Content of supplemental material

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Supplementary Table S1: PRISMA 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.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5ff
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.	5
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.	5ff
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.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7 and Table S3
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).	7, 10, Figure S1
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.	6, 7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, 8, 9
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.	6

Supplementary Table S1: PRISMA Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
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.	8-9

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).	6, 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10 and protocol in Table S2
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.	PRISMA diagram in Figure S1
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.	Included studies table in Table S4
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).	Risk of bias summary in Table S5
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.	Figure S2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12, Figure S3, Figures_1-5
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Risk of bias graph in Table

Supplementary Table S1: PRISMA Checklist

			S5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13, Tables 1-3
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).	20
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).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-20
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.	2

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(6): e1000097. doi:10.1371/journal.pmed1000097

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

Supplementary Table S2

Protocol

Review title and timescale

1 **Review title**

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Has the antipsychotic drug efficacy in schizophrenia decreased over the last 60 years and why? Bayesian meta-analysis and meta-regression

2 **Original language title**

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 **Anticipated or actual start date**

Give the date when the systematic review commenced, or is expected to commence.

01/09/2012

4 **Anticipated completion date**

Give the date by which the review is expected to be completed.

31/08/2014

5 **Stage of review at time of this submission**

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

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

Provide any other relevant information about the stage of the review here.

Review team details

6 **Named contact**

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Stefan Leucht

7 **Named contact email**

Enter the electronic mail address of the named contact.

stefan.leucht@lrz.tum.de

8 **Named contact address**

Enter the full postal address for the named contact.

Klinik fuer Psychiatrie und Psychotherapie der TU-Muenchen Klinikum rechts der Isar Ismaningerstr. 22 81675 Muenchen Germany

9 **Named contact phone number**

Enter the telephone number for the named contact, including international dialing code.

+498941404249

10 **Organisational affiliation of the review**

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Department of Psychiatry and Psychotherapy, Technische Universität München, Klinikum rechts der Isar

Website address:

http://www.cfdm.de/

11 **Review team members and their organisational affiliations**

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Professor	Stefan	Leucht	Department of Psychiatry and Psychotherapy, Technische Universität München, Klinikum rechts der Isar
Mr	Maximilian	Huhn	Department of Psychiatry and Psychotherapy, Technische Universität München, Klinikum rechts der Isar
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Ms	Sarah	Longhi	Department of Psychiatry and Psychotherapy, Technische Universität München, Klinikum rechts der Isar
Professor	John	Davis	Department of Psychiatry and Psychotherapy, University of Illinois at Chicagots der Isar

12 **Funding sources/sponsors**

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Bundesministerium für Bildung und Forschung (BMBF) Grant: 01K61115

13 **Conflicts of interest**

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

Yes

In the last three years Stefan Leucht has received honoraria for consulting/advisory boards from Alkermes, BristolMyersSquibb, EliLilly, Janssen, Johnson&Johnson, Lundbeck, Medavante, Roche, lecture honoraria from AstraZeneca, BristolMyersSquibb, EliLilly, EssexPharma, Janssen, Johnson&Johnson, Lundbeck, Pfizer, SanofiAventis, and EliLilly has provided medication for a trial with Stefan Leucht as the primary investigator. Markus Dold has received a travel grant fram Janssen. Claudia Leucht is Stefan Leucht's spouse so that the same conflict of interest may also relate to her.

14 **Collaborators**

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Professor	Georgia	Salanti	Department of Hygiene and Epidemiology, University of Ioannina

Review methods

15 **Review question(s)**

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

To provide a Bayesian model systematic review and meta-analysis of the efficacy of antipsychotic drugs compared to placebo in schizophrenia and to identify factors that moderate drug-placebo differences by meta-regression.

16 **Searches**

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

1. Electronic searches: We will search the 'Cochrane Schizophrenia Group Trials Register' for relevant studies. This register is compiled by regular methodical searches in numerous electronic databases (BIOSIS, CINAHL, Dissertation Abstracts, EMBASE, LILACS, MEDLINE, PSYNDEX, PsycINFO, RUSSMED, Sociofile), supplemented by the regular hand searching of relevant journals and numerous conference proceedings (for details see the description of the Cochrane Schizophrenia Group. The register contains controlled clinical trials on people with schizophrenia. The search term will be "placebo" using the following fields: title, abstract, key words or index terms. 2. Previous reviews: We will search previous reviews and Cochrane Reviews on single drugs. 3. Personal contact: We will contact the first author of each included study published in the last 30 years for missing information. 4. Drug companies: We will contact the manufacturers of the antipsychotic drugs and ask them for further relevant studies and for missing information on identified studies. There will be no extra hand search for this review, because a number of psychiatric journals (especially old issues which are important for this project) and the abstract books of major conferences are regularly hand searched anyways for the 'Cochrane Schizophrenia Group Trials Register'.

17 **URL to search strategy**

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

18 **Condition or domain being studied**

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Schizophrenia

19 **Participants/population**

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

People with schizophrenia or related disorders (schizoaffective- or schizophreniform disorder). We will include adult people (age = 18, no upper age limit, no restriction in setting, gender, ethnicity) with schizophrenia, schizophreniform or schizoaffective disorders with an acute exacerbation, primarily irrespective of the diagnostic criteria used. There is no clear evidence that the latter schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches. It is also a general strategy of the Cochrane Schizophrenia Group to include not only studies that used specific diagnostic criteria such as ICD-10 or DSM-IV, because these criteria are not meticulously used in clinical routine either. Nevertheless, the diagnostic criteria applied will be examined as a moderator factor. Studies in which less than 20% of the participants were suffering from other psychiatric disorders (e.g. depression or mental retardation) will be included. We will exclude studies in participants with no or only subclinical symptoms at baseline that are usually conducted to address the relapse preventing effects of antipsychotics, studies in patients with predominant negative symptoms and studies including exclusively participants with major concomitant somatic illness or psychiatric disorders (e.g. substance abuse).

20 **Intervention(s), exposure(s)**

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

Antipsychotic drugs It should be noted that according to all major treatment guidelines there is no major difference in the efficacy between the available antipsychotics (except for clozapine which will thus be excluded) justifying the inclusion of all major antipsychotic drugs. Nevertheless, the individual antipsychotic used will be a factor in the statistical analysis. We will include all antipsychotics as long as they are available in at least one country. We will include all these compounds in any oral form of administration (tablets or liquid), while depot medications are mainly used for relapse prevention and will therefore be excluded. We will include all studies with flexi ble doses, because here the doctor has the possibility to titrate the dose for the individual patient. In fixed soes studies we will only include target to maximus doses as suggested by an international consensus study (Gardner et al., American Journal of Psychiatry 2010, 167 (6): 686-693).

21 **Comparator(s)/control**

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

The comparator will be placebo (active or inactive).

22 **Types of study to be included initially**

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Design of primary studies: randomized, controlled, double-blind trials. Study quality will be assessed with the risk of bias tool described in the Cochrane Collaboration Handbook. This tool encourages consideration of how the sequence was generated, how allocation was concealed, the integrity of blinding at outcome, the completeness of outcome data, selective reporting and other biases. We will not include studies were sequence generation was at high risk of bias (e.g. randomization by the date of birth or day of the week) or where allocation was clearly not concealed. We will also only include double-blind studies because we recently showed that non-blinded studies can exaggerate differences between treatments in this area. The minimum duration of follow-up will be 3 weeks.

23 **Context**

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

We will include adult people (age = 18, no upper age limit, no restriction in setting, gender, ethnicity) with schizophrenia, schizophreniform or schizoaffective disorders with an acute exacerbation, primarily irrespective of the diagnostic criteria used. There is no clear evidence that the latter schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches. It is also a general strategy of the Cochrane Schizophrenia Group to include not only studies that used specific diagnostic criteria such as ICD-10 or DSM-IV, because these criteria are not meticulously used in clinical routine either. Nevertheless, the diagnostic criteria applied will be examined as a moderator factor. Studies in which less than 20% of the participants were suffering from other psychiatric disorders (e.g. depression or mental retardation) will be included. We will exclude studies in participants with no or only subclinical symptoms at baseline that are usually conducted to address the relapse preventing effects of antipsychotics, studies in patients with predominant negative symptoms and studies including exclusively participants with major concomitant somatic illness or psychiatric disorders (e.g. substance abuse).

24 **Primary outcome(s)**

Give the most important outcomes.

Outcomes: Mean reduction in overall symptoms of schizophrenia, response to treatment

Give information on timing and effect measures, as appropriate.

The minimum duration of follow-up will be 3 weeks and we will always use endpoint data. We

will group the results according to time (3- 12 weeks (primary outcome), medium-term 13-26 weeks and long-term > 26 weeks). In the case of cross-over studies we will use only the first cross-over phase to avoid the problem of carry-over effects. 1. The primary outcome will be overall symptoms of schizophrenia as measured by rating scales such as the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS –) or of any other validated scale (e.g. the Manchester Scale) for the assessment of overall schizophrenic symptomatology. Overall symptoms of schizophrenia as measured by such scales was the primary outcome in numerous previous systematic reviews. As not all studies will have used the same scale, we will apply the following hierarchy: mean change of the PANSS total score from baseline to endpoint, if not available mean change of the BPRS, or if again not available the mean values at endpoint of the PANSS/ BPRS. The results of other rating scales will only be used if the instrument has been published in a peer-reviewed journal, because it has been shown that unvalidated schizophrenia scales exaggerate differences. 2. Clinically important response to treatment. We will consider the following definitions of clinically important response in descending order: at least 50% reduction of the baseline score of the PANSS, 50% reduction of the BPRS or 50% reduction of any other global schizophrenia rating scale, at least much improved (score of 2) on the Clinical GIobal-Impressions-Improvement Scale (CGI). We showed in a validation study that 50% PANSS/BPRS reduction and a CGI of 2 describe a similar degree of response which is clinically meaningful. But if none of these definitions is available, we will use the original authors' primary definition.

25 **Secondary outcomes**

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Dropouts: 1. Dropout due to any reason 2. Dropouts due to inefficacy of treatment 3. Dropouts due to side-effects.

Give information on timing and effect measures, as appropriate.
The minimum duration of follow-up will be 3 weeks and we will always use endpoint data. We will group the results according to time (3- 12 weeks (primary outcome), medium-term 13-26 weeks and long-term > 26 weeks). In the case of cross-over studies we will use only the first cross-over phase to avoid the problem of carry-over effects.

26 **Data extraction, (selection and coding)**

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

1. Selection of trials: Two reviewers will independently inspect all abstracts identified in the searches. Disagreement will be resolved by discussion, and where doubt still remains, we will acquire the full article for further inspection. Once the full articles are obtained, at least two reviewers will independently decide whether the studies meet the review criteria. If disagreement can not be resolved by discussion, we will resolve it with a third reviewer or seek further information from the study authors. 2. Data extraction: Two reviewers will independently extract data from all selected trials on simple, standard forms. When disagreement arises we will resolve it by discussion with a third reviewer. Where this is not possible we will contact the study authors.

27 **Risk of bias (quality) assessment**

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Study quality in terms of sequence generation, allocation concealment, blinding, the completeness of outcome data, selective reporting and other biases will be assessed with the Cochrane Collaboration risk of bias tool.

28 **Strategy for data synthesis**

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

In general we will use Bayesian methods to estimate the summary effect size using a random effects model, but a fixed effects model will be used in a sensitivity analysis. Bayesian methodology is most appropriate for synthesis of complex data as in our meta-analysis. Effect sizes of the individual studies: 1. Continuous outcomes: The effect size measure for continuous outcomes will be the standardized mean difference (SMD), calculated as Hedges's g, because we expect the studies to use different rating scales of overall schizophrenia symptomatology (mainly the PANSS or the BPRS). SMDs will be calculated for both: a) differences between drug and placebo b) the change from baseline to endpoint in the placebo group only. The latter analyses will be carried out to analyse placebo response in antipsychotic drug trials. Intention-to-treat (ITT) data will be used whenever available. If mixed-effect model repeated measure (MMRM) is available we prefer it to last observation carried forward (LOCF). Missing standard deviations: When standard errors instead of standard deviations (SD) are presented, the former will be converted to standard deviations. If both are missing and can not be obtained from the authors we will estimate SDs from confidence intervals or p-values as described in Section 7.7.3 of the Cochrane Handbook for Systematic Reviews of Interventions or we will use the mean SD of the other studies. 2. Dichotomous outcomes: The effect size for dichotomous outcomes will be the odds ratio (OR) and its 95% confidence interval (CI). The main reason to prefer odds ratios to relative risks is that a major focus of the current analysis is the identification of factors moderating drug-placebo differences. We expect that different definitions of 'response to treatment' will be used and in such a situation the odds ratio has been shown to yield the most consistent results which are largely independent from the response cut-off used. Therefore, although the relative risk is more intuitive for clinicians, the odds ratio has clear advantages for the purpose of our review. We will again carry out an intention to treat analysis ('once randomized always analyse'). Everyone allocated to the intervention will be counted, whether they completed the follow up or not. If the authors applied such a strategy, we will use their results. If the original authors presented only the results of the per-protocol or completer population, we will assume that those participants lost to follow-up would not have responded (conservative approach). 3.Publication bias: We will examine potential publication bias by 'contour enhanced funnel-plots'. The problem of conventional statistical tests to analyse funnel-plot asymmetry such as that by Egger et al. is that they can not distinguish between asymmetry that is due to publication bias and asymmetry that is due to other factors such as heterogeneity or lower quality of small trials. In 'contour enhanced funnel-plots' ´contour lines representing conventional significance levels (e.g. p-values <0.01, <0.05) are drawn in the funnel plot. If missing studies are found in areas of statistical non-significance this indicates that the source of funnel plot asymmetry is publication bias rather than other possible factors.

