as outpatients (18 to 60-year-old).	PANSS SAS	12.2	6 weeks	n= 155; 157 n= 153	Cariprazine 3, 6 mg/day Placebo
(Durgam et al., 2016)[13]	Include patients had a schizophrenia diagnosis for 1 year or longer based on the DSM-IV-TR, with a current psychotic episode less than 4 weeks in duration and at least one other psychotic episode in the past year that required hospitalization or change in antipsychotic medication. At both screening and randomization, all patients had a PANSS total score of 80–120 (inclusive), a score of 4 or higher on either the PANSS delusions item or the hallucinatory behavior item, a score of 4 or higher on either the PANSS conceptual disorganization item or the suspiciousness/persecution item, and a CGI-S score of 4 or higher. Inpatients were included. These patients could continue the study as outpatients (18 to 65-year-old).	PANSS SAS	17.6	6 weeks	n= 128; 134 n= 130	Cariprazine 1.5-4.5, 6-12 mg/day Placebo
(Kane et al., 2015)[14]	Patients with a current diagnosis of schizophrenia defined by criteria from the DSM-IV-TR were included. Participants had been diagnosed for 1 year or more and had a current psychotic episode of less than 2 weeks' duration with at least 1 psychotic episode that required hospitalization or change in antipsychotic therapy during the previous year. A CGI-S score of 4 or higher, PANSS total score of 80 or more and 120 or less, and a score of 4 or higher on at least 2 of the following 4 PANSS items: delusions, hallucinatory behavior, conceptual disorganization, or suspiciousness/persecution were required. Inpatients were included. These patients could continue the study as outpatients (18 to 65-year-old).	PANSS SAS	10.7	6 weeks	n= 151; 148 n= 147	Cariprazine 3-6, 6-9 mg/day Placebo
Lurasidone						
(Higuchi et al., 2019)[15]	Included patients had DSM-IV-TR criteria for schizophrenia with disorganized, paranoid, or undifferentiated subtypes. Patients were required to have an exacerbation of psychotic symptoms within 60 days before screening, with a PANSS total score of ≥80, including a score of ≥4 (moderate) on two or more of the following PANSS items: delusions (P1), conceptual disorganization (P2), hallucinations (P3), suspiciousness (P6), and unusual thought content (G9) at screening and baseline visits. Inpatients were included (18 to 74-year-old).	PANSS DIEPSS	15	6 weeks	n= 150; 154 n= 151	Lurasidone 40, 80 mg/day Placebo
(Loebel et al., 2013)[16]	Included patients had a DSM-IV-TR criteria for a primary diagnosis of schizophrenia as determined by clinical interview using the Mini International Neuropsychiatric Interview. Subjects were also required to have an illness duration greater than 1 year with the current acute exacerbation of psychotic symptoms no longer than 2 months and, at the Screening and Baseline visits, to have a CGI-S score ≥4 (moderate or greater) and a PANSS total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Inpatients were included (18 to 75-year-old).	PANSS SAS	11.4	6 weeks	n= 125; 121 n= 121	Lurasidone 80, 160 mg/day Placebo

(Meltzer et al., 2011)[17]	Enrolled patients met DSM-IV criteria for a primary diagnosis of schizophrenia as determined by the Mini International Neuropsychiatric Interview. Patients were also required to have an illness duration of at least 1 year and to have been hospitalized for ≤2 weeks for an acute exacerbation of psychotic symptoms and, at the screening and baseline visits, to have a CGI-S score ≥4 (moderate or greater) and a PANSS total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Inpatients were included (18 to 75-year-old).	PANSS SAS	13.5	6 weeks	n= 118; 118 n= 114	Lurasidone 40, 120 mg/day Placebo
(Nasrallah et al., 2013)[18]	Patients were enrolled if they presented a DSM-IV criteria for a primary diagnosis of schizophrenia, as established by structured clinical interview using the MINI, had received a diagnosis of schizophrenia ≥1 year previously, and were currently experiencing an acute exacerbation of psychotic symptoms (lasting ≤2 months). Additional criteria for eligibility included a CGI-S score≥4 (moderate or greater) and PANSS total score ≥80, including a score ≥4 (moderate) on two or more of the following five items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Inpatients were included (18 to 75-year-old).	PANSS SAS	14.1 [e]	6 weeks	n= 121; 118; 123 n= 124	Lurasidone 40, 80, 120 mg/day Placebo
(Ogasa, Kimura, Nakamura, & Guarino, 2013)[19]	The study enrolled patients with a DSM-IV criteria for primary diagnosis of schizophrenia who were hospitalized for an acute exacerbation of symptoms. Patients were also required to have illness duration of at least 1 year, no psychiatric hospitalization within the 3 months prior to study entry, a BPRS derived from the PANSS of ≥42, a score of ≥4 on two or more items of the positive symptoms subscale on the PANSS, and a CGI-S score of ≥4 (moderate). Inpatients were included. These patients could continue the study as outpatients (18 to 64-year-old).	PANSS SAS	n.a.	6 weeks	n= 50; 49 n= 50	Lurasidone 40, 120 mg/day Placebo
Olanzapine						
(Beasley, Sanger, et al., 1996)[20]	All patients enrolled met the DSM-IILR criteria for schizophrenia (295.1-295.3, 295.9) as established by clinical interview and chart review. Residual type 295.6 was excluded. Patients were required to have a minimum BPRS, total score (BPRS items scored 0-6) extracted from the PANSS of at least 24. Also, patients were required to have a CGI-S score >4. Patients with a diagnosis of a DSM-III-R organic mental disorder or substance-use disorder active within 3 months of study entry were excluded as were patients at serious suicidal risk. Inpatients and outpatients were included. Inpatients could continue the study as outpatients (18 to 65-year-old).	PANSS SAS	12.7 [e]	6 weeks	n= 51; 49 n= 49	Olanzapine 1, 10 mg/day Placebo
(Beasley, Tollefson, et al., 1996)[21]	All patients enrolled met the DSM-III-R criteria for schizophrenia with an acute exacerbation, as established by clinical interview and chart review. In addition, patients were required to have a minimum BPRS total score (items scored 0 to 6) of 24. Patients with a diagnosis of a DSM-III-R organic mental disorder or substance-use disorder active within 3 months of study entry were excluded as were patients at serious suicidal risk. Patients were required to be off oral neuroleptics for at least 2 days and off depot neuroleptics for at least 6 weeks prior to starting the study.	PANSS SAS	14 [e]	6 weeks	n= 65; 64; 69 n= 68	Olanzapine 6.6, 11.6, 16.3 mg/day Placebo
Olanzapine (LAI)						
(Lauriello et al., 2008)[22]	The study enrolled patients with a DSM-IV or DSM-IV-TR criteria for primary diagnosis of schizophrenia. At enrollment, patients were required to have a PANSS-derived BPRS score of ≥30. For patients treated previously with a depot antipsychotic,	PANSS SAS	17.1 [e]	8 weeks	n= 106; 100; 100 n= 98	Olanzapine LAI 210, 300, 405 mg/day Placebo

	the last injection must have been received at least 2 weeks or 1 injection interval, which was longer before double-blind treatment. Inpatients and outpatients were included. Patients were initially all hospitalized, and could then continue the study as outpatients (18 to 75-year-old).					
Paliperidone ER						
(Canuso et al., 2010)[23]	Included patients met the DSM-IV criteria for an acute exacerbation of a schizoaffective disorder. Patients were required to have a PANSS total score of at least 60 and a score ≥4 on at least 2 of the following PANSS items (Pt, P4, G4, G8, G14). In addition, subjects needed to have prominent mood symptoms with a score ≥16 on the Young Mania Rating Scale; and/or on the Hamilton Depression Rating Scale 21-item versions. Inpatients were included. Patients were initially all hospitalized, and could then continue the study as outpatients (18 to 65-year-old).	PANSS SAS	4.7[d]	6 weeks	n= 105; 98 n= 107	Paliperidone ER 5.7, 11.6 mg/day Placebo
(Davidson et al., 2007)[24]	Included patients required a diagnosis of schizophrenia according to DSM-IV criteria for at least 1 year prior to screening and have agreed to voluntary hospitalization for a minimum of 14 days. Patients were initially all hospitalized for a minimum duration of 14 days, and could then continue the study as outpatients (≥18-year-old).	PANSS SAS	11.7	6 weeks	n= 127; 125; 115 n= 123	Paliperidone ER 3, 9, 15 mg/day Placebo
(Kane et al., 2007)[25]	Patients enrolled experienced an acute episode of schizophrenia, as represented by a PANSS total score between 70 and 120. Patients must have been diagnosed with schizophrenia according to DSM-IV criteria for at least 1 year prior to screening. Patients were initially all hospitalized for a minimum duration of 14 days, and could then continue the study as outpatients (≥18-year-old).	PANSS SAS	10.2	6 weeks	n= 123; 122; 129 n= 126	Paliperidone ER 6, 9, 12 mg/day Placebo
Paliperidone (LAI)						
(Gopal et al., 2010)[26]	Included patients presented a diagnosis of schizophrenia for at least 1 year before screening, a Positive and Negative Syndrome Scale (PANSS) total score at screening and baseline between 70 and 120 (inclusive), and with a body mass index (BMI) >17.0 kg/m2. Patients were initially all hospitalized for a minimum duration of 8 days, and could then continue the study as outpatients (≥18-year-old).	PANSS SAS	14.5[e]	13 weeks	n= 94; 97; 30 n= 136	Paliperidone LAI 50, 100, 150 mg/day Placebo
(Kramer et al., 2010)[27]	Enrolled patients had a diagnosis of schizophrenia according to DSM-IV criteria for at least 1 year had a PANSS total score of 70–120, inclusive, at screening, and 60–120 inclusive, on day 1 before the start of double-blind study drug, and had a body mass index (BMI) range of 15–35 kg/m2. Patients were initially all hospitalized for a minimum duration of 14 days, and could then continue the study as outpatients (18-65-year-old).	PANSS SAS	12.3[e]	5 weeks	n= 79; 84 n= 84	Paliperidone LAI 50, 100 mg/day Placebo
(Pandina et al., 2010)[28]	Included patients were affected by an acute exacerbation of an established diagnosis of schizophrenia defined by the DSM-IV, whose disease diagnosis was able to be documented as present for at least 1 year before study screening, who demonstrated PANSS total score between 70 and 120 at screening and between 60 and 120 at baseline. Patients were initially all hospitalized for a minimum duration of 8 days, and could then continue the study as outpatients (≥18-year-old).	PANSS SAS	n.a.	13 weeks	n= 160; 165; 163 n= 164	Paliperidone LAI 25, 100, 150 mg/day Placebo
(Nasrallah et al., 2010)[29]	Eligible patients who met the diagnostic criteria for schizophrenia according to the DSM-IV-TR for at least 1 year before screening. Patients had a PANSS total score at screening and baseline of 70–120 and a body mass index (BMI)>15.0 kg/m2. Patients were initially all hospitalized for a minimum duration of 8 days, and could then continue the study as outpatients (≥18-year-old).	PANSS SAS	13.3[e]	13 weeks	n= 130; 128; 131 n= 125	Paliperidone LAI 25, 50, 100 mg/day Placebo
Quetiapine IR						
(Arvanitis & Miller, 1997)[30]	On inclusion, patients presented a diagnosis of acute exacerbation of their chronic or subchronic schizophrenia, as defined by the DSM-III-R. Additionally, at trial entry and before randomization, patients were required to have a minimum total score of 27	PANSS SAS	14.7[e]	6 weeks	n= 53; 48; 52; 51;54 n= 51	Quetiapine IR 75, 150, 300, 600, 750 mg/day Placebo

	on the 18-item BPRS (0-6 scoring), a score of 3 (moderate) on at least two items from the BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), and a score of 4 (moderately ill) on the CGI Severity of illness item. This study gives no information concerning the exact hospitalization duration (18-65-year-old).					
(Lindenmayer, Brown, Liu, Brecher, & Meulien, 2008)[31]	Patients with a DSM-IV diagnosis of schizophrenia-catatonic (DSM-IV diagnostic code 295.20); disorganized (295.10); paranoid (295.30); or undifferentiated (295.90) were eligible to participate. To be included in the study, patients had to meet the following criteria: a PANSS total score ≥60; a score of ≥4 for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution; a Clinical Global Impressions-Severity of Illness (CGI-S) score ≥4 (at least moderately ill) and, in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks. Patients who were screened as outpatients were hospitalized when enrolled and could be discharged from the hospital on day 10 at the investigator's discretion (18-65-year-old).	PANSS SAS	15.7 [e]	6 weeks	n= 85; 80 n= 78	Quetiapine IR 300, 600 mg/day Placebo
Quetiapine ER						
(Cutler et al., 2010)[32]	Included patients were a documented DSM-IV diagnosis of catatonic (DSM-IV diagnostic code 295.20), disorganized (295.10), paranoid (295.30), or undifferentiated (295.90) schizophrenia. The key inclusion criteria were: a PANSS total score ≥70 at enrollment and randomization; a score of ≥4 at randomization for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/ persecution; a Clinical Global Impressions Severity of Illness (CGI-S) score ≥4 (moderate to severe); and, in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks. Patients were initially all hospitalized for a minimum duration of 2 weeks, and could then continue the study as outpatients (≥18-year-old).	PANSS SAS	17.85	6 weeks	n= 40; 44; 45 n= 49	Quetiapine ER 400, 600, 800 mg/day Placebo
(Kahn et al., 2007)[33]	Included patients presented a DSM-IV diagnosis of acute schizophrenia: diagnosis of catatonic (DSM-IV diagnostic code 295.20), disorganized (295.10), paranoid (295.30), or undifferentiated (295.90). Key inclusion criteria were a PANSS total score ≥70; a CGI-S score ≥4; and in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks; a PANSS score ≥4 for at least one of the following items: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution. Both inpatients and outpatients were included (18-65-year-old).	PANSS SAS	8.4	6 weeks	n= 111; 111; 117 n= 115	Quetiapine ER 400, 600, 800 mg/day Placebo
(Lindenmayer et al., 2008)[31]	Patients with a DSM-IV diagnosis of schizophrenia-catatonic (DSM-IV diagnostic code 295.20); disorganized (295.10); paranoid (295.30); or undifferentiated (295.90) were eligible to participate. To be included in the study, patients had to meet the following criteria: a PANSS total score ≥60; a score of ≥4 for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution; a Clinical Global Impressions-Severity of Illness (CGI-S) score ≥4 (at least moderately ill) and, in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks. Patients who were screened as outpatients were hospitalized when enrolled and could be discharged from the hospital on day 10 at the investigator's discretion (18-65-year-old).	PANSS SAS	15.1 [e]	6 weeks	n= 83; 87; 85 n= 78	Quetiapine ER 300, 600, 800 mg/day Placebo
Risperidone						
(Chouinard et al., 1993)[34]	Included patients presented a diagnosis of chronic schizophrenia based on the DSM-III-R criteria, with a PANSS score between 60 and 120.	PANSS ESRS[i]	16 [e]	8 weeks	n= 24; 22; 22; 24 n= 22	Risperidone 2, 6, 10, 16 mg/day Placebo