29 **Analysis of subgroups or subsets**

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

The following potential effect moderators will be explored by subgroup or meta-regression analysis: 1. Chronicity of the patients: Chronic patients are thought to respond worse than patients with a recent onset of their illness. 2. First epidode patients 3. Percentage women: women might have a better outcome than men. 4. Duration of the current episode: acutely ill patients who are treated early after the start of their episode are thought to respond better to medication. 5. Severity of illness at baseline: there may be floor effects that limit drug-placebo differences in less severely ill populations. 6. Diagnostic criteria: The diagnostic criteria used before the 10th Version of the International Classification of Diseases (ICD-10) or the 3rd version of the Diagnostic and Statistical Manual (DSM-III) or the Feighner criteria or the Research Diagnostic Criteria were not operationalised. Therefore, studies using earlier criteria may have included participants that would nowadays not be diagnosed as suffering from schizophrenia. The use of DSM-III/III-R/IV/IV-R, ICD-10, Research Diagnostic Criteria or Feighner Criteria versus earlier, not operationalised criteria will therefore be analysed. 7. The antipsychotic drug used: all guidelines state that except for clozapine which is excluded from our analysis the efficacy of all antipsychotic drugs is the same. Nevertheless, to control for the effects of specific antipsychotics, drug will be included in the model. 8. Trial quality in terms of randomization, allocation and blinding as measured by the 'risk of bias tool', because short-comings in these domains lead to overestimation of effects. 9. Duration of wash-out period: carry-over effects from pre-trial treatment may reduce drug-placebo differences in the case of short wash-out phases. 10. Sample sizes and number of sites: due to apparently decreasing drug-placebo differences more participants have been recruited in recent trials making more

sites necessary. Paradoxically, this can increase inter-rater variability and thus decrease effect sizes as it was shown for mania trials. 11. Two-arm (antipsychotic versus placebo) versus three-arm (new antipsychotic versus standard antipsychotic versus placebo) design: In depression trials two-arm studies had higher drug-placebo differences than three arm studies which was explained by a better blinding in a three-arm trial. 12. Study duration: it takes some time until antipsychotics develop their full effects, therefore, longer trials should yield higher drug-placebo differences. 13. Percentage of participants randomized to placebo group. In depression, studies with smaller percentage randomized to placebo found smaller drug-placebo differences. This was interpreted by expectancy effects. If the raters can expect that most patients receive active treatment, placebo response may increase and drug-placebo differences decrease. 14. Publication year: It seems that effect-sizes have become smaller over time. 15. Medication dose: medication doses will be converted to chlorpromazine equivalents according to international consensus for this assessment. 16. Fixed or flexible medication dose 17. Sponsor (industry or public): 'industry bias' could inflate effect sizes. 18. Intention-to-treat analysis or not: we would hypothesize that the effects in ITT (once randomized – always analyse) analyses are smaller than in per protocol analyses. Sensitivity analyses: We plan a priori to carry out sensitivity analyses excluding completer analyses and to apply a fixed-effects instead of a random effects model.

Review general information

30 **Type of review**

Select the type of review from the drop down list.

Treatment

31 **Language**

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 **Country**

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Germany

33 **Other registration details**

List places where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute). The name of the organisation and any unique identification number assigned to the review by that organization should be included.

34 **Reference and/or URL for published protocol**

Give the citation for the published protocol, if there is one.

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

35 **Dissemination plans**

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

The results will be published in major psychiatric journals and presented at major international and German psychiatric conferences. Our findings will be rapidly implemented in national and international treatment guidelines, for some of which Stefan Leucht is a co-author. The potential economic impact is that health care costs are exploding and resources need to be carefully allocated. In this context it is important to know the efficacy of drug groups such as the antipsychotics.

Do you intend to publish the review on completion?

Yes

36 **Keywords**

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

schizophrenia
antipsychotics
placebo
meta-analysis

37 **Details of any existing review of the same topic by the same authors**

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 **Current review status**

Review status should be updated when the review is completed and when it is published.

Ongoing

39 **Any additional information**

Provide any further information the review team consider relevant to the registration of the review.

40 **Details of final report/publication(s)**

This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.

Give the URL where available.

I. Differences between protocol and review

The following protocol changes were made post-hoc, but importantly before knowing the results.

1. We extracted, but did not analyze the outcome drop-out due to adverse events, because in recent studies dropouts due to adverse events are often a mix of tolerability and efficacy related events (e.g. exacerbation of psychosis) so that results would not have been meaningful.

2. We added several other outcomes when more resources as planned were available.

3. We decided to use relative risks rather than odds ratios, because the latter can be interpreted more intuitively by clinicians, but we present odds ratios in sensitivity analyses.

4. As the vast majority of the studies was short-term, we did not classify the studies by their duration, but rather examined study duration as a moderator in a meta-regression

5. We added a few potential moderators which had been addressed by research that was published after our protocol[1, 2]: degree of response in the placebo and in the drug arms, country (USA versus other countries) and the number of academic sites. As it turned out that many different antipsychotics had been used for which usually only a few trials were available, we restricted our analysis of the moderator 'drug' to second-generation versus first-generation antipsychotic, and only explored for haloperidol separately whether its effect size had decreased over time.

6. Following reviewer requests we a) added an analysis of the frequency of which moderators have changed over the years, b) added "differential dropout reasons between drug and placebo group" to the assessment of the risk of bias item "incomplete outcome data". We had initially not done this, because there is no scientific evidence from which difference in dropout between drug and placebo groups bias may occur. We decided to choose a cutoff of 15% absolute difference in dropouts either due to any reason, or due to inefficacy or due to adverse events between drug and placebo to indicate potential bias. 15% was chosen because it lies between the average difference between drug and placebo based on our two a priori chosen criteria "good response" (approximately 10% difference) and any response (approximately 20%). c) We compared results based on the PANSS rather than the BPRS. d) Instead of comparing first-generation antipsychotics versus second-generation antipsychotic as an effect moderator, we classified antipsychotics by mechanism of action according to the "Neuroscience-based Nomenclature (NbN)" (84): M1 = receptor antagonists (D2) clopenthixol, fluphenazine, haloperidol, perphenzaine, pimozide, pipotiazine, sulpiride, trifluoperazine. M2 = receptor antagonists (D2, 5-HT2) chlorpromazine, iloperidone, loxapine, lurasidone, olanzapine, sertindole, thioridazine, ziprasidone, zotepine. M3 = receptor partial agonists (D2, 5-HT1A) aripiprazole, brexpiprazole, cariprazine. M4= receptor antagonists (D2, 5-HT2, NE alpha2) asenapine, paliperidone, risperidone. M5= receptor antagonist (D2, 5-HT2) and reuptake inhibitor (NET) quetiapine. A few old drugs had not been classified by NbN yet.

II. Details on statistical model

1. Model implementation

We fitted all models using Markov Chain Monte Carlo (MCMC) simulations in WinBUGS 1.4.3[1]. We employed normal or binomial likelihood for the mean scores (i.e. continuous outcomes) or the number of events (i.e. dichotomous outcomes) respectively in each study arm. We assumed a half-normal prior distribution for the heterogeneity standard deviation $\tau \sim N(0,1)$ with $\tau \geq 0$. Normal vague priors $N(0,10^4)$ were given to location parameters as well as to the regression coefficients. We evaluated convergence by visual inspection of the mixing of two chains with different initial values. For all models we run 150000 MCMC cycles after discarding the first 30000.

2. Code for standard meta-analysis model

```
model{
        for (i in 1:N){
        prec.c[i]<-1/(se.c[i]*se.c[i])
        prec.t[i]<-1/(se.t[i]*se.t[i])
        se.c[i]<-sdc[i]/sqrt(nc[i])
        se.t[i]<-sdt[i]/sqrt(nt[i])
        pooled.sd[i]<-sqrt(((nc[i]-1)*sdc[i]*sdc[i]+(nt[i]-1)*sdt[i]*sdt[i])/(nc[i]+nt[i]-2))
        smd[i]<- (yt[i]-yc[i])/pooled.sd[i]
        var[i]<- ((nt[i]+nc[i])/(nt[i]*nc[i]))+(smd[i]*smd[i])/(2*(nt[i]+nc[i]))
        w[i]<-1/var[i]
        w.sq[i]<-pow(w[i],2)
        yc[i]~dnorm(phi.c[i],prec.c[i])     # normal likelihood
        yt[i]~dnorm(phi.t[i],prec.t[i])
        phi.c[i]<-u[i]*pooled.sd[i]
        phi.t[i]<-(u[i]+theta1[i])*pooled.sd[i]
        theta1[i]<-theta[i]
        theta[i]~dnorm(SMD,SD)
        u[i]~dnorm(0,.0001)          # priors
        }
        SMD~dnorm(0,.0001)
        SD<-1/pow(tau,2)
        tau~ dnorm(0,1)I(0,)
        SMDtrans<--SMD     # transformed SMD - the larger the better
        I.sq<-pow(tau,2)/(pow(tau,2)+sigma.sq)
        sigma.sq<-sw*(N-1)/(pow(sw,2)-sw.sq)
        sw<-sum(w[])
        sw.sq<-sum(w.sq[])
```

3. Code for univariable meta-regression model

```
model{
        for (i in 1:N){
        prec.c[i]<-1/(se.c[i]*se.c[i])
        prec.t[i]<-1/(se.t[i]*se.t[i])
        se.c[i]<-sdc[i]/sqrt(nc[i])
        se.t[i]<-sdt[i]/sqrt(nt[i])
        pooled.sd[i]<-sqrt(((nc[i]-1)*sdc[i]*sdc[i]+(nt[i]-1)*sdt[i]*sdt[i])/(nc[i]+nt[i]-2))
#    x1[i]<-x[i]-2  ##### for Narms, Nmed
#    x1[i]<-(x[i]-mean(x[])) ##### for continous moderatos
    x1[i]<-x[i]  ##### for dichotomous moderators
        yc[i]~dnorm(phi.c[i],prec.c[i])     # normal likelihood
        yt[i]~dnorm(phi.t[i],prec.t[i])
        phi.c[i]<-u[i]*pooled.sd[i]
        phi.t[i]<-(u[i]+theta1[i])*pooled.sd[i]
        theta1[i]<-theta[i]+B*x1[i]
        theta[i]~dnorm(SMD,SD)
        u[i]~dnorm(0,.0001)          # priors
        }
        SMD~dnorm(0,.0001)
        SD<-1/pow(tau,2)
        tau~ dnorm(0,1)I(0,)
        B~dnorm(0,.0001)
        SMDtrans<--SMD
        Btrans<--B
```

4. Code for multivariable meta-regression model

```
model{
```

```
for (i in 1:N){
        prec.c[i]<-1/(se.c[i]*se.c[i])
        prec.t[i]<-1/(se.t[i]*se.t[i])
        se.c[i]<-sdc[i]/sqrt(nc[i])
        se.t[i]<-sdt[i]/sqrt(nt[i])
        pooled.sd[i]<-sqrt(((nc[i]-1)*sdc[i]*sdc[i]+(nt[i]-1)*sdt[i]*sdt[i])/(nc[i]+nt[i]-2))
        var[i]<- (((nt[i]+nc[i])/(nt[i]*nc[i]))+(smd[i]*smd[i])/(2*(nt[i]+nc[i])))
                smd[i]<- ((yt[i]-yc[i])/pooled.sd[i])
                yc[i]~dnorm(phi.c[i],prec.c[i])     # normal likelihood
                yt[i]~dnorm(phi.t[i],prec.t[i])
                phi.c[i]<-u[i]*pooled.sd[i]
                phi.t[i]<-(u[i]+theta1[i])*pooled.sd[i]
                theta1[i]<-theta[i]+b[1]*(x1[i]-mean(x1[]))+b[2]*(x2[i]-mean(x2[]))+b[3]*(x3[i]-
mean(x3[]))+b[4]*(x4[i]-mean(x4[]))+b[5]*x5[i]+b[6]*x6[i]+b[7]*(x7[i]-
2)+b[8]*x8[i]+b[9]*x9[i]+b[10]*x10[i]+b[11]*x11[i]+b[12]*x12[i]+b[13]*x13[i]+b[14]*(x14[i]-
mean(x14[]))        # meta-regression model
                theta[i]~dnorm(SMD,prec)
                u[i]~dnorm(0,.0001)          # priors
        }
                SMD~dnorm(0,.0001)
                prec<-1/pow(tau,2)
                tau~ dnorm(0,1)I(0,)
                SMDtrans<--SMD
        for(i in 1:14){
                b[i]~dnorm(0,0.0001)
                btrans[i]<--b[i]
        }
}
```

5. Description of the selection model

5.1 Selection models

A variety of visual-based and regression-based methods that explore for small-study effects exist; an association between observed effect sizes and some measure of its precision (usually the standard error). One of the possible causes for small-study effects could be publication bias, but it can also be caused due to true heterogeneity. For example, small trials may include severely ill patients that are harder to recruit and for whom the intervention is more effective.[4]

Publication bias occurs when the probability of a study being missing depends on the magnitude and direction of results. Publication bias is a missing data problem. When studies are missing for reasons that relate to the outcome of the study, just like in publication bias where probability of publication relates to the magnitude of the effect, we say that studies are missing not at random. In such a scenario, the observed studies are not a representative sample of all studies conducted and their analysis will give biased results (usually by exaggerating efficacy).

Selection models have been suggested to explain the selection mechanism; the mechanism by which studies are selected for publication. If the probability of publication is associated with the magnitude of effect, then we have publication bias. We cannot test the selection mechanism because the actual data needed to check it are missing (unpublished studies). For this reason, we have to resort to assumptions about what may cause the studies to be missing and conduct a sensitivity analysis with an aim to explore robustness of results. Copas (1999)[3] developed a selection model in which the probability of publication for a study depends both on its effect size and standard error. The model needs to determine a-priori the probabilities of publication for the largest and smallest studies included in the meta-analysis. One way to achieve this is by using expert opinion (Mavridis et al. 2013[4]). Alternatively one could conduct a sensitivity analysis assuming various probabilities of publication for the largest and smallest observed study and explore how robust is the summary intervention effect as these probabilities become smaller (as selection bias becomes more severe).