	Patients were initially all hospitalized for a duration of 21 days, and could then continue the study as outpatients (18-65-year-old).					
(Marder & Meibach, 1994)[35]	Included patient met the DSM-III-R criteria for schizophrenia. To be included in the study, each patient was also required to have a total score on the PANSS scale of no less than 60 and no greater than 120. The mean length of hospitalization was different among each inclusion center (see Table 2 of this study) (18-65-year-old).	PANSS ESRS	15.8[e]	8 weeks	n= 63; 64; 65; 64 n= 66	Risperidone 2, 6, 10, 16 mg/day Placebo
(Study-20272/S007, 1996)[36]	Eligible patients met a DSM-IV diagnosis of schizophrenia (any subtype). Subjects were required at baseline to be inpatients and to have a PANSS score of 80-120 and a score of at least 8 on any two of the BPRS psychosis cluster items combined. Subjects were required at baseline to be inpatients, and had to remain at least 2 weeks at hospital (18-65-year-old).	PANSS	n.a.	4 weeks	n= 85; 78; n= 83	Risperidone 4, 8 mg/day Placebo

Risperidone (LAI)

(Kane et al., 2003)[37]	Patients with a DSM-IV criteria of schizophrenia were enrolled. Inclusion criteria included a PANSS total score of 60 to 120 and good general health. Inpatients and outpatients were included (18-55-year-old).	PANSS ESRS	n.a.	12 weeks	n= 99; 103; 100; n= 98	Risperidone LAI 25, 50, 75 mg/day Placebo

Sertindole

(Zimbroff et al., 1997)[1]	All patients had a primary diagnosis of DSM-III-R or DSM-IV schizophrenia, with no other primary psychiatric diagnoses. A combined score of at least eight on any two of the positive symptoms (hallucinatory behavior, conceptual disorganization, unusual thought content, or suspiciousness) of the BPRS was required in order to enroll patients with active psychosis of at least moderate severity. Scores of less than three on each item of the AIMS were also required to restrict individuals with tardive dyskinesia from entry, which ensured the exclusion of patients with even mild tardive dyskinesia. Inpatients were included (18 to 65-year-old).	SANS SAS	16.2[e]	8 weeks	n= 76; 68; 72 n= 73	Sertindole 12, 20, 24 mg/day Placebo

Ziprasidone

(Daniel et al., 1999)[38]	Included patients presented an acute exacerbation of chronic or subchronic schizophrenia (295.x3) or schizoaffective disorder (295.x4) as defined in DSM-III-R were eligible to enter. They were to have been hospitalized within the previous 4 weeks and been diagnosed at least 6 months before the study. The patients were required to have a total score > 60 on the PANSS and a score of at least 4 on two or more core items in the PANSS (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) in the 24 hours before study treatment was started. In addition, the patients were required to have a score of 3 (minimally improved) or greater (worse) on the CGI-I at baseline as compared with screening (≥18-year-old).	PANSS SAS	14.2	6 weeks	n= 106; 104 n= 92	Ziprasidone 80, 160 mg/day Placebo
(Keck et al., 1998)[39]	Included patients presented an acute exacerbation of chronic or subchronic schizophrenia or schizoaffective disorder as defined in DSM-III-R who had been hospitalized within the previous 3 weeks were allowed to enter the study. Patients were required to have a minimum duration of illness of at least 1 year. At screening and 24 h before study treatment was started, patients were required to have a total score of greater than 37 on the BPRS (anchored version, 1-7 rating system) and a score of at least four (moderate) on two or more of the BPRS core items (suspiciousness, conceptual disorganization, hallucinatory behavior, unusual thought content). All patients were inpatients (18 to 64-year-old).	PANSS SAS	16.2[e]	4 weeks	n= 44; 47 n= 48	Ziprasidone 80, 160 mg/day Placebo
(Study-20-825, 1998)[40]	Included patients presented a primary diagnosis of chronic or subchronic schizophrenia. A baseline CGI-S score ≤5 was required at inclusion. Excluded from	PANSS		52 weeks	n= 76; 72; 71 n= 75	Ziprasidone 20, 40, 80 mg/day Placebo

	this study were patients scoring ≥5on the hostility and uncooperativeness items of the PANSS. Inpatients were included (≥18-year-old).

a BPRS: Brief Psychiatric Rating Scale

b SANS: Scale for the Assessment of Negative Symptoms

c PANSS: Positive and Negative Syndrome Scale

d SAS: Simpson-Angus rating Scale

e The mean duration of illness was deduced using the mean age at age of onset of the illness (years)

f CGI-S: Clinical Global Impression Severity of Illness

g DIEPSS: drug induced extrapyramidal symptoms scale

h In order to avoid duplication of database, we have not included the results reported by Correll et al. 2016 studies, that duplicate results of the Correll et al. 2015 and the Kane et al. 2015 studies, and that add a flexible dose phase 2 study

i ESRS: Extrapyramidal Symptom Rating Scale

j No placebo arm was available for amisulpride. Considering that only one study was available, we used the 100 mg dose as comparator, and reported this sensitivity analysis in the main analysis.

Supplementary Table 2. Risk of bias assessment for included RCTs

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other potential biases
Studies on first-generation antipsychotics							
Haloperidol							
Zimbroff et al. 1997	Low risk	Low risk	Unclear	Unclear	Low risk	High risk	High risk No mention of conflict of interest
Studies on second generation antipsychotics							
Amisulpride							
Puech et al. 1998	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Aripiprazole (oral)							
Cutler et al. 2006	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	High risk No mention of conflict of interest
McEnvoy et al. 2007	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Potkin et al. 2003	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk
Aripiprazole (LAI)							
Correll et al. 2019	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Asenapine							
Kane et al. 2010	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
Kinoshita et al. 2016	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Brexpiprazole							
Correll et al. 2015	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Ishigooka et al. 2018	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Kane et al. 2015b	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cariprazine							
Durgam et al. 2014	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Durgam et al. 2015	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Durgam et al. 2016	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk

Kane et al. 2015a	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Haloperidol							
Zimbroff et al. 1997	Low risk	Low risk	Unclear	Unclear	Low risk	High risk	High risk No mention of conflict of interest
Lurasidone							
Higuchi et al. 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Loebel et al. 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Meltzer et al. 2011	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nasrallah et al. 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ogasa et al. 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Olanzapine							
Beasley et al. 1996a	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Beasley et al. 1996b	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Olanzapine (LAI)							
Lauriello et al. 2008	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Paliperidone							
Canuso et al. 2010a	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Davidson et al. 2007	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kane et al. 2007	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Paliperidone (LAI)							
Gopal et al. 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kramer et al. 2010	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Pandina et al. 2010	Low risk	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk
Nasrallah et al. 2010	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Quetiapine IR							
Arvanitis et al. 1997	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Lindenmayer et al. 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Quetiapine ER							
Cutler et al. 2010	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Kahn et al. 2007	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	High risk No mention of conflict of interest
Lindenmayer et al. 2008	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Risperidone							
Chouinard et al. 1993	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Marder et al. 1994	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk No mention of conflict of interest
Study 20-588S002	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Risperidone (LAI)							
Kane et al. 2002	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	High risk No mention of conflict of interest
Sertindole							
Zimbroff et al. 1997	Low risk	Low risk	Unclear	Unclear	Low risk	High risk	High risk No mention of conflict of interest
Ziprasidone							
Daniel et al. 1999	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Keck et al. 1998	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Study 20-825	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk

Criteria for judging risk of bias in the 'Risk of bias' assessment tool:

Low risk: the investigators describe a random component for considered risk

Unclear: insufficient information to permit judgment of 'Low risk' or 'High risk'
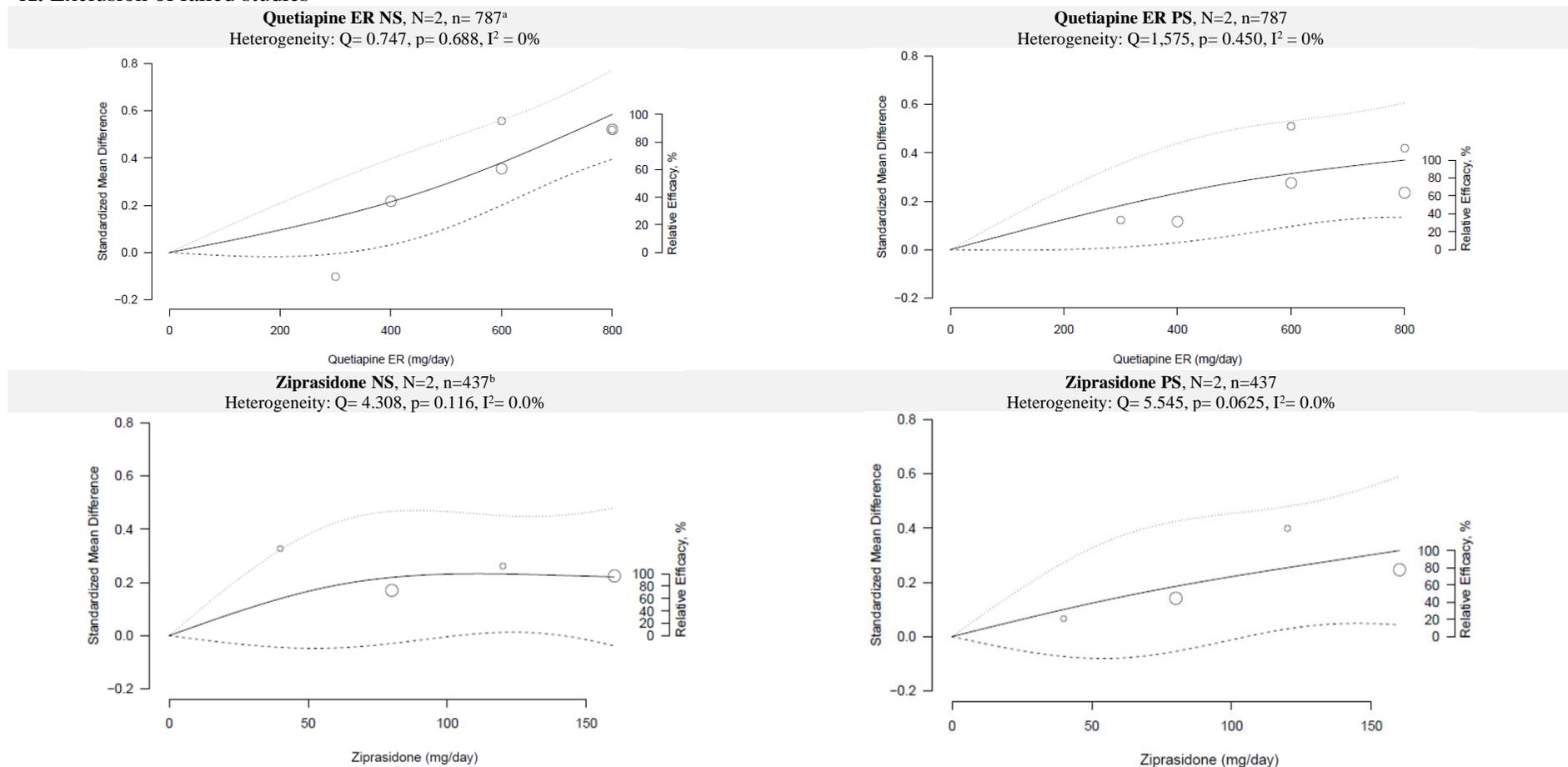
High risk: the investigators describe a non-random component; there is a high probability of bias.

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┌──────────────┐  ┌─────────────────────────────────────────────────┐  ┌────────────────────────┐
│              │  │ *Unique titles identified though database search,│  │ *Additional records    │
│              │  │ n= 4390                                          │  │ identified though other│
│Identification│  │  • Electronic databases, n= 4390 (PUBMED, n=3799;│  │ sources, n= 8          │
│              │  │ EMBASE, n=4346; MEDLINE, n=2982; Cochrane Database│  │                        │
│              │  │ of Systematic Reviews, n= 4280).                 │  │                        │
│              │  │ • Registry at clinicaltrials.gov, n= 814         │  │                        │
│              │  │ • International Clinical Trials Registry Platform,│  │                        │
│              │  │ n= 549                                           │  │                        │
└──────────────┘  └─────────────────────────────────────────────────┘  └────────────────────────┘
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Unique titles identified,
n= 4398

Screening of trial protocols, and/or abstracts,
n= 3261

Excluded, n= 3786
Data not relevant to our research subject, n=1137
Review, n=182
Article not relevant to research subject, n= 2095
Add-on medication, n= 58
Patients with FEP, n= 198
Article on genetic, n= 116

Clinical trials and Randomized clinical trials, full-text articles reviewed for eligibility, n= 612

Exclusion after review of full-text articles, n= 572
Stable patients, n= 273
Not an RCT, n= 234
Studies still ongoing, or with no results published, n= 29
Duplication, n= 7
Non relevant intervention, n= 6
Article not reporting negative symptoms, n= 23

RCTs included in qualitative synthesis,
n= 40

RCTs included in quantitative synthesis,
(meta-analysis)
n= 40

Identification · Screening · Eligibility · Included

Supplementary Figure 1. Systematic review PRISMA flowchart

Supplementary Figure 2. Dose-response curves for quetiapine ER and ziprasidone after exclusion of failed studies. The figures represent pooled dose-response association between one antipsychotic and the mean change in the negative or the positive subscale scores of the PANSS (solid line). The antipsychotic dosage is modeled with restricted cubic splines in a random-effects model. Dash lines represent the 95 % confidence intervals for the spline model. The placebo group (dose= 0) served as the referent group. Circles indicate observed mean differences in individual studies; size of bubbles is proportional to precision (inverse of variance) of the standardized mean differences. Right axis represents percentage of the maximum predicted effect

A. Exclusion of failed studies

Quetiapine ER NS, N=2, n= 787[a]
Heterogeneity: Q= 0.747, p= 0.688, I² = 0%

Quetiapine ER PS, N=2, n=787
Heterogeneity: Q=1,575, p= 0.450, I² = 0%

Ziprasidone NS, N=2, n=437[b]
Heterogeneity: Q= 4.308, p= 0.116, I²= 0.0%

Ziprasidone PS, N=2, n=437
Heterogeneity: Q= 5.545, p= 0.0625, I²= 0.0%

a The exclusion of Cutler et al. 2010 study, reduced the observed heterogeneity from 58 % to 0% when considering results for negative symptoms. The ED95 was similar for negative symptoms (772.3 mg/day) and unchanged for positive symptoms.

b The exclusion of study 104 did not change results. The ED95 was slightly raised from 71.6 to 82.2 for negative symptoms, and almost unchanged for positive symptoms (150 mg/day).

B. Exclusion of studies that only includes patients affected with schizoaffective disorders

Paliperidone NS, N=2, n= 979[a]
Heterogeneity: Q= 0.9112, p= 0.634, I² = 0%
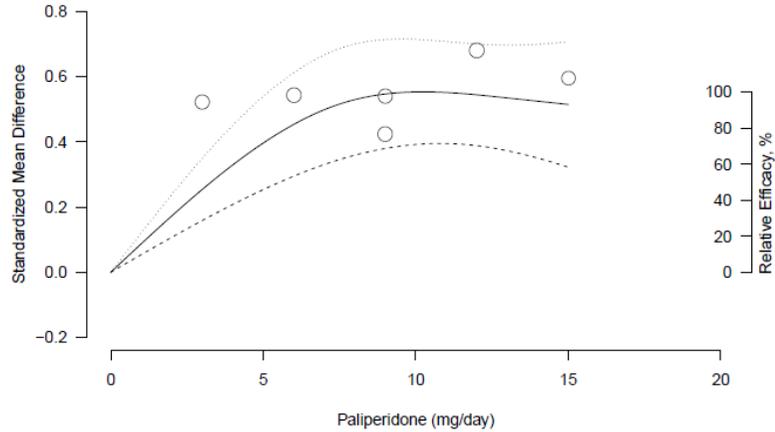
Paliperidone PS, N=2, n=979
Heterogeneity: Q=1.956, p= 0.376, I² = 0%
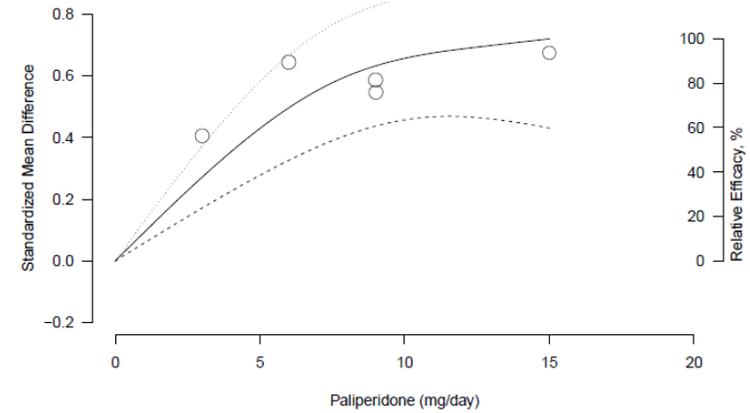
a A reduction of both negative symptoms and positive symptom heterogenity was observed (from 55 and 72.8% to 0 and 0% respectively). The ED95 for negative smyptoms changed from 7.2 to 7.85 mg/day, and for positive symptoms raised the ED95 from 7 to 11 mg/day for positive symptoms.

C. Exclusion of studies including subtherapeuthic doses

Olanzapine NS, N=1, n= 257[a]
Heterogeneity: n.a.
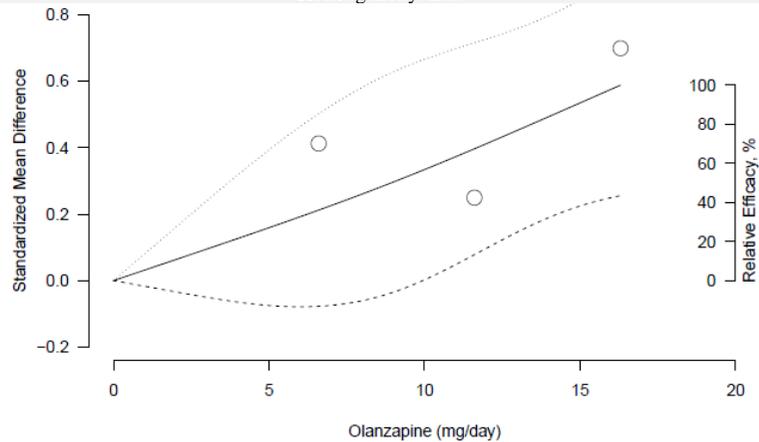
Olanzapine PS, N=1, n=257
Heterogeneity: n.a.
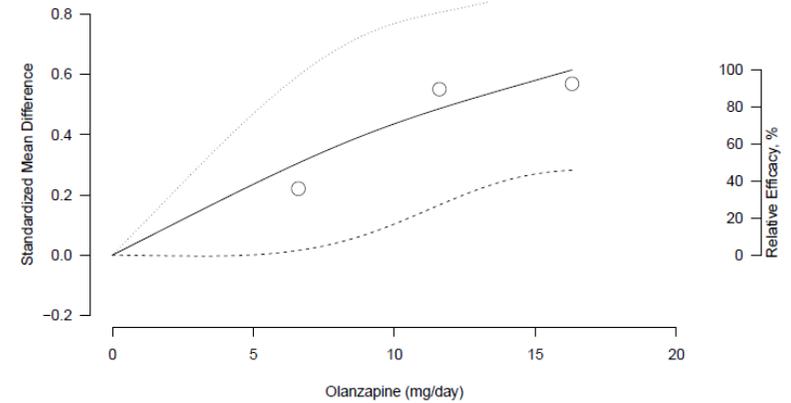
a The ED95 for negative symptoms was unchanged, however, for positive symptoms the ED95 raised from 9.52 to 15.15 mg/day

Supplementary Figure 3. Dose-response curves of each antipsychotics regarding extra-pyramidal symptoms.