The model can also be fit in a Bayesian setting.[4] A major advantage of this model when applied in a Bayesian framework is that is allows us to estimate the actual correlation between probability of publication and effect size along with its 95% credible interval. If zero is included in this interval then we cannot claim that there is publication bias. With few studies, uncertainty about the correlation would be large and it could be the case that we lack power to detect publication bias. If zero is not included in the 95% credible interval then there is an association between probability of publication and magnitude of effect which is the actual definition of publication bias. We can monitor this correlation coefficient across the sensitivity analyses. A selection model will also give an adjusted, corrected for publication bias, summary estimate and we will be able to see how much the observed data exaggerate the intervention effect or if assuming different degrees of selection may change direction of results.

We employed this model in OpenBUGS.[5] In this network of 93 antipsychotic placebo control trials reporting the primary outcome (overall efficacy), the largest study had 671 participants and the smallest study had 12 participants. We assumed four scenarios that are described below

- Scenario 1: A large study of about 700 participants has an 90% chance of being published and a small study of about 10 participants has a 50% chance of being published.
- Scenario 2: A large study of about 700 participants has an 90% chance of being published and a small study of about 10 participants has a 30% chance of being published.
- Scenario 3: A large study of about 700 participants has an 80% chance of being published and a small study of about 10 participants has a 40% chance of being published.
- Scenario 4: A large study of about 700 participants has an 70% chance of being published and a small study of about 10 participants has a 10% chance of being published.

These probabilities of publication are expressed via uniform distributions on intervals of 0.10 units length. For example, the probabilities for the first scenario (0.9 and 0.5 respectively) are expressed by uniform distributions on [0.85,0.95] and [0.45,0.55] respectively. We assumed these scenarios to explore how robust results are to the extent of the selection bias. We also assigned a standard normal distribution truncated at zero prior distribution for the heterogeneity standard deviation and a vague normal distribution centered at zero for the summary estimate. At the end of this text we present the Open BUGS code used in this analysis. Appendix Table 1 shows the four scenarios, the correlation between probability of publication and magnitude of effect with its 95% credible interval is given in the fourth column. Based on our a priori judgement we considered scenario 2 (that a study with 10 patients has a probability of being published of 30% and a study with 700 participants of 90%) as the primary one. We should note that a non-zero correlation is the actual definition of publication bias as it suggests that the probability of publication depends on the magnitude of results and therefore the published studies is not a representative sample of the studies conducted on the topic. We see in Appendix Table 1 that in all scenarios we have a non-zero correlation. The adjusted for publication bias summary estimate with its 95% credible interval are given in the fifth column. We see that the adjusted summary estimate decreases as we increase the amount of selection bias. These adjusted results are compared to the unadjusted summary estimate of 0.49. We see that all adjusted estimates do not include the unadjusted summary estimate (0.49) in their 95% credible intervals. Hence, if any of these scenarios is true, the analysis of the published studies exaggerates effectiveness. We should note that under all scenarios there is a significant effect. We also note that the trim-and-fill method led to a similar adjusted effect size (0.38, 95% Cri 0.33,0.43; 31 missing studies imputed).[6] However, the trim-and-fill method is based on an even stronger assumption than the selection model, namely that all funnel-plot asymmetry is due to publication bias.{Mavridis, 2014 #1436} There is empirical evidence that selection models are preferable to the trim and fill method.[7] Therefore, we only used the trim-and-fill method to corroborate our results.

Appendix Table 1: Four scenarios of selection bias

The correlation between probability of publication and magnitude of effect (a zero correlation suggests evidence against publication bias) with its 95% credible interval is given in the fourth column. The adjusted for publication bias summary estimate with its 95% credible interval are given in the fifth column. We note the unadjusted estimate is 0.49 (95% CrI 0.44-0.54). In all sensitivity analyses, the adjusted estimate is reduced around 20% in comparisons with the unadjusted estimate.

Scenario	Probability of publication for the smallest trial (10 patients)	Probability of publication for the largest trial (700 patients)	Correlation between probability of publication and magnitude of effect	Adjusted summary estimate	Heterogeneity standard deviation
1	0.5	0.9	0.85(0.53,1.00)	0.41 (0.36,0.46)	0.17 (0.13,0.22)
2	**0.3**	**0.9**	**0.82 (0.52,0.99)**	**0.39 (0.34,0.44)**	**0.17 (0.13,0.22)**
3	0.4	0.8	0.84 (0.54,0.99)	0.39 (0.34,0.44)	0.18 (0.13,0.22)
4	0.1	0.7	0.66 (0.38,0.90)	0.36 (0.29,0.42)	0.17 (0.12,0.22)

The bolded model is the primary one

5.2 Stochastic Search Variable Selection

Consider that we have a response variable whose variation we would like to account for by including a set of predictors. The major question is which predictors explain some of the response variable's variation. Methods used to answer this problem are called variable selection methods. A method called Stochastic Search Variable Selection (SSVS) was introduced by George and McCulloch[8] with an aim to identify promising subsets of predictors for a response variable in a Bayesian setting. The method considers the regression equation to be the core of a larger hierarchical model with key feature that its regression coefficient is modeled a-priori as a mixture of two normal distributions with mean zero but with different variances. The method associates a latent indicator variable to each regression coefficient. The latent variable assumes value one if the corresponding predictor is to be included in the model and value zero otherwise. If a variable is not to be included in the regression equation (latent variable assumes value zero), then the variance of the regression coefficient is small enough to constraint the regression coefficient to take a-posteriori a value close to zero. The indicator variable can be estimated in each MCMC draw and after running thousands of MCMC draws we can estimate its distribution and see each value is more probable (zero or one) to decide whether the specific variable should be kept in the analysis or not. More specifically, with p predictors there are p latent indicator variables that are estimated by running a long MCMC chain. In the end we will count the proportion of times each predictor was selected for inclusion in the model during the MCMC draws. We may choose to include those with probabilities of inclusion larger than 0.5 (median selection criterion). Alternative, we may choose this pattern of predictors that had the higher frequency of selection during the MCMC draws. We employed the analysis in OpenBUGS.[5] We standardized all predictors and assumed that the probability of inclusion in the model for each predictor follows a Bernoulli distribution with a 0.5 probability. The prior distribution for a regression coefficient was assigned to be a normal distribution with zero mean and standard deviation similar to that estimated from a pilot regression model if the corresponding predictor is to be included in the model and the standard deviation was multiplied by 10 if the corresponding predictor is not to be included in the model. For each of the MCMC draws, we check how likely are the simulated values for each

regression coefficient to be derived from these distributions with an aim to decide, in a stochastic way, if the corresponding predictor should be included in the model. More information can be found in George and McCulloch (1993).[8] We also assigned a standard normal distribution truncated at zero prior for the heterogeneity standard deviation and a vague normal distribution centered at zero for the summary estimate. The code used in the paper is presented at the end of this text.

5.3 OpenBUGS Codes for selection model and the stochastic search variable selection algorithm

Code for the selection model in winbugs

OpenBUGS code used in the paper by Mavridis et al. 2013[4]

The code requires study-level data. More specifically, it requires the observed effect sizes, the corresponding standard errors and the number of studies.

We also need to assign two probability distributions, one for observing the largest study in the sample and one for the smallest study in the sample. The smallest study has a Uniform distribution on [L1,L2] and the largest study has a Uniform distribution on [U1,U2]

```
model{
lower~dunif(l1,l2)
upper~dunif(u1,u2)
smin<-ranked(s[],1)
smax<-ranked(s[],N)
invNCDFU<-5.531*(pow((1-upper)/upper,0.1193)-1)*step(0.5-upper)-5.531*(pow((1-
upper)/upper,0.1193)-1)*step(upper-0.5)
invNCDFL<-5.531*(pow(lower/(1-lower),0.1193)-1)*step(0.5-lower)-5.531*(pow((lower)/(1-
lower),0.1193)-1)*step(lower-0.5)
beta<-(invNCDFL-invNCDFU)/(1/smax-1/smin)
alpha<-invNCDFU-beta/smin
for(i in 1:N){u[i]<-alpha+beta/s[i]
prob.pub[i]<-phi(u[i])
pub.stud[i]<-1/prob.pub[i]}
for(i in 1:N){z[i]~dnorm(u[i],1)T(0,)
y[i]~dnorm(my[i],w[i])
my[i]<-mu[i]+rho*s[i]*(z[i]-u[i])
vy[i]<-pow(s[i],2)*(1-pow(rho,2))
w[i]<-1/vy[i]
mu[i]~dnorm(mean,prec)}
rho1~dunif(0,2)
rho<-rho1-1
mean~dnorm(0,0.0001)
prec<-1/pow(tau,2)
tau~dnorm(0,1)T(0,)
tot.pub<-sum(pub.stud[1:N])}
list(N=105,l1=0.25,l2=0.35,u1=0.85,u2=0.95,y=c(-0.60259992178083, -0.600955510890836, -
0.220175897552412,
-0.711979061547328, -0.663860277711781, -1.47555157660876, -0.327764758659764,
-0.733851734863555, -0.587049244241413, -0.364605244307876, -0.666258291039483,
-0.313815007782107, -1.03475620370191, -0.79960552793955, -0.851103345905764,
-0.812133000199301, -0.578616352201258, -0.385818372743474, -0.32687256135012,
-0.548110251889547, -0.752374136897279, -1.02738580935594, -0.43192705046391,
-0.464318407242905, -0.967741935483871, -0.327510917030568, -0.254250176104386,
-0.128620360230212, -0.492710016821291, -0.687129972547463, -1.59742030507428,
-0.594620175648966, -0.507657437831229, -0.602769215888656, -0.23470564822711,
0.0952548714382716, -1.2423195988393, -0.694175265562771, -0.921810174768514,
-0.713541431985938, -0.342719606234092, -0.488340920685264, -0.134330236330879,
```

-0.775193798449612, -0.393283088029764, -0.439475010856266, -0.735370308560916,
-0.320130314589803, -0.473308339405223, -0.250378313925739, -0.255102022322193,
-0.640327045674849, -0.458242910523129, -0.430257055115497, -0.521855096079678,
-0.623335841568804, -0.764285714285714, -0.580237123571166, -0.459191314937191,
-0.377660919739033, -0.59854665855608, -0.695626108983674, -0.688158456368155,
-0.494043423913189, -0.585144358196043, -0.00638941348299581,
-0.483632143188439, -0.410395493058603, -0.203787666135144, -0.294971601120217,
-0.761929368684899, -0.295641362498887, -0.385013481002378, -0.27955205692842,
-0.783424086448706, -0.453502930297463, -0.370057772741133, -0.747431923558448,
-0.318430345434855, -0.266023029564635, -0.409013408218831, -0.557130205652991,
-1.03748817972675, -0.178169156869949, -0.212440667004588, -0.874249301680174,
-0.588503332333437, -1.01711004259853, -0.653619508574476, -0.468707515962158,
-0.593080854719082, -0.509336734650731, -0.396076376334595, -0.264791773597281,
-0.35186565619566, -0.238296237035525, -0.392127320070985, -0.40087483786338,
0.167737242111564, -0.405433744203929, -0.607614686911184, -0.328273110886443,
-0.800883496590289, -0.122882446404732, -0.525023409664375)
, s=c(0.164303835272551, 0.119473163832737, 0.199631356809023, 0.208462237761915,
0.148732563883815, 0.275652151020311, 0.410435332645296, 0.476393193589325,
0.170420280394965, 0.195895301558864, 0.135521528304817, 0.279053376887781,
0.308174623489146, 0.329260914783547, 0.272872465571115, 0.335579811137393,
0.350539955099196, 0.272248003837223, 0.289120322036197, 0.35724657714165,
0.415406079838355, 0.433332549772096, 0.170828510061758, 0.194567879550458,
0.158675690919416, 0.150685127705698, 0.0976830786104298, 0.106460035145051,
0.177380566619894, 0.113985308045687, 0.708934116510964, 0.145636890428814,
0.149832274072948, 0.553900213923314, 0.112764204939312, 0.130904395276373,
0.612713386378129, 0.47087033185956, 0.481598438025417, 0.116651342936374,
0.120260464302315, 0.126043063651918, 0.173860871748403, 0.379557827605769,
0.104949976206657, 0.115768140277263, 0.101786366092748, 0.10667285361621,
0.205063926128869, 0.1565182958041, 0.129953720979347, 0.15679196845133,
0.113252302068502, 0.121034175589037, 0.147185051699274, 0.119289611718074,
0.220562656730598, 0.599742360381231, 0.115927885051776, 0.160789340761631,
0.278422095963823, 0.248315722984881, 0.326444240610391, 0.149698620154959,
0.178946951553204, 0.137533628157868, 0.139013182386713, 0.150649675207028,
0.104258569692281, 0.10800837743558, 0.108168801650678, 0.114196590155669,
0.100674398355586, 0.0925426238544508, 0.216385553724039, 0.165632100930506,
0.1389973644513, 0.378562156318883, 0.199815798523331, 0.177256714603352,
0.118967500698703, 0.135190146262167, 0.35057708368964, 0.170782568970086,
0.187694504264653, 0.275879757352228, 0.171481570394913, 0.185438991926809,
0.29148840494776, 0.247168389912314, 0.278309605612755, 0.0933590181061578,
0.0950763255848033, 0.1275764036451, 0.117952267313158, 0.0915756932087625,
0.0924945795486918, 0.162353006776145, 0.282699703710523, 0.110617602548502,
0.0945996234549639, 0.129322222885624, 0.236982290174067, 0.13389633865265,
0.120110613871636))