a. **Haloperidol**, N=1, n=281
Heterogeneity: n.a.; ED50= 3.92 mg/day; ED95= 11.44 mg/day

b. **Amisulpride**[a], N=1, n=331
Heterogeneity: n.a.; ED50= 317.3 mg/day, ED95= 758.5 mg/day

c. **Aripiprazole**, N=1, n=360
Heterogeneity: n.a.; ED50= 8.47 mg/day; ED95= 9.85 mg/day

d. **Asenapine**, N=1, n= 336
Heterogeneity: n.a.; ED50= 2.73 mg/day; ED95= 4.82 mg/day
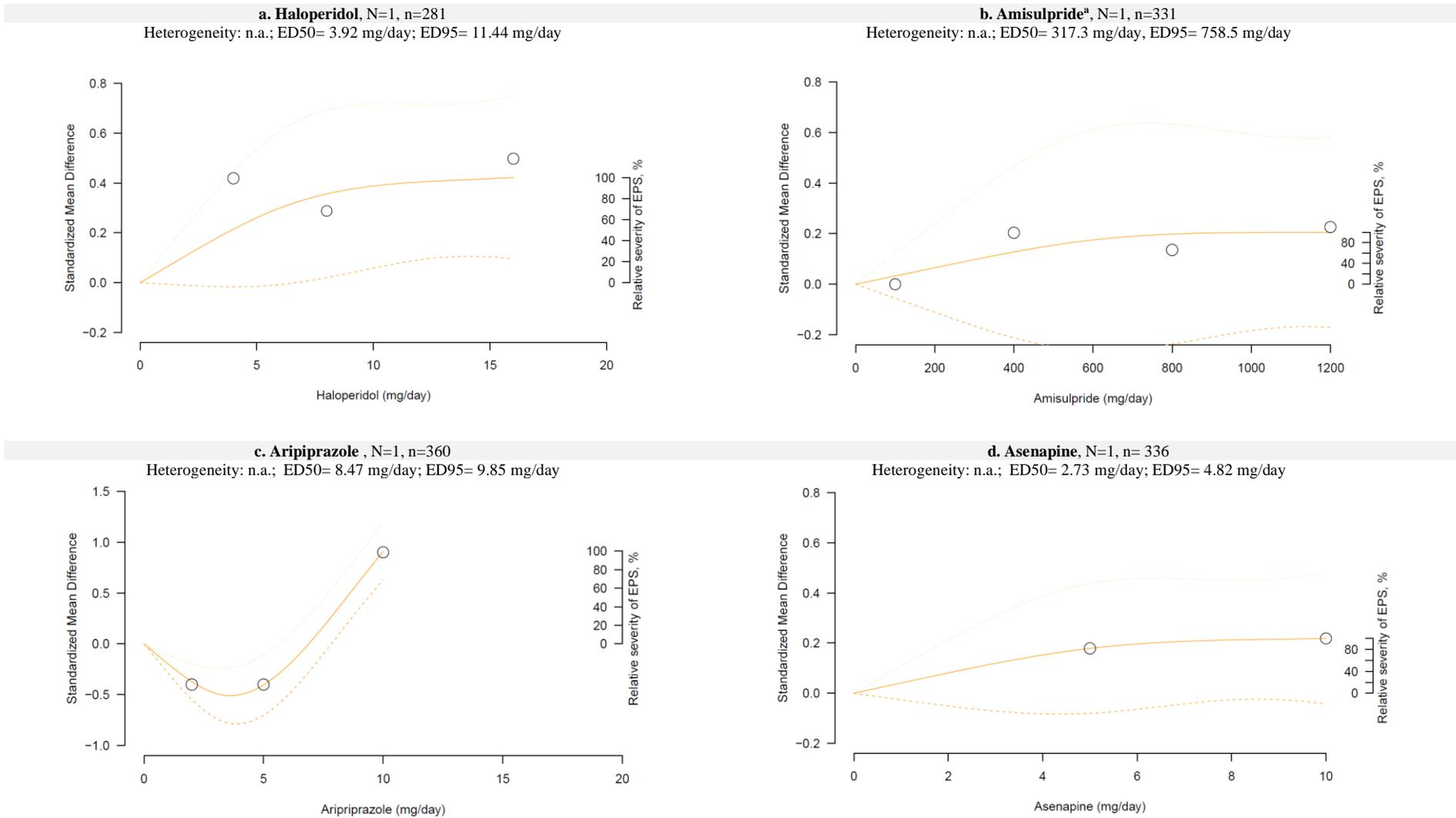
e. Brexpiprazole, N=2, n=1280

Heterogeneity: Q= 230.1, p< 0.001, I²=99.1%; ED50= 3.78 mg/day; ED95= 3.91 mg/day
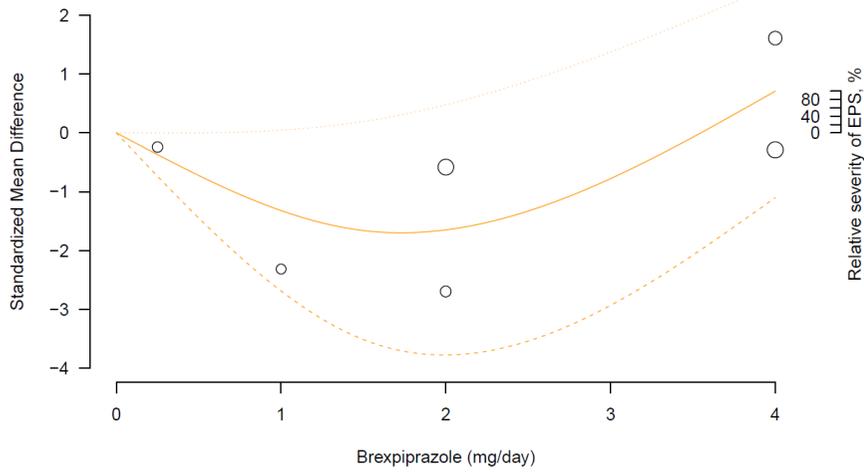
f. Cariprazine, N=2, n=844

Heterogeneity: Q= 0.0679, p= 0.966, I²= 0.0%; ED50= 5.27 mg/day; ED95= 8.63 mg/day
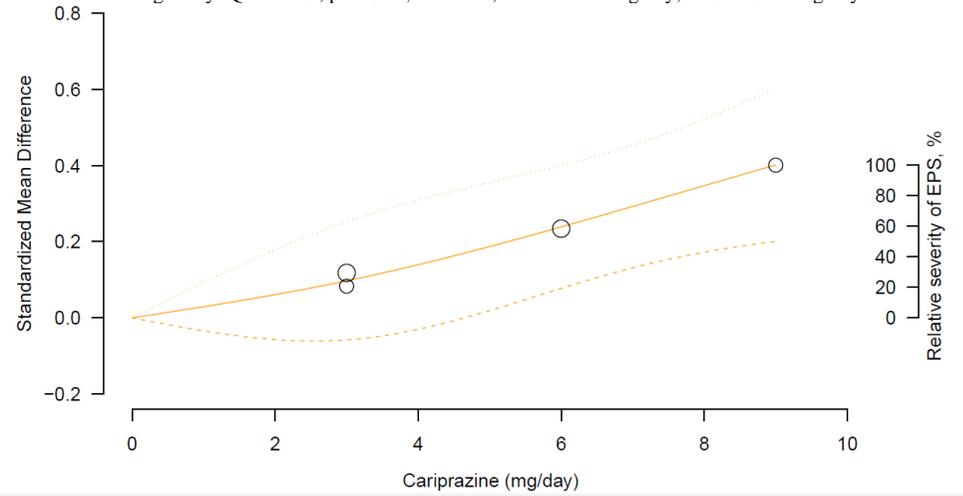
g. Lurasidone, N=2, n=391