Code for the stochastic search variable selection algorithm

```
model{
for (i in 1:N){
      prec.c[i]<-1/(se.c[i]*se.c[i])
      prec.t[i]<-1/(se.t[i]*se.t[i])
      se.c[i]<-sdc[i]/sqrt(nc[i])
      se.t[i]<-sdt[i]/sqrt(nt[i])
      pooled.sd[i]<-sqrt(((nc[i]-1)*sdc[i]*sdc[i]+(nt[i]-1)*sdt[i]*sdt[i])/(nc[i]+nt[i]-2))
      var[i]<- (((nt[i]+nc[i])/(nt[i]*nc[i]))+(smd[i]*smd[i])/
(2*(nt[i]+nc[i])))
```

```
      smd[i]<- ((yt[i]-yc[i])/pooled.sd[i])

      yc[i]~dnorm(phi.c[i],prec.c[i])     # normal likelihood
      yt[i]~dnorm(phi.t[i],prec.t[i])

      phi.c[i]<-u[i]*pooled.sd[i]
      phi.t[i]<-(u[i]+theta1[i])*pooled.sd[i]

      theta1[i]<-theta[i]+b[1]*(x1[i]-mean(x1[]))+b[2]*(x2[i]-mean(x2[]))+b[3]*(x3[i]-
mean(x3[]))+b[4]*(x4[i]-mean(x4[]))+b[5]*x5[i]+b[6]*x6[i]        # meta-regression model

      theta[i]~dnorm(SMD,prec)
      u[i]~dnorm(0,.0001)        # priors
   }
        SMD~dnorm(0,.0001)
      prec<-1/pow(tau,2)
      tau~ dnorm(0,1)I(0,)
           for(i in 1:6){
b[i]~dnorm(0,prior.precision[i])
gamma[i]~dbern(0.5)
}
   prior.precision[1] <- gamma[1]*10000 + (1-gamma[1])*1000000
   prior.precision[2] <- gamma[2]*1000 + (1-gamma[2])*100000
   prior.precision[3] <- gamma[3]*10000 + (1-gamma[3])*10000000
   prior.precision[4] <- gamma[4]*10000 + (1-gamma[4])*10000000
   prior.precision[5] <- gamma[5]*20 + (1-gamma[5])*2000
   prior.precision[6] <- gamma[6]*1000 + (1-gamma[6])*100000
   }
```

data for the stochastic search variable selection algorithm

```
list(N=78,
yt=c(-7.1816,-12.3000,-13.5708,46.4000,-10.3000,-8.1000,-15.7000,-17.6907,34.7750,38.0000,
32.0644,37.8062,27.2392,-10.4893,-5.7000,-31.5000,-11.3000,-12.1078,-15.1600,-17.0000,
-17.2108,-26.5437,-26.2000,-17.7598,-8.7500,-9.3044,-15.0000,-28.4000,-13.5596,-19.6020,
-20.2626,-10.1000,-20.6800,-10.7000,-10.0528,-17.1780,-13.0400,-14.0000,-19.7000,-19.1200,
-14.6931,-18.0316,37.7481,41.6480,-19.7000,-12.4261,-12.0253,-18.0000,-21.0000,-20.5235,
-25.4351,-10.5415,-13.8220,-14.0106,-13.4500,-13.1000,-20.3300,41.2000,-14.6000,-10.6200,
-10.4259,-8.9719,-14.9000,-17.0000,-8.2400,-14.7000,-22.9000,16.7700,37.9706,-23.9545,
-21.4774,-13.4000,-16.6000,-13.2187,-21.6712,-8.7800,-16.8293,-24.9000)
,
sdt=c(14.7702,21.8000,15.1889,4.5000,16.4590,16.0000,14.9000,29.5340,8.5923,15.9000,
14.9793,10.3124,10.3752,18.1845,15.0000,19.5300,18.3200,19.1694,21.4585,19.2800,
21.0119,23.5549,23.3600,19.1947,17.4500,17.9614,26.0200,23.8600,24.2469,20.5289,
17.6467,13.1000,24.2500,20.4000,20.1459,19.5360,24.5400,19.9000,19.3000,35.0000,
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19.9180,20.5123,28.3168,23.3325,15.7243,25.8353,19.1000,10.1000,14.6400,21.1700,
21.5487,14.4853,16.7700,20.1900,14.8400,20.2200,16.9200,11.2300,10.9125,20.6567,
18.0626,14.9000,21.4585,20.1973,16.4458,6.4600,19.5269,19.7000)
,
nt=c( 154,  49, 195,   9, 106,  53, 116,  43,  30,  17,
  57,  37,  25, 103,  51,  93,  94, 427, 433,  51,
```

249, 237, 91, 311, 12, 180, 70, 458, 298, 502,
326, 51, 62, 252, 127, 327, 200, 95, 151, 34,
289, 114, 54, 40, 96, 207, 158, 90, 362, 357,
362, 229, 295, 519, 66, 108, 157, 15, 76, 101,
224, 268, 61, 45, 22, 71, 81, 27, 51, 563,
455, 75, 124, 351, 156, 30, 140, 198)
,
yc=c(1.7100,2.8000,-3.1000,50.5000,-0.6000,-2.1000,-5.3000,4.6000,41.7500,47.2000,
37.4800,41.1800,32.9200,-2.9000,1.8000,-12.6000,-5.3000,-7.1000,-12.4000,-6.0000,
-2.8000,-12.5800,-14.4000,-13.2000,5.0000,3.8000,-11.7000,-18.8000,-2.9000,-4.1000,
-14.6000,-4.1000,-14.6000,-5.6000,3.3000,-8.0000,-2.3300,-4.2000,-7.7000,7.6300,
-5.0000,-8.5000,47.6000,51.9300,-4.6000,-12.3000,-0.4000,-7.8000,-17.0000,-12.9000,
-10.3000,-4.1000,-3.5000,-7.6000,-1.1000,-1.4000,-12.6100,48.9000,-9.9000,-5.0000,
-1.2000,-0.9000,-11.9000,-12.7000,4.8200,-2.7000,-6.4000,25.3900,43.0000,-13.3000,
-14.3000,-7.4000,-7.9000,-0.9500,-16.2000,-0.9900,-14.4000,-14.5000)
,
sdc=c(14.7100,20.6000,17.5000,6.4000,16.6500,16.9000,16.3000,17.7000,8.5800,15.9000,
10.3406,10.3406,10.3406,16.3000,17.1000,19.5300,18.3200,21.2300,21.4585,23.8500,
20.8900,23.2000,23.1300,20.1000,23.0300,18.8800,22.8400,26.5000,24.2800,23.1600,
17.8000,12.2000,24.3000,18.6000,22.2000,21.5000,25.5400,17.6000,19.2000,35.0000,
21.1400,26.4000,10.3406,8.9500,26.4000,19.5500,23.1100,24.4000,20.0000,25.6000,
19.7000,24.1000,23.6000,21.5000,15.8400,25.7300,24.0000,10.5000,15.0000,21.0300,
24.5600,14.5000,16.8900,20.2700,14.9900,20.5600,15.1300,15.1800,10.3406,21.8900,
18.3000,15.0300,21.4585,20.1800,17.0100,11.1400,20.1300,20.0000)
,
nc=c(51, 49, 62, 10, 54, 53, 114, 22, 14, 17,
18, 18, 12, 53, 58, 85, 85, 140, 111, 91,
120, 61, 93, 106, 8, 138, 63, 115, 102, 126,
122, 47, 122, 78, 64, 105, 107, 96, 144, 62,
103, 60, 25, 13, 49, 71, 80, 90, 124, 114,
120, 117, 152, 152, 35, 57, 79, 15, 38, 47,
106, 71, 79, 78, 41, 71, 55, 23, 25, 148,
149, 80, 253, 174, 99, 53, 93, 112)
,
x1=c(1997,1996,1996,1991,1992,1996,2008,1993,1970,1970,
1971,1972,1975,2000,2000,2004,2006,2008,2010,1999,
2005,2009,2012,2009,1984,2007,2008,2007,2002,2007,
2010,1998,2011,2008,1994,2004,2007,2004,2007,2007,
2003,2007,1976,1972,2010,2010,1998,2010,2010,2010,
2010,2008,2008,2008,2002,2002,1996,1969,2008,1996,
1995,1997,2014,2013,2014,2014,2012,1992,1975,2014,
2015,2015,2014,2015,2015,2016,2016,2016) #year
,
x2=c(2.0000,2.8000,-5.0000,-5.0000,-1.0000,-3.0000,-5.3000,4.6000,5.0000,-2.1000,
-8.0000,-2.0000,-9.0000,-4.0000,2.0000,-12.6000,-5.3000,-7.1000,-12.4000,-6.0000,
-2.8000,-12.5800,-14.4000,-13.2000,7.0000,3.8000,-11.7000,-18.8000,-2.9000,-4.1000,
-14.6000,-5.0000,-14.6000,-5.6000,3.3000,-8.0000,-2.3300,-4.2000,-7.7000,7.6300,
-5.0000,-8.5000,-7.0000,17.0000,-4.6000,-12.3000,-0.4000,-7.8000,-17.0000,-12.9000,
-10.3000,-4.1000,-3.5000,-7.6000,-1.1000,-1.4000,-12.6100,5.0000,-9.9000,-5.0000,
-1.2000,0.7000,-11.9000,-12.7000,4.8200,-2.7000,-18.4000,-5.0000,-25.0000,-13.3000,
-14.3000,-7.4000,-7.9000,-0.9500,-16.2000,0.9900,-14.4000,-14.5000) #changePLA
,
x3=c(630.8, 300, 712.5, 800, 840, 245.6, 600, 900, 559.5, 600, 664.6667,
811.455, 895, 507, 482, 450, 200, 675, 520, 600, 450.15, 600,
680, 411.25, 1200, 350.1, 400.2, 440.8, 525, 453.485, 426.25,
450, 450, 533.6, 900, 450.15, 348.4, 600, 600, 450, 550, 425,

```
814, 1200, 497.5, 488.4375, 675, 500, 499.375, 474.375, 612.9688,
637.5, 578.8125, 626.375, 900, 600, 591, 539, 560.28, 483.3,
780, 599.4, 450, 450, 450, 450, 450, 480, 1000, 400, 200, 400,
400, 377.095, 350, 600, 300, 608.75) #meanDOSE
,
x4=c(  208,  100,  270,   19,  160,  109,  239,   65,   44,   34,
   86,   55,   43,  159,  121,  180,  182,  606,  565,  196,
  376,  307,  184,  417,   23,  321,  135,  588,  414,  630,
  458,   95,  184,  351,  196,  444,  314,  196,  303,   97,
  404,  182,   87,   57,  149,  285,  246,  180,  500,  478,
  488,  375,  463,  706,  103,  188,  246,   30,  114,  153,
  348,  354,  142,  130,   63,  155,  194,   65,   82,  729,
  617,  167,  438,  532,  262,   86,  235,  311) #Ntotal
,
x5=c(  1,  1,  1,  0,  1,  1,  0,  1,  1,  0,
  0,  1,  1,  1,  1,  0,  1,  1,  1,  1,
  1,  0,  0,  1,  0,  1,  1,  1,  1,  1,
  1,  1,  0,  1,  1,  1,  1,  0,  0,  0,
  1,  1,  0,  0,  1,  1,  1,  1,  1,  1,
  1,  1,  1,  1,  1,  1,  1,  0,  1,  1,
  1,  1,  0,  0,  0,  0,  0,  0,  1,  1,
  1,  0,  0,  1,  1,  0,  1,  1) #sponsor
,
x6=c(  1,  1,  1,  1,  1,  1,  1,  1,  0,  0,
  0,  0,  0,  0,  0,  1,  1,  1,  1,  1,
  1,  1,  1,  1,  0,  0,  1,  1,  1,  1,
  1,  1,  1,  1,  1,  1,  1,  1,  1,  1,
  1,  1,  0,  0,  1,  1,  1,  1,  1,  1,
  1,  1,  1,  1,  1,  1,  1,  0,  1,  1,
  1,  1,  1,  1,  1,  1,  1,  0,  0,  1,
  1,  1,  0,  1,  1,  1,  1,  1) #MinSevCrityesno)
```

References

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Supplementary Table S3

Description of the search strategy

ALL ELECTRONIC SEARCHES HAVE BEEN UPDATED IN OCTOBER 2016. THE SEARCH TERMS WERE THE SAME AS THOSE IN AN INITIAL SEARCH IN JUNE 2014

1. **Search in June 2014**

Database: Ovid MEDLINE(R) <1946 to May Week 4 2014>
Search Strategy:

---

1 (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Bromperidol or Butaperazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Lithium or Loxapine or Loxapinsuccinate or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol).mp. (124527)
2 (Antipsychoti$ or Anti-psychotic$ or Neurolepic$ or Neurolept$).mp. (60102)
3 Antipsychotic Agents/ (41474)
4 or/1-3 (153726)
5 exp Placebos/ (32622)
6 placebo.tw. (150333)
7 or/5-6 (163940)
8 exp schizophrenia/ (85058)
9 exp Paranoid Disorders/ (3708)
10 schizo$.mp. (125268)
11 hebephreni$.mp. (263)
12 oligophreni$.mp. (1009)