Heterogeneity: Q=1.072, p= 0.585 I² = 0.0%; ED50= 44.2 mg/day; ED95= 135.96 mg/day
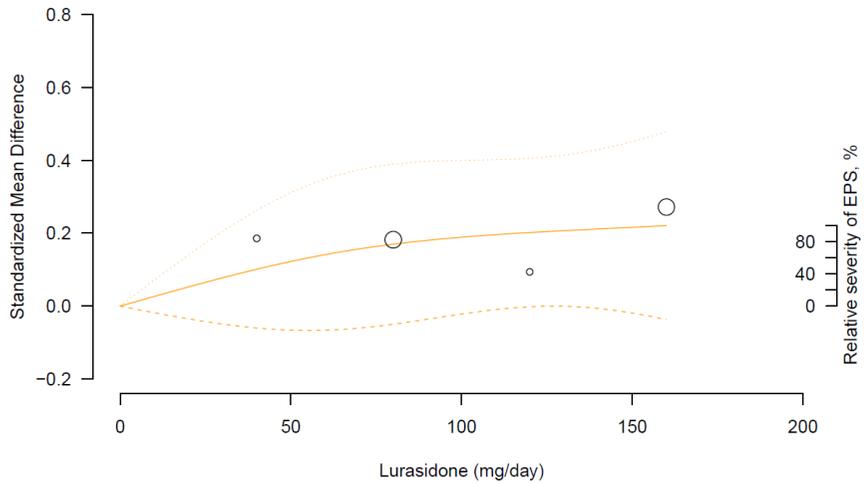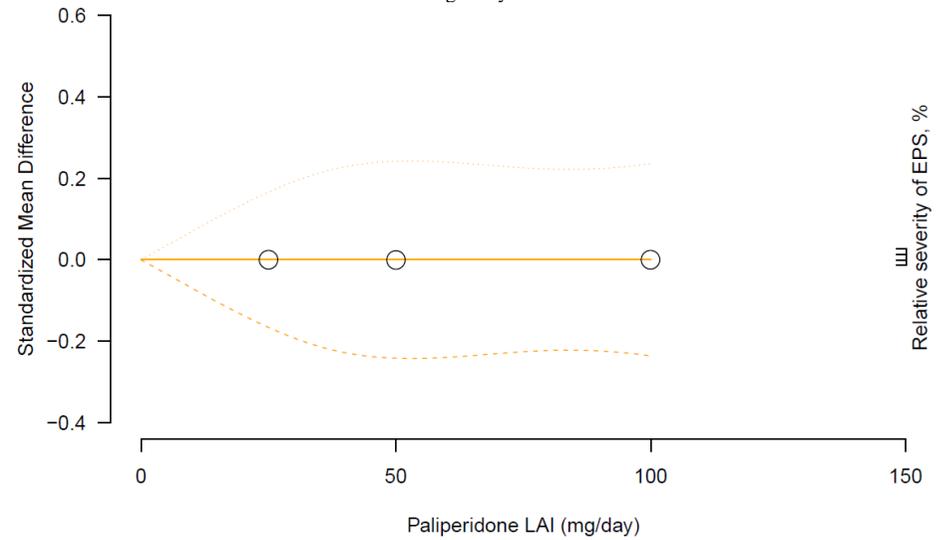
h. Olanzapine, N=2, n=406