13 psychotic$.mp. (47123)
14 psychosis.mp. (22339)
15 psychoses.mp. (18152)
16 or/8-15 (168577)
17 exp clinical trial/ (767995)
18 exp randomized controlled trials/ (94410)
19 exp double-blind method/ (126086)
20 exp single-blind method/ (19151)
21 exp cross-over studies/ (34260)
22 randomized controlled trial.pt. (374960)
23 clinical trial.pt. (487713)
24 controlled clinical trial.pt. (88427)
25 (clinic$ adj2 trial).mp. (578941)
26 (random$ adj5 control$ adj5 trial$).mp. (488092)
27 (crossover or cross-over).mp. (63590)
28 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (173169)
29 randomi$.mp. (561477)
30 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (162626)
31 or/17-30 (1058069)
32 4 and 7 and 16 and 31 (2206)
33 limit 32 to ed=20080101-20140606 (664)

Database: PsycINFO <1806 to June Week 1 2014>
Search Strategy:
---
1 (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Bromperidol or Butaperazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Lithium or Loxapine or Loxapinsuccinate or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or

Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol).mp. (37053)
2 (Antipsychoti$ or Anti-psychotic$ or Neurolepic$ or Neurolept$).mp. (33227)
3 neuroleptic drugs/ (17095)
4 or/1-3 (54135)
5 exp Placebo/ (3789)
6 placebo.tw. (30796)
7 or/5-6 (30862)
8 exp Schizophrenia/ (71992)
9 exp psychosis/ (91562)
10 schizo$.mp. (107980)
11 hebephreni$.mp. (530)
12 oligophreni$.mp. (517)
13 psychotic$.mp. (37181)
14 psychosis.mp. (41536)
15 psychoses.mp. (14369)
16 or/8-15 (150168)
17 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (19669)
18 (random$ adj5 (assign$ or allocat$)).mp. (30325)
19 randomi$.mp. (48490)
20 crossover.mp. (5171)
21 or/17-20 (83740)
22 7 and 16 and 21 (2094)
23 limit 22 to up=20080101-20140606 (922)

Database: Embase <1974 to 2014 June 05>
Search Strategy:
---
1 (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Bromperidol or Butaperazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Lithium or Loxapine or Loxapinsuccinate or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or

Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol).mp. (253265)
2 (Antipsychoti$ or Anti-psychotic$ or Neurolepic$ or Neurolept$).mp. (96478)
3 neuroleptic agent/ (59264)
4 or/1-3 (292544)
5 exp placebo/ (252940)
6 placebo.tw. (201157)
7 or/5-6 (329462)
8 exp schizophrenia/ (139848)
9 exp psychosis/ (215368)
10 schizo$.mp. (173747)
11 hebephreni$.mp. (837)
12 oligophreni$.mp. (1650)
13 psychotic$.mp. (37139)
14 psychosis.mp. (96238)
15 psychoses.mp. (14607)
16 or/8-15 (265465)
17 (clin$ adj2 trial).mp. (993618)
18 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (207858)
19 (random$ adj5 (assign$ or allocat$)).mp. (114281)
20 randomi$.mp. (692773)
21 crossover.mp. (65244)
22 exp randomized-controlled-trial/ (345386)
23 exp double-blind-procedure/ (115986)
24 exp crossover-procedure/ (39104)
25 exp single-blind-procedure/ (18341)
26 exp randomization/ (62272)
27 or/17-26 (1394279)
28 4 and 7 and 16 and 27 (5205)
29 ("2008??" or "2009??" or "2010??" or "2011??" or "2012??" or "2013??" or "2014??").em. (7563542)
30 28 and 29 (2593)

BIOSIS Citation IndexSM

# 16	**440**	#15 AND #14 AND #13 AND #10 AND #1 *Indexes=BCI Timespan=2008-2014*
# 15	**36,402**	**TOPIC:** ((schizo* or hebephreni* or oligophreni* or psychotic* or psychosis or psychoses)) *OR* **TITLE:** ((schizo* or hebephreni* or oligophreni* or psychotic* or psychosis or psychoses)) *Indexes=BCI Timespan=2008-2014*
# 14	**29,564**	**TOPIC:** (Placebo*) *OR* **TITLE:** (Placebo*) *Indexes=BCI Timespan=2008-2014*
# 13	**31,966**	#12 OR #11 *Indexes=BCI Timespan=2008-2014*
# 12	**22,586**	**TOPIC:** (Antipsychoti* or Anti-psychotic* or Neurolepic* or Neurolept*) *OR* **TITLE:** (Antipsychoti* or Anti-psychotic* or Neurolepic* or Neurolept*) *Indexes=BCI Timespan=2008-2014*
# 11	**18,913**	**TOPIC:** (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Bromperidol or Butaperazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Lithium or Loxapine or Loxapinsuccinate or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol) *OR* **TITLE:** (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Bromperidol or Butaperazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Lithium or Loxapine or Loxapinsuccinate or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or

		Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol) *Indexes=BCI Timespan=2008-2014*
# 10	**100,084**	#9 OR #8 OR #7 OR #6 OR #3 OR #2 *Indexes=BCI Timespan=2008-2014*
# 9	**8,718**	TS=crossover* OR TI=crossover* *Indexes=BCI Timespan=2008-2014*
# 8	**118**	TS=(randomi* Near/1 assign*) or TI=(randomi* Near/1 assign*) *Indexes=BCI Timespan=2008-2014*
# 7	**22**	TS=(randomi* Near/1 allocate*) or TI=(randomi* Near/1 allocate*) *Indexes=BCI Timespan=2008-2014*
# 6	**24,582**	#5 AND #4 *Indexes=BCI Timespan=2008-2014*
# 5	**48,336**	TS=(mask* OR blind*) OR TI=(mask* OR blind*) *Indexes=BCI Timespan=2008-2014*
# 4	**535,073**	TS=(singl* OR Doubl* OR Tripl* OR Trebl*) OR TI=(singl* OR Doubl* OR Tripl* OR Trebl*) *Indexes=BCI Timespan=2008-2014*
# 3	**88,783**	TI=(randomi*) OR TS=(randomi*) *Indexes=BCI Timespan=2008-2014*
# 2	**55,789**	TS=(Randomized clinical trial*) OR TI=(Randomized clinical trial*) *Indexes=BCI Timespan=2008-2014*
# 1	**1,990,883**	TA=(Hominidae) *Indexes=BCI Timespan=2008-2014*

Search phrases Clinicaltrials.gov 09-06-14

schizophrenia and placebo and random | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 471

psychosis and placebo and random and antipsychotic | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 384

psychosis and placebo and random and Acepromazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Acetophenazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Amisulpride | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 10

psychosis and placebo and random and Aripiprazole | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 45

psychosis and placebo and random and Asenapine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 7

psychosis and placebo and random and Benperidol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Blonanserin | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Bromperidol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Butaperazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Carpipramine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Chlorproethazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Chlorpromazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 4

psychosis and placebo and random and Chlorprothixene | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Clocapramine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Clopenthixol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Clopentixol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Clothiapine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Clotiapine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Clozapine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 26

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psychosis and placebo and random and Dixyrazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Droperidol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Fluanisone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Flupehenazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Flupenthixol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Flupentixol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Fluphenazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 2

psychosis and placebo and random and Fluspirilen | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Fluspirilene | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Haloperidol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 14

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psychosis and placebo and random and Levomepromazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Levosulpiride | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

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psychosis and placebo and random and Loxapinsuccinate | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Lurasidone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 16

psychosis and placebo and random and Melperone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Mepazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Mesoridazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Methotrimeprazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Molindone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Moperone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Mosapramine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Olanzapine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 48

psychosis and placebo and random and Oxypertine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Paliperidone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 25

psychosis and placebo and random and Penfluridol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Perazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Periciazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

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psychosis and placebo and random and Perospirone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Perphenazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Pimozide | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Pipamperone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 3

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psychosis and placebo and random and Promethazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 12

psychosis and placebo and random and Prothipendyl | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Quetiapine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 50

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psychosis and placebo and random and Reserpine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Riospirone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Risperdal | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 69

psychosis and placebo and random and Risperidone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 69

psychosis and placebo and random and Seroquel | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 50

psychosis and placebo and random and Sertindole | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Stelazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Sulpiride | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 6

psychosis and placebo and random and Sultopride | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 10

psychosis and placebo and random and Thiopropazate | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

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psychosis and placebo and random and Thioridazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Tiospirone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Thiothixene | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Tiapride | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

psychosis and placebo and random and Tiotixene | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Trifluoperazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Trifluperidol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and trifluoperidol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Triflupromazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and trifluperazine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Veralipride | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Ziprasidone | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 15

psychosis and placebo and random and Zotepine | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 0

psychosis and placebo and random and Zuclopenthixol | Interventional Studies | received from 01/01/2008 to 06/12/2014 = 1

237 trials found for: schizo* and placebo and random* limited to 2008-2014

116 ials found for: psycho* and placebo and random* limited to 2008-2014

2. **Search in the register of controlled trials of the Cochrane Schizophrenia Group.**

This register was only available to us in its version August 2009. To avoid missing articles that had come up only in 2009, we included the year 2008 in the search of the databases above.

The search term was “placebo” in the fields, title, abstract, index field or keyword

The Cochrane schizophrenia group regularly searches of more than 15 databases, clinical trial registers, hand searches and conference proceedings. The detailed search strategy can be found at the homepage of the Cochrane schizophrenia group (http://szg.cochrane.org/cszg-specialised-register). To search this register was particularly important for identifying old schizophrenia studies.

3. **Search of included studies in other reviews**

We searched the following previous reviews, for which extensive searches had also be undertaken. In particular the reviews of our group had also searched the documents that pharmaceutical companies had sent to the FDA for the approval of their compounds

1.) Klein DF, Davis JM. Diagnosis and drug treatment of psychiatric disorders. Baltimore: Williams and Wilkins; 1969

2.) Agid O, Siu CO, Potkin SG, et al. Meta-regression analysis of placebo response in antipsychotic trials, 1970-2010. Am J Psychiatry 2013;170:1335-44.

3.) Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol Psychiatry 2009a;14:429-47

4.) Adams CE, Awad G, Rathbone J. Chlorpromazine versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2007

5.) Joy CB, Adams CE, Lawrie SM. Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev 2006:CD003082

6.) Shen X, Xia J, Adams CE. Flupenthixol versus placebo for schizophrenia. Cochrane Database Syst Rev 2012;11:CD009777

7.) Matar HE, Almerie MQ. Oral fluphenazine versus placebo for schizophrenia. Cochrane Database Syst Rev 2007:CD006352

8.) Hartung B, Wada M, Laux G, Leucht S. Perphenazine for schizophrenia. Cochrane Database of Systematic Reviews 2005:CD003443

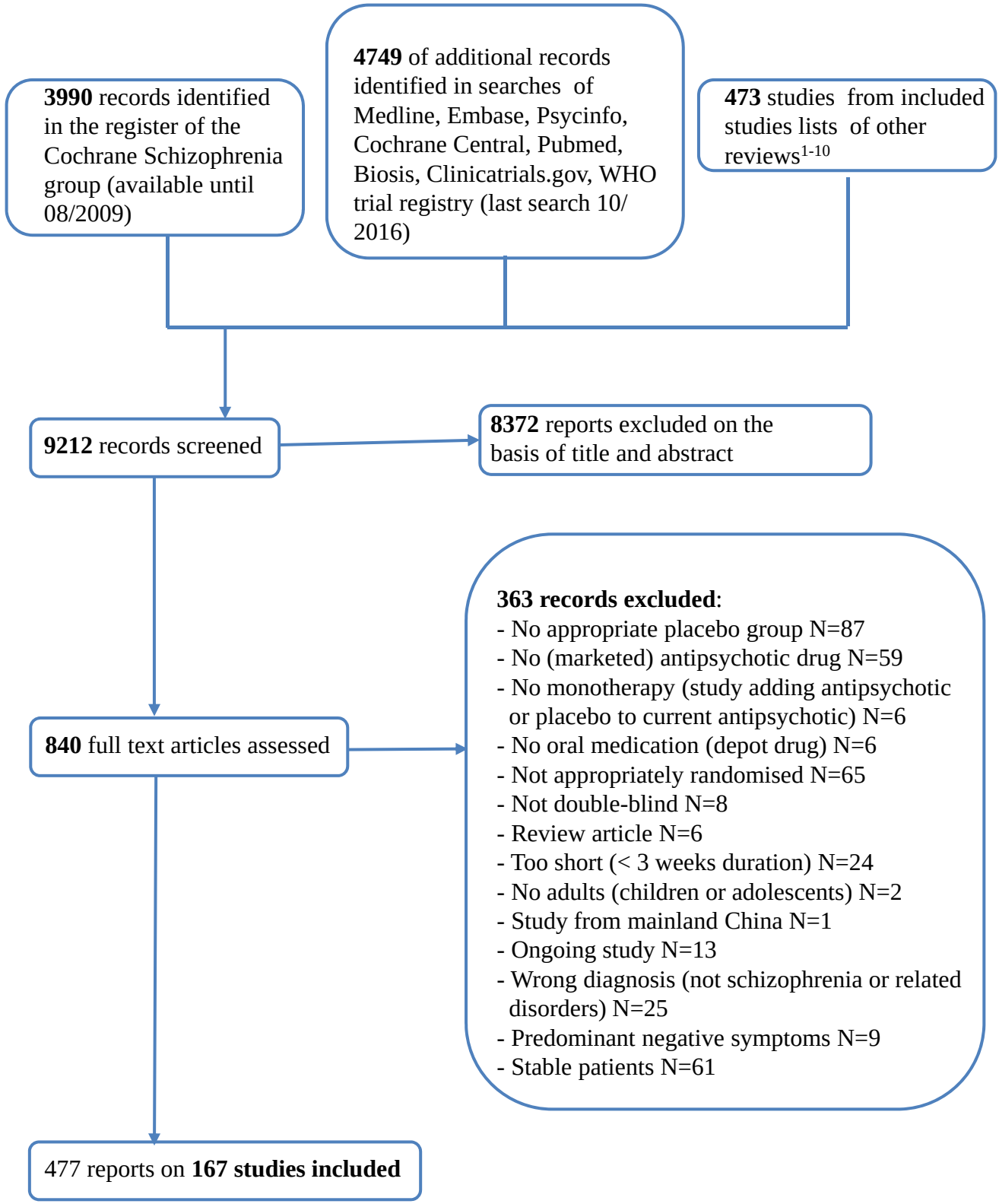
9.) Omori IM, Wang J. Sulpiride versus placebo for schizophrenia. Cochrane Database Syst Rev 2009:CD007811

10.) Fenton M, Rathbone J, Reilly J, Sultana A. Thioridazine for schizophrenia. Cochrane Database Syst Rev 2007:CD001944

Supplementary Figure S1

Description of the search process (PRISMA diagram)

Supplementary Figure S1 PRISMA diagram of the search process



References:

1.) Klein DF, Davis JM. Diagnosis and drug treatment of psychiatric disorders. Baltimore: Williams and Wilkins; 1969
2.) Agid O, Siu CO, Potkin SG, et al. Meta-regression analysis of placebo response in antipsychotic trials, 1970-2010. Am J Psychiatry 2013;170:1335-44.
3.) Leucht S, Arbter D, Engel RR, Kissling W, Davis JM. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. Mol Psychiatry 2009a;14:429-47
4.) Adams CE, Awad G, Rathbone J. Chlorpromazine versus placebo for schizophrenia. Cochrane Database of Systematic Reviews 2007
5.) Joy CB, Adams CE, Lawrie SM. Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev 2006:CD003082
6.) Shen X, Xia J, Adams CE. Flupenthixol versus placebo for schizophrenia. Cochrane Database Syst Rev 2012;11:CD009777
7.) Matar HE, Almerie MQ. Oral fluphenazine versus placebo for schizophrenia. Cochrane Database Syst Rev 2007:CD006352
8.) Hartung B, Wada M, Laux G, Leucht S. Perphenazine for schizophrenia. Cochrane Database of Systematic Reviews 2005:CD003443
9.) Omori IM, Wang J. Sulpiride versus placebo for schizophrenia. Cochrane Database Syst Rev 2009:CD007811
10.) Fenton M, Rathbone J, Reilly J, Sultana A. Thioridazine for schizophrenia. Cochrane Database Syst Rev 2007:CD001944

Supplementary Table S4

Description of included studies

Table S4: Description of included studies

Numbers in squared brackets refer to doses that have not been analysed, neither in the primary analysis nor in a sensitivity analysis. The number of references is lower than the number of included studies, because some publications reported on two or more studies

Study Degree of blinding (double if not specified differently)	Antipsychotics and daily dose in mg, on flexible dosage mean value (range)	N	Duration in weeks	Mean duration of illness in years	Diagnosis
Adelson 1962[1]	CPZ 1800 (-3000) PERP 181 (-750) PROC 338 (-450) TRIFLUP 621 (-240) PBO	48 48 48 48 48	17	n.i.	Chronic schizophrenia (clinical diagnosis)
Ahmed et al. 2007[2]	OLA 15 PBO [Bifeprunox 20; 30]	150 150 [154; 150]	6	n.i.	Schizophrenia in acute exacerbation (DSM-IV-TR)
Arvanitis et al. 1997[3]	QUE 300; 600; 750 [75; 150] HAL 12 PBO	52; 51; 54 [50; 48] 52 51	6	15	Acute exacerbation of (sub-) chronic schizophrenia (DSM-III-R)
Augustin 1996[4]	HAL n.i. PBO	18 18	6	n.i.	Schizophrenia (n.i.)
Baker 1959[5]	CPZ 270 (300) PBO [Ethylcrotonylurea 1200]	7 8 10	5	n.i.	Schizophrenia (clinical diagnosis)
Ban et al. 1975e[6]	CPZ n.i. (200-800) PBO THIOT n.i. (10-40)	10 10 10	12	n.i.	Schizophrenia (clinical diagnosis)
Barbato et al. 2007c[7]	OLA 15 PBO [Bifeprunox 20; 30]	150 145 [149; 146]	6	n.i.	Schizophrenia in acute exacerbation (DSM-IV)
Barbato et al. 2007d[7]	HAL 10 PBO [Bifeprunox 1; 10]	52 51 [59; 46]	6	n.i.	Schizophrenia in acute exacerbation (DSM-IV)
Barron 1963[8]	CARP n.i. (75-150) PBO	10 10	n.i.	n.i.	Schizophrenic reaction (1 chronic brain syndrome with psychotic reaction)
Beasley et al. 1996a[9]	OLA 10 [1] PBO	50 [52] 50	6	16	Schizophrenia with an acute exacerbation (DSM-III-R)
Beasley et al. 1996b[10]	OLA 10±2.5; 15±2.5 [5±2.5] HAL 14.0 PBO	64; 69 [65] 69 68	6	14	Acute exacerbation of schizophrenia (DSM-III-R)
Bechelli et al. 1983[11]	HAL 11.5 (10-20) PIP 21.4 (20-40) PBO	30 29 31	4	n.i.	Acute schizophrenia (ICD-9)

Bishop 1964[12]	BUTA n.i. (0-200) TRIFLUP n.i. (0-40) PBO	14 14 14	10	12.5	Chronic schizophrenia (clinical diagnosis)
Bishop and Gallant 1963c[13]	CPZ n.i. (≤800) PBO [Benzquinamide]	10 10 [10]	10	n.i.	Chronic schizophrenia (clinical diagnosis)
Borison et al. 1989[14]	HAL n.i. (15-75) PBO TIOS n.i. (45-225) THIOR n.i. (150-750)	8 8 [8] [8]	6	n.i.	Schizophrenia (DSM-III), acutely exacerbated
Borison et al. 1991a[15]	CPZ 800 (400-1600) PBO	9 10	4	n.i.	Schizophrenia (DSM-III) in acute exacerbation
Borison et al. 1992[16]	RIS 7.8 (2-10) HAL 15.0 (4-20) PBO	53 53 54	6	15	Schizophrenia (DSM-III-R)
Borison et al. 1996[17]	QUE 307 (75-750) PBO	54 55	6	15	Acute exacerbation of (sub-) chronic schizophrenia (DSM-III-R)
Bugarski-Kirola 2014[18]	OLA 15 PBO [Bitopterin 10; 30]	63 80 [80;77]	4	13.3	Acute exacerbation of schizophrenia (DSM-IV)
Canuso et al. 2010[19] (Johnson NCT00397033)	PAL 7.5 (6; 9) PBO	209 (109; 100) 107	6	4.8	Acute episode of schizoaffective disorder (DSM-IV)
Canuso et al. 2010a[20] (Johnson NCT00412373)	PAL n.i. (3-12) PBO	216 95	6	n.i.	Acute episode of schizoaffective disorder (DSM-IV)
Casey 1960[21]	CPZ 400 PBO	170 178	10	n.i.	Schizophrenic reaction (clinical diagnosis
Casey et al. 2008[22]	RIS 6 PBO [Bifeprunox 5; 10; 20]	120 119 [115; 120; 115]	6	n.i.	Acute exacerbation of schizophrenia (DSM-IV-TR)
Charalampous 1974[23]	LOX 147.5 (50-150) THIOT 51.9 (20-60) PBO	20 21 19	4	2.5	Schizophrenia (clinical diagnosis)
Chouinard 1975[24]	PERP 20 PBO	24 24	12	11.1	Schizophrenia (RDC)
Chouinard 1990[25]	CPZ 555 (300-1200) PBO [Remoxipride]	21 21 [20]	4	13.95	Schizophrenia (DSM-III)
Chouinard et al. 1993[26]	RIS 6 [2;10;16] HAL 20 PBO	22 [24;22;24] 21 22	8	16	Chronic Schizophrenia (DSM-III-R)
Clark 1968 (01383)[27]	CPZ 663(258-835) TRIFLUP 6.7 (5.1-8.3) PBO No drug	18 18 18 18	14	15.2	Chronic schizophrenia (clinical diagnosis)

Clark 1968[28]	CPZ 842.3 [<1000] BUTA 81.1 [<100] PBO	23 23 23	16	19	Chronic schizophrenia (clinical diagnosis)
Clark 1969[29]	CPZ n.i. (200-1600) HAL (3-15) PBO	14 14 16	12	n.i.	Chronic schizophrenia (criteria n.i.)
Clark 1975[30]	Loxapine 71 (-100) TRIFLU 36 (-50) Placebo	15 15 13	4	8.98	Chronic schizophrenia (clinical diagnosis)
Clark 1977[31]	LOX 47.2 (-50) LOX 93.1 (-100) PBO	13 12 13	12	17.5	Chronic schizophrenia (DSM-II)
Clark et al. 1970a[32]	CPZ 684 (200-1000) PBO MOL	15 14 15	12	n.i.	Chronic schizophrenia (clinical diagnosis), inpatients
Clark et al. 1970b[33]	CPZ 459 (300; 600) [150] PBO	Unclear [unclear] unclear	12	16.6	Chronic schizophrenia (clinical diagnosis)
Clark et al. 1971a[34]	CPZ 718 (-1000) PBO FLUPH 7.3 (-10) THIOR 760 (-1000)	23 21	4	n.i.	Chronic schizophrenia (clinical diagnosis), newly admitted and acutely exacerbated
Clark et al. 1972[35]	CPZ 817 (-1000) PBO Loxapine 80.6 (-100)	19 18 [18]	13	n.i.	Chronic schizophrenia (clinical diagnosis)
Clark et al. 1977a[36]	CPZ n.i. (100-1000) BUTA PBO	9 9 9	12	21.78	Chronic schizophrenia (clinical diagnosis)
Cockburn 1959[37]	RES 4 PBO Extract of Alstonia Constricta	10 10 10	4	n.i.	Schizophrenia (clinical diagnosis)
Cole 1964[38]	CPZ 654.8 (200-1600) FLUPH 6.4 (2-16) THIOR 700 (200-1600 PBO	112 115 111 125	6	2.7	Acute schizophrenia (clinical diagnosis)
Cooper et al. 2000a[39]	ZOT 241 (300, reduceable to 150) CPZ 532 (600, reduceable to 300) PBO	53 53 53	8	11	Acute exacerbation of (sub-) chronic schizophrenia (DSM-III-R)
Cooper et al. 2000b [40]	ZOT n.i. (150-300) PBO	63 58	26	14	Chronic schizophrenia (DSM-III-R)
Coppola et al. 2011[41] (Johnson NCT00524043)	PAL 6 [1.5] PBO	70 [66] 65	6	n.i.	Acute episode of schizophrenia (DSM-IV)
Correll et al. 2015[42]	BRE 0.25;2;4 PBO	90;182;180 184	6	12.7	Schizophrenia (DSM-IV-TR)
Corrigan et al. 2004[43]	OLA 15 PBO	93 87	6	13	Schizophrenia (DSM-IV)

Cutler et al. 2006[44]	ARI 10 [2; 5] PBO	94 [93; 92] 88	6	n.i.	Hospitalized patients in acute relapse of schizophrenia (DSM-IV)
Cutler et al. 2008[45]	ILO 24 PBO ZIP 160	303 152 151	4	n.i.	Schizophrenia (DSM-IV)
Cutler et al. 2010[46]	QUE XR400; XR600; XR800; IR800 PBO	114; 105;113; 116 117	6	17.7	Acute exacerbation of schizophrenia (DSM-IV)
Daniel et al. 1999[47]	ZIP 80; 160 PBO	106; 104 92	6	14	Acute exacerbation of (sub-)chronic schizophrenia or schizoaffective disorder (DSM-III-R)
Davidson et al. 2007[48]	OLA 10 PAL 9 [3;15] PBO	128 125 [127;115] 123	6	11.9	Acute episode of schizophrenia (DSM-IV)
Downing 2014[49]	RIS 4 [LY 40; 80] PBO	142 [292;280] 295	6	14.7	Schizophrenia (DSM-IV)
Durgam et al. 2014[50]	CAR 1.5;3;4.5 RIS 4 PBO	145;146;147 140 151	6	11.6	Schizophrenia (DSM-IV-TR), all subtypes
Egan 2013[51]	OLA 15 PBO [(MK-8998) 16]	47 83 86	4	10.88	Schizophrenia (DSM-IV-TR)
Engelhardt 1969[52]	CPZ 180 (50-800) [Promazine 180 (50-800)] PBO	103 [109] 99	12	n.i.	Chronic schizophrenia (clinical diagnosis)
Evans 1972[53]	THIOR 400 PBO	27 27	3	n.i.	Schizophrenia (newly hospitalised, clinical diagnosis)
Fabre 1995[54]	QUE 113(25-250) PBO	8 4	3	12	(Sub-)chronic schizophrenia (DSM-IIIR)
Fincle 1965[55]	CPZ n.i. (300-600) PBO	48 49	4	n.i.	Chronic schizophrenia (clinical diagnosis)
Fleming et al. 1959[56]	CPZ 112.5 (n.i.) PBO [Promazine 203]	12 12 [12]	4	16.7	Chronic schizophrenia (clinical diagnosis)
Gallant 1963[57]	CPZ n.i. (-800) PBO	n.i.	12	n.i.	Chronic schizophrenia (clinical diagnosis)
Garcia et al. 2009[58]	HAL 10 PBO [BLO 2.5; 5; 10]	60 64 [61; 58; 64]	6	n.i.	Schizophrenia (acute exacerbation) (DSM-IV-TR)
Garry and Leonard 1962b[59]	HAL 4.2 (slowly increased) PBO	26 26	12	14.5	Chronic schizophrenia (paranoid, catatonic, hebephrenic, simple) (clinical diagnosis)
Geffen et al. 2012[60]	RIS n.i. (2-8) PBO **[**BL-1020 (10;20-30)**]**	91 93 **[**179**]**	6	8.6	Chronic Schizophrenia (DSM-IV-TR) with acute exacerbation within 30 days
Goldberg 1972[61]	CPZ 680 (200-1600) ACE 146 (40-320) PBO	n.i.	5	n.i.	Acute schizophrenia (clinical diagnosis)
Hall et al. 1955[62]	CPZ n.i. (≤ 750) PBO	87 88	9	n.i.	Chronic schizophrenia (clinical diagnosis)