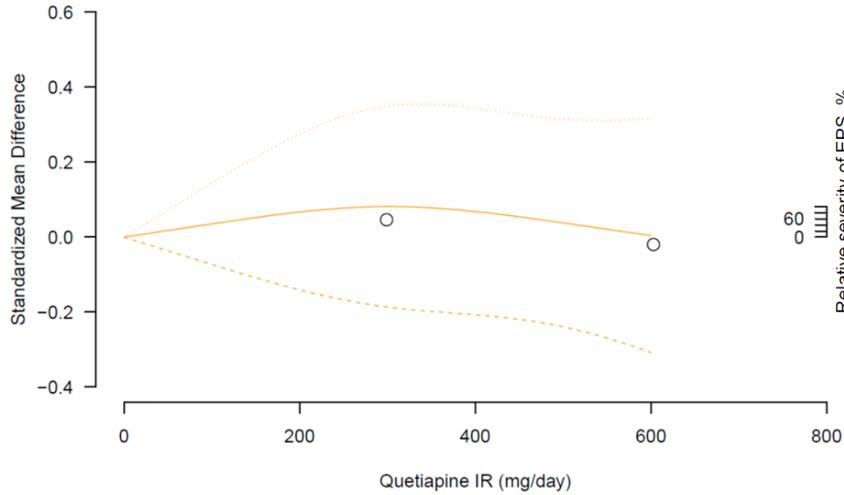Heterogeneity: Q = 1.7602, p= 0.4147, I²= 0.0%; ED50= 1.99 mg/day; ED95= 4.64 mg/day
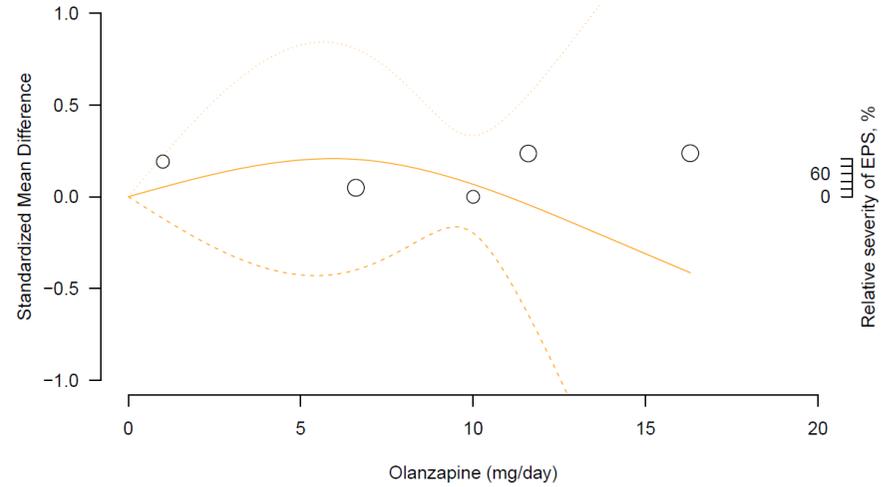
i. Olanzapine LAI[b], N=1, n=404
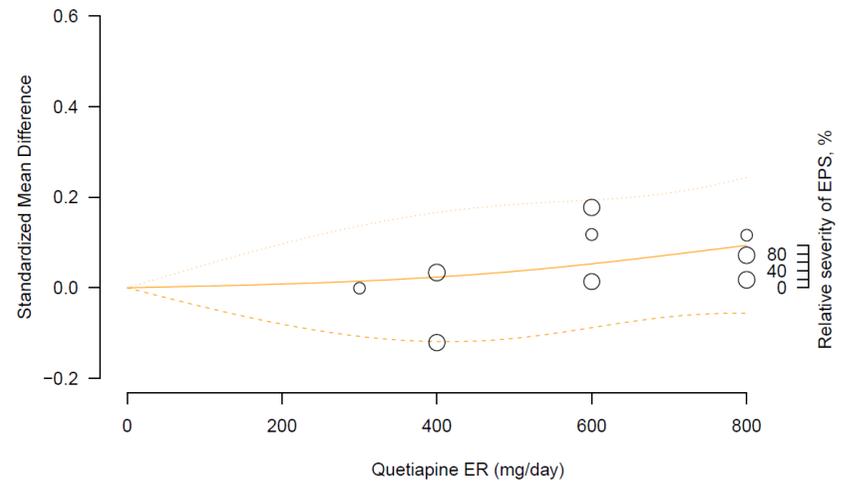Heterogeneity: n.a.; ED50= n.a. mg/day; ED95= n.a.
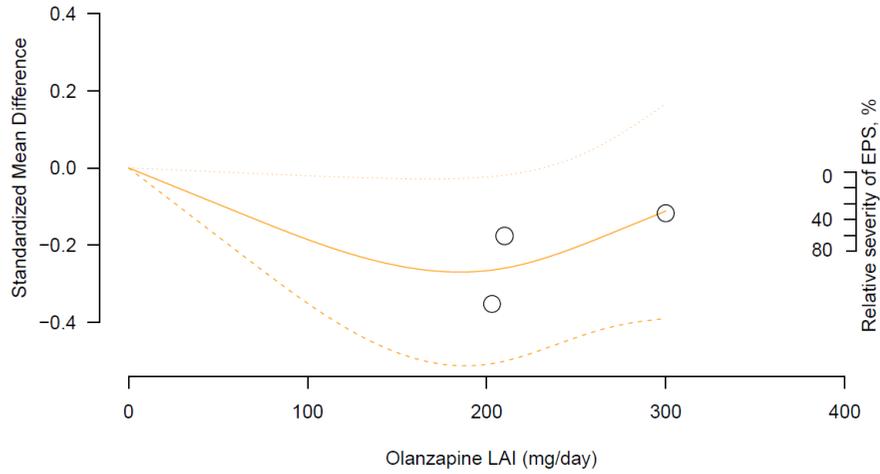
j. Paliperidone LAI[c], N=1, n=514
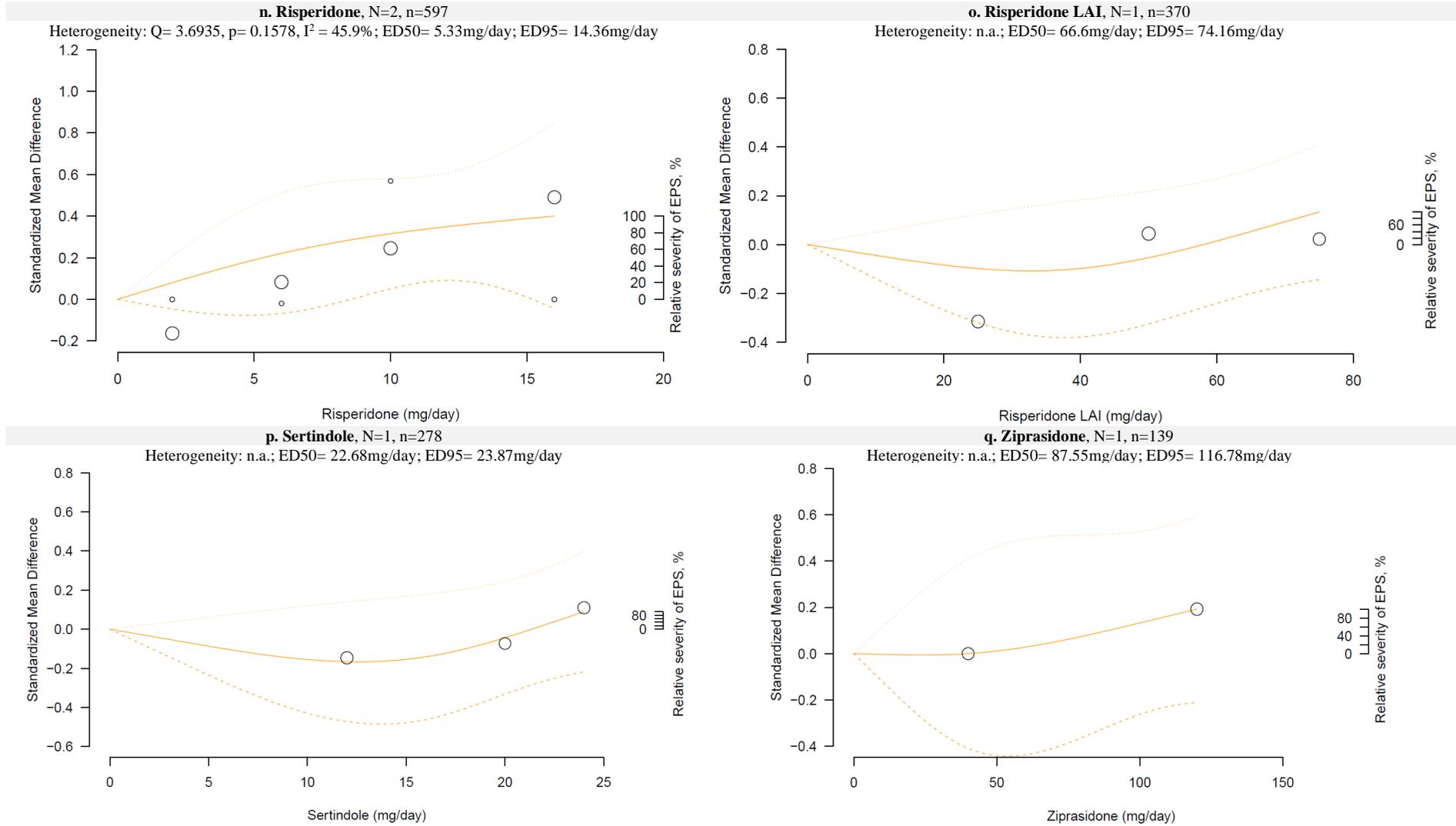Heterogeneity: n.a.

l. Quetiapine IR, N=1, n=323
Heterogeneity: Q= 6.899, p= 0.0318, I² = 71%; ED50= 111.8 mg/day; ED95= 193.3 mg/day

m. Quetiapine ER, N=3, n=1236
Heterogeneity: Q= 0.1871, p= 0.995, I² = 0.0%; ED50= 566.6mg/day; ED95= 711.6 mg/day

n. Risperidone, N=2, n=597
Heterogeneity: Q= 3.6935, p= 0.1578, I² = 45.9%; ED50= 5.33mg/day; ED95= 14.36mg/day

o. Risperidone LAI, N=1, n=370
Heterogeneity: n.a.; ED50= 66.6mg/day; ED95= 74.16mg/day

p. Sertindole, N=1, n=278
Heterogeneity: n.a.; ED50= 22.68mg/day; ED95= 23.87mg/day

q. Ziprasidone, N=1, n=139
Heterogeneity: n.a.; ED50= 87.55mg/day; ED95= 116.78mg/day

a- No placebo arm was available for amisulpride. We considered the 100 mg arm as comparator for this sensitivity analysis.

b- In this study, olanzapine LAI doses are used (210 mg and 300 mg each 2 weeks and 405 mg each 4 weeks, that correspond to dosages of 10, 15 and 10 mg per day respectively)

c- The obtained curve for paliperidone is flat and thus not clinically relevant, as minimal changes in EPS were reported in only one study.

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