Hamilton 1960[63]	CPZ 300 PBO [Thiopropazate 30]	18 18 [18]	8	n.i.	Chronic schizophrenia (clinical diagnosis)
Hamilton 1963[64]	TRIFLU n.i. PROC n.i. PBO n.i.	21 21 21	17	n.i.	Schizophrenia (clinical diagnosis)
Harnryd 1989[65]	MEL 275 (200-300) PBO	10 10	4	5.12	Schizophrenia (RDC criteria)
Hera 041-021[66]	ASE 10; 20 OLA 15 PBO	106; 102 103 106	6	n.i.	Schizophrenia (DSM-IV)
Hera 041-022[67]	ASE 15 (10-20) OLA (10-20) PBO	91 93 93	6	n.i.	Schizophrenia in acute exacerbation (DSM-IV)
Herrera 1990[68]	THIOR 700 (400-1000) PBO	9 5	4	9.62	Acute schizophrenia (DSM-III)
Hickerson 1956[69]	RES n.i. (2-8) PBO [ECT]	24 26	13	n.i.	Acute schizophrenia (clinical diagnosis)
Hine 1958[70]	CPZ n.i. (-750) PBO	11 11	20	n.i.	Chronic schizophrenia (clinical diagnosis)
Hirayasu et al.[71] (Janssen CR012625)	OLA 10 PAL 6 PBO	47 136 138	6	n.i.	Schizophrenia (DSM-IV)
Honigfeld et al. 1984a[72]	CPZ 1183 (-1800) [CLO 608 (-900)] PBO	15 [16] 8	4	n.i.	Acute exacerbation of schizophrenia (clinical diagnosis)
Howard 1974[73]	HAL n.i. (600-8000) THIOT n.i. (600-8000) PBO	17 16 16	12	20.5	Treatment resistant and chronic schizophrenia (clinical diagnosis)
Jann et al. 1997[74]	HAL 29.0 (15-75) PBO	18 18	6	n.i.	Schizophrenia (DSM-III-R-criteria)
Johnstone 1978[75]	FLUPE 8.4 (6-9) PBO	15 15	4	n.i.	Schizophrenia (PSE-criteria)
Judd 1973[76]	THIOR 400 PBO	12 12	3	n.i.	Schizophrenia (newly hospitalised, clinical diagnosis)
Kahn et al. 2007[77]	QUE IR400; XR400; XR600; XR800 PBO	123; 113; 113; 121 118	6	8.3	Acute schizophrenia (DSM-IV)
Kane et al. 2002[78]	ARI 15; 30 HAL 10 PBO	102; 102 104 106	4	16.3	Schizophrenia or schizoaffective disorder with acute relapse (DSM-IV)
Kane et al. 2007b[79]	OLA 10 PAL 6; 9; 12 PBO	128 123; 122; 130 127	6	10.1	Acute episode of schizophrenia (DSM-IV)
Kane et al. 2010a[80]	ASE 10; 20 HAL 8 PBO	114;106 115 123	6	n.i.	Schizophrenia and acute exacerbation (DSM-IV-TR)
Kane et al. 2015[81]	BRE 1;2;4 PBO	120;186; 184 184	6	12.9	Schizophrenia (DSM-IV-TR)

Karn 1961 [82]	CHLOR 300 PBO	52 51	6	n.i.	Chronic schizophrenia (clinical diagnosis)
Keck et al. 1998[83]	ZIP 120 [40] PBO	47 [44] 48	4	16	Acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R)
King 1959 [84]	CPZ 400 PROC 100 PBO	24 24 24	10	n.i.	Schizophrenia (clinical diagnosis)
Kinon et al. 2011[85]	OLA 15 **[**LY2140023 (5; 20; 40; 80)**]** PBO	**[**121; 122; 120; 122**]** 62 122	4	n.i.	Schizophrenia (DSM-IV)
Klein 1973[86]	CPZ 900 (300-1200) PBO	46 42	6	n.i.	Schizophrenia (clinical diagnosis)
Klieser 1989[87]	HAL 20 PBO [Trazodone 400] [Amitriptyline 150]	22 16 17 20	3	n.i.	Acute schizophrenia DSM-III
Kurland et al. 1961[88]	CPZ 401.4 (300-1200.) [Promazine 439 (300-1600)] [Mepazine135.5 (75-450)] TRIFLUPR 110.5 (75-300) PROC 45.4 (30-125) PERPH 8 (24-96) [Phenobarbital] PBO	33 [32] [34] 32 36 36 37 37	6	n.i.	Predominantly schizophrenic patients (clinical diagnosis), newly admitted
Lemmer 1993[89]	HAL n.i. PBO	n.i.	4	n.i.	Acute schizophrenia (n.i.)
Levita 1961[90]	CPZ n.i. (50-400) PBO	n.i.	13	n.i.	Schizophrenia (clinical diagnosis)
Lieberman et al. 2016[91]	RIS 4 [ITT 0074 60;120] PBO	82 84;83 85	4	16	Schizophrenia (SCID-CT)
Lindenmayer et al. 2008[92]	QUE 518 (SR 300, 600; 800; IR 300, 600) PBO	448 (91; 92; 89; 90 ; 86) 84	6	15.2	Acute exacerbation of schizophrenia (DSM-IV)
Litman et al. 2016[93]	RIS 4 [AZD8529 40] PBO	31 [58] 58	4	n.i.	Schizophrenia (DSM-IV)
Litmann 2014[94]	OLA 15 PBO [(AZD2624) 40]	22 41 43	4	n.i.	Schizophrenia (DSM-IV)
Little 1958[95]	CPZ 150 PBO	n.i.	3	n.i.	Schizophrenia, paraphrenia (clinical diagnosis)
Loebel 2013[96] (Study 233)	LURA 80; 160 PBO QUE 600	125; 121 122 120	6	11.7	Schizophrenia (DSM-IV)
Loebel et al. 2016[97]	LUR [20];96 PBO	[101];199 112	6	14.2	Schizophrenia (DSM-IV-TR)
Mahal 1976 [98]	CPZ 250 PBO	27 27	9	0.5	Schizophrenia (clinical diagnosis)

Marder et al. 1994[99]	RIS 6 [2;10;16] HAL 20 PBO	64 [63;65;64] 66 66	8	16	Chronic schizophrenia (DSM-III-R)
Marder et al. 2007c[100]	OLA 10 PAL 6; 12 PBO	110 111; 111 110	6	16.4	Acute episode of schizophrenia (DSM-IV)
McDonald 1956[101]	RES 3 (3-8) PBO	13 14	10	n.i.	Chronic schizophrenia (clinical diagnosis)
McEvoy et al. 2007b[102]	ARI 10; 15; 20 PBO	106; 106; 100 108	6	n.i.	Schizophrenia with acute relapse (DSM-IV)
McIness 1978[103]	PIM n.i. PBO	n.i.	13	n.i.	Chronic schizophrenia
Meltzer 2004[104]	HAL 10 PBO [5-$HT_{2a/2c}$-Ant.] [NK_3-Ant.] [CB_1-Ant.] [NTS_1-Ant.]	98 98 74 70 72 69	6	n.i.	Acute schizophrenia (DSM-IV)
Meltzer et al. 2007a[105]	RIS 6 PBO [Bifeprunox 30; 40]	154 149 [140 ; 141]	6	n.i.	Acute exacerbation of schizophrenia (DSM-IV-TR)
Meltzer et al. 2011[106] (Study 231)	LURA 40; 120 OLA 15 PBO	120; 119 123 116	6	13.4	Schizophrenia (DSM-IV)
Montgomery 1992[107]	THIOR 400 [Desenkephalin 10] PBO	32 31 33	4	n.i.	Acute exacerbation of schizophrenia (DSM-III)
Nakamura et al. 2009[108] (Study 196)	LURA 80 PBO	90 90	6	n.i.	Schizophrenia (DSM-IV)
Nasrallah 2013[109] (Study 229)	LUR 40; 80;120 PBO	125; 123; 124 128	6	14,2	Schizophrenia (DSM-IV)
NCT00905307 Correll et al. 2016[110]	BRE [0.25];1±0.5; 2.5±0.5;5±0.5 ARI 15 PBO	[42];89;90; 93 50 95	6	n.i.	Schizophrenia (DSM-IV-TR)
NCT01098110 Kinoshita et al. 2016[111]	ASE [5];10 PBO	[176] 182 174	6	n.i.	Schizophrenia (DSM-IV-TR)
NCT01104766 Durgam et al. 2015[112]	CAR 3;6 ARI 15 PBO	155;157 152 153	6	12.5	Schizophrenia (DSM-IV-TR), acute exacerbation
NCT01490086 Cantillon 2014[113]	ARI 15 [RP5063 15;30;50] PBO	20 [58;59;58] 39	6	n.i.	Schizophrenia (DSM-IV-TR)
NCT016171[114]	ASE [5];10 OLA 15 PBO	[98];113 46 103	6	n.i.	Schizophrenia (DSM-IV-TR)
Nistico 1974[115]	PEN 40 (30-50) PBO	10 10	6	n.i.	Chronic schizophrenia (clinical diagnosis)
Ogasa et al. 2012[116] (Study 006)	LURA 40; 120 PBO	50; 49 50	6	n.i.	Schizophrenia (DSM-IV)

Paredes 1966[117]	CPZ n.i. PBO	n.i.	24	n.i.	Schizophrenia (clinical diagnosis)
Pathiraja 1995[118]	HAL 12.5 (5-20) RIS 9 (2-16) PBO	n.i.	n.i.	n.i.	Schizophrenia (DSM-III-R)
Patil et al. 2007[119]	OLA 15 PBO [LY2140023]	34 63 [98]	4	n.i.	Schizophrenia (DSM-IV-TR)
Payne 1960[120]	CPZ 237.5 (75-300) TRIFLUPR 237.5 (75-300) PBO	7 7 7	6	n.i.	Chronic schizophrenia (clinical diagnosis)
Peet 1981[121]	CPZ 225 (50-400) PBO [Propanolol (40-640)]	16 18 19	4	24	Chronic schizophrenia (Feighner criteria)
Pfizer 2008[122]	ARI 15 [pf-00217830 (2;15)] PBO	n.i.	3	n.i.	Acute exacerbation of schizophrenia (DSM-IV)
Pi 1990[123]	THIO 500 (200-800) PBO [HAL (0.3 mg/kg) open conditions]	7 5 5	4	8.41	Acute exacerbation of chronic schizophrenia (DSM-III)
Potkin 2001[124]	HAL 10 [M100907 (10; 20)] PBO	56 [124; 123] 110	6	n.i.	Schizophrenia or schizoaffective disorder (DSM-IV)
Potkin et al. 2003[125]	ARI 20; 30 PBO RIS 6	101; 101 103 99	4	n.i.	Schizophrenia or schizoaffective disorder with acute relapse (DSM-IV)
Potkin et al. 2007c[126]	ASE 10 RIS 6 PBO	60 60 62	6	n.i.	Acute schizophrenia (DSM-IV)
Prien and Cole 1968a[127]	CPZ 300 [2000] PBO	208 [210] 212	8	17.4	Chronic schizophrenia (clinical diagnosis)
Ramu 1999[128]	CPZ 250 (-300) PBO [Tagara (Ayurveda) Brahmadiyoga]	27 27 27 27	8	n.i.	Acute schizophrenia (clinical diagnosis)
Ramu 1999a[129]	CPZ 375 (-450) PBO [Brahmadiyoga]	22 20 15	8	4.65	Chronic schizophrenia (clinical diagnosis)
Rappaport et al. 1978[130]	CPZ n.i. (300-900) PBO	39 41	6	n.i.	Acute schizophrenia (clinical diagnosis)
Sakalis 1977[131]	CPZ 1000 PBO	33 17	4	n.i.	Acute schizophrenia(RDC criteria)
Sandison 1960[132]	THIOR 300 PBO	8 7	12	5.5	Schizophrenia (relapsing, clinical diagnosis)
Saretsky 1966[133]	CPZ 100 PBO	20 20	13	n.i.	Schizophrenic reaction (clinical diagnosis)
Scanlan 1963[134]	CHLOR 300 PBO	n.i.	12	n.i.	Chronic schizophrenia (clinical diagnosis)
Schmidt 2012 [135]	OLA 15 PBO	93 101	12	10.8	Acute schizophrenia (DSM-IV)
Selman et al. 1976[136]	HAL 8.8 (4-12) PBO LOX 110 (50-150)	29 29 29	12	n.i.	Acute schizophrenia, acute exazerbation of chronic schizophrenia (clinical diagnosis made independently by 2 psychiatrists)

Serafetinides et al.1972[137]	CPZ 830 (-1000) HAL 12.3 (-15) PBO Clopenthixol 205(50-250)	14 14 14 15	12	14.7	Chronic schizophrenia (clinical diagnosis)
Shen 2014[138]	OLA 15 PBO	77 78	6	n.i.	Acute schizophrenia (DSM-IV-TR)
Shepherd 1956[139]	CPZ 300 PBO	8 16	6	n.i.	Severe schizophrenia (clinical diagnosis)
Simpson 1974[140]	HAL (6;30) PBO	16 8	14	12	Chronic schizophrenia (clinical diagnosis)
Sittampalan 1962[141]	PROC 150 PBO	9 9	12	n.i.	Chronic schizophrenia (clinical diagnosis)
Small et al. 1997[142]	QUE 360 (250-750) [<250] PBO	96 [94] 96	6	15	Acute exacerbation of (sub-) chronic schizophrenia (DSM-III-R)
Somerville 1960[143]	CPZ 472 (200-800) THIOR 472 (200-800) PBO	15 15 30	6	9.32	Schizophrenia or Paraphrenia (clinical diagnosis)
Spohn et al. 1977[144]	CPZ n.i. (≥ 200) PBO	20 20	8	≥ 2	Chronic schizophrenia (clinical diagnosis)
Study 049[145]	LURA 40; 80 [20] HAL 10 PBO	69; 71 [71] 73 72	6	n.i.	Schizophrenia (DSM-IV)
Study 115 2000[146]	ZIP 120; 200 [40] HAL 15 PBO	78; 86 [87] 85 83	6	n.i.	Acute exacerbation of schizophrenia or schizoaffective disorder (DSM-III-R)
Study 3000[147] (Potkin 2008a)	ILO 12 [4; 8] HAL 15 PBO	124 [121; 125] 124 127	6	15.6	Acute or subacute exacerbation of schizophrenia or schizoaffective disorder (DSM-IV)
Study 3004[147] (Potkin 2008b)	ILO (10-16) [4-8] RIS 7.0 (4-8) PBO	154 [153] 153 156	6	n.i.	Acute or subacute exacerbation of schizophrenia or schizoaffective disorder (DSM-IV)
Study 3005[147] (Potkin 2008c)	ILO 12-16; 20-24 RIS 7.1 (6-8) PBO	244; 145 157 160	6	n.i.	Acute or subacute exacerbation of schizophrenia or schizoaffective disorder (DSM-IV)
Study 93202[148]	ARI 30 (5-30) HAL 20 (5-20) PBO	34 34 35	4	n.i.	Schizophrenia with acute relapse (DSM-III-R)
Study 94202[149]	ARI 10; 30 [2] HAL 10 PBO	61; 60 [59] 63 64	4	n.i.	Schizophrenia with acute relapse (DSM-IV)
Study RGH-MD-03 Durgam et al. 2016[150]	CAR 1.5-4.5; [6-12] PBO	128; [134] 130	6	17.5	Schizophrenia (DSM-IV-TR)
Study RGH-MD-05 Kane et al. 2015[151]	CAR 3-6; [6-9] PBO	151[148] 147	6	11.5	Schizophrenia (DSM-IV-TR)

Study RIS-USA-72 1996[152]	RIS 4; 8 PBO	85; 78 83	4	n.i.	Chronic or subchronic schizophrenia (DSM-III-R)
Swanson 2005[153]	OLA 15 [SB-773812 60] PBO	n.i.	12	n.i.	Acute schizophrenia (n.i.)
Tetreault 1969[154]	FLUPH 22 (10-30) PBO	11 11	12	n.i.	Chronic schizophrenia (clinical diagnosis)
Tetreault et al. 1969a[155]	CPZ 539 (fixed titration schedule) PBO [TPS-23]	15 15 [15]	12	n.i.	Chronic schizophrenia (clinical diagnosis)
Tzimos et al. 2008[156]	PAL 8.4 (3-12) PBO	76 38	6	34.3	Acute episode of schizophrenia (DSM-IV)
Van der Felde 1975[157]	LOX 103 (100-150) THIOT 50 (40-60) PBO	26 28 28	6		Acute exacerbation of schizophrenia (clinical diagnosis)
Van Kammen 1996[158]	SER 12; 20 [8] PBO	51; 54 [52] 48	6	14	Schizophrenia, history of a previous response to antipsychotic drugs (DSM-III-R)
Vichaiya 1971[159]	HAL 4.5 (n.i.) PBO	15 15	6	n.i.	Chronic schizophrenia (clinical diagnosis)
Walsh 1959[160]	CPZ 255 (-300) TRIFLUPR (-300) PBO	22 22 22	8	n.i.	Chronic schizophrenia (clinical diagnosis)
Wolpert 1968[161]	THIOT 10 (-60) THIOR 200 (-1200) PBO	35 29 28	31	n.i.	Chronic schizophrenia (clinical diagnosis)
Wyeth 2005[162]	OLA 15 [SCA-136 (200;400)] PBO	n.i.	6	n.i.	Schizophrenia (n.i.)
Zborowski et al. 1995[163]	SER 20 [SER 24] HAL 16 PBO	117 [113] 115 116	8	15	Schizophrenia (DSM-III-R or DSM-IV)
Zimbroff et al. 1997[164]	SER 12; 20 [SER 24] HAL 4; 8; 16 PBO	76; 68 [72] 71; 67; 70 73	8	16	Schizophrenia, history of a previous response to antipsychotic drugs (DSM-III-R or DSM-IV)

n= number of patients, AMI = Amisulpride, ARI = Aripiprazole, ASE = Asenapine, BLO = Blonanserin, BRE = Brexpiprazol, BUTA = Butaperazine, CAR = Cariprazine, CARP = Carphenazine, CLO = Clozapine, CLOP = Clopenthixol, CPZ = Chlorpromazine, FLUPH = Fluphenazine, HAL = Haloperidol, ILO = Iloperidone, LEV= Levomepromazine, LOX = Loxapine, LUR = Lurasidone, MEL = Melperone, MOL = Molindone, OLA = Olanzapine, PAL = Paliperidone, PERPH = Perphenazine, PIP = pipothiazine, PROC = Prochlorpromazine, QUE = Quetiapine, RES = Reserpine, RIS = Risperidone, SER = Sertindole, TIOS = Tiospirone, THIOR = thioridazine, THIOT = Thiothixene, TRIFLU = Trifluperazine, TRIFLUP = Trifluperidol, TRIFLUPR=Triflupromazine, ZIP = Ziprasidone, ZOT=Zotepine, PBO= Placebo, ICD 9/10 = International Classification of Diseases, 9th/10th Revision, DSM-III, -III-R, -IV = different versions of the Diagnostic and Statistical Manual of Mental Disorders, n.i. = not indicated, IR= immediate release, XR= extended release

[drug groups or numbers in squared brackets were not used in any analysis, neither the primary one nor in a sensitivity analysis]

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The number of references is lower than the number of included studies, because some publications reported on two or more studies

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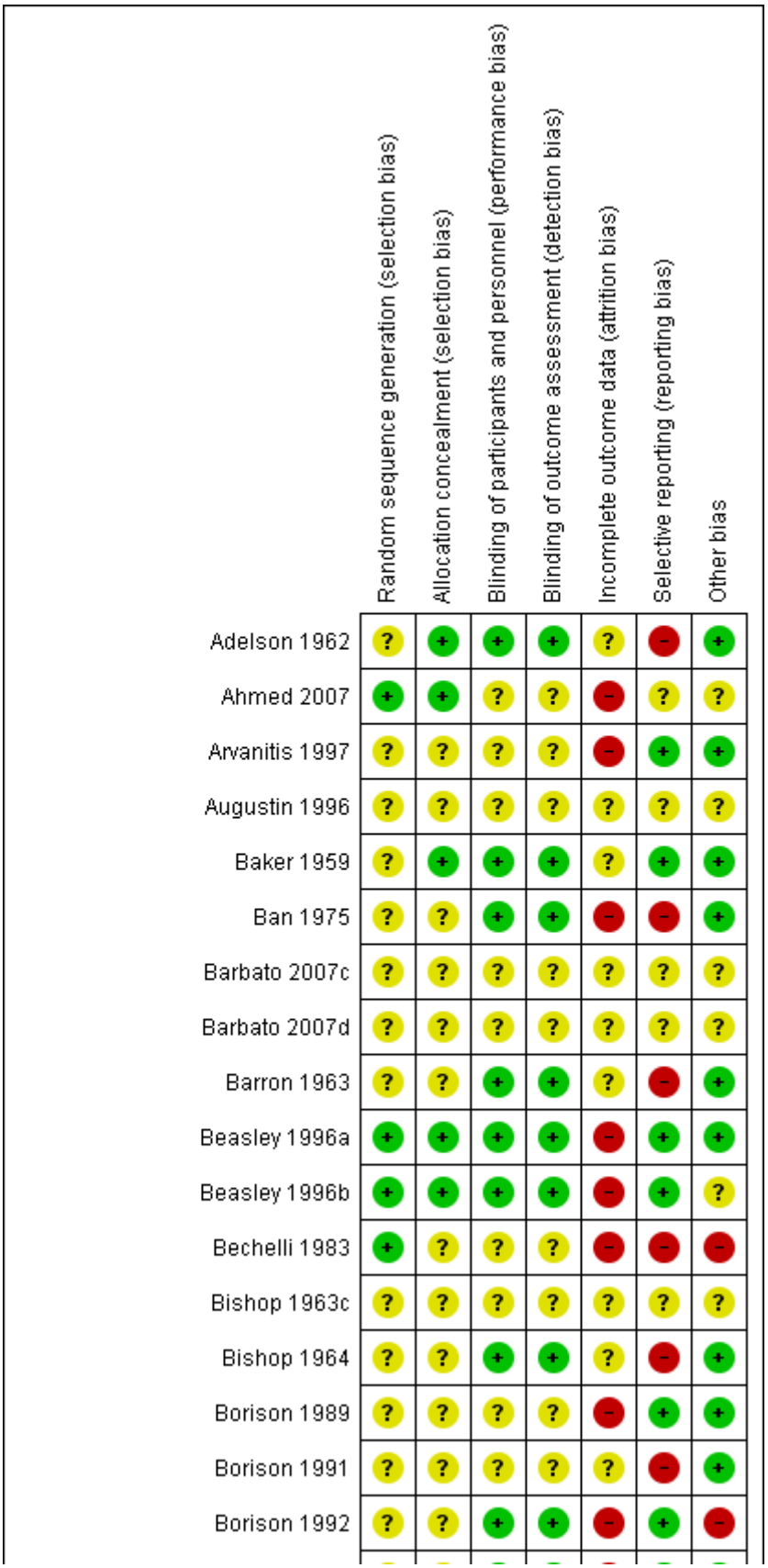
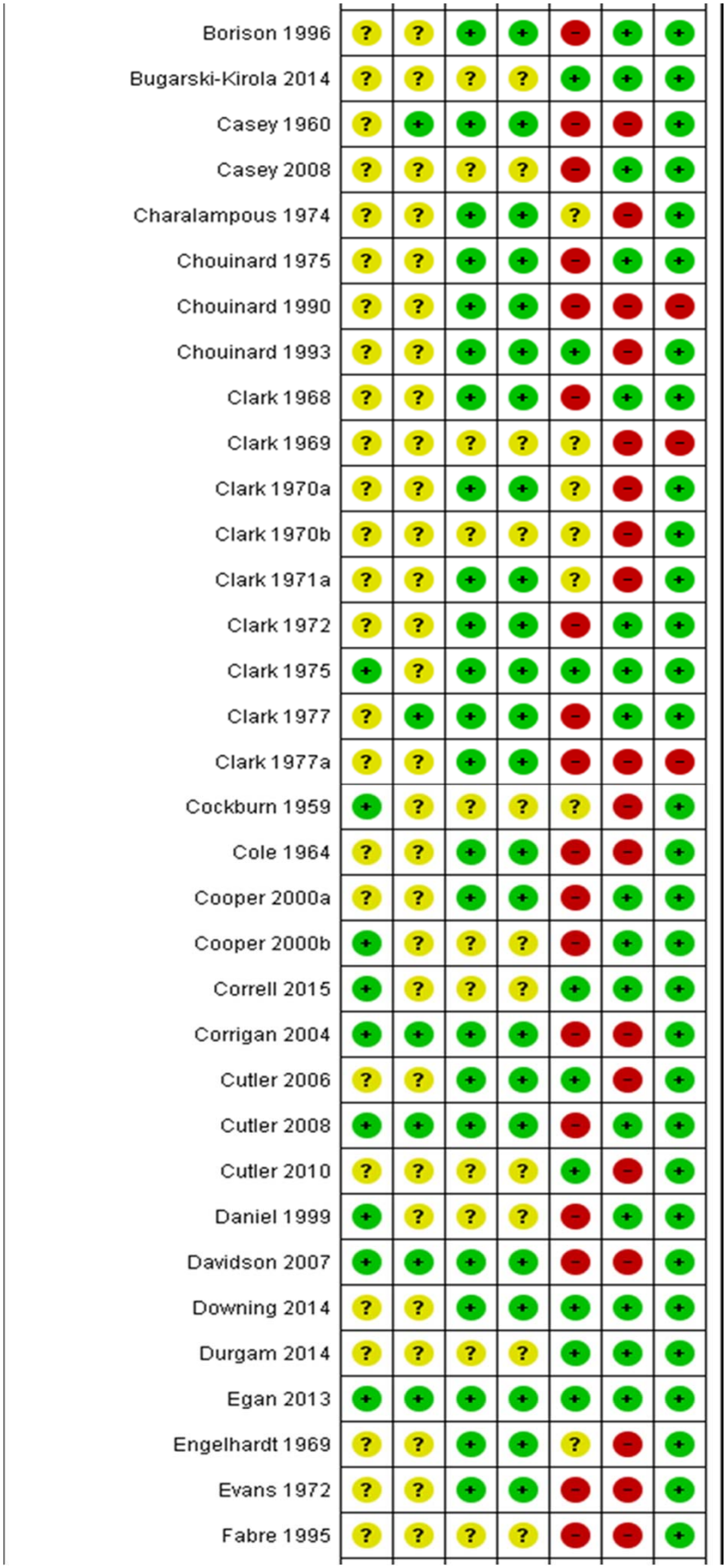
Supplementary Table S5

Assessment with the Cochrane risk of bias tool

Table S5a: Risk of bias summary: judgements about each bias item for each study

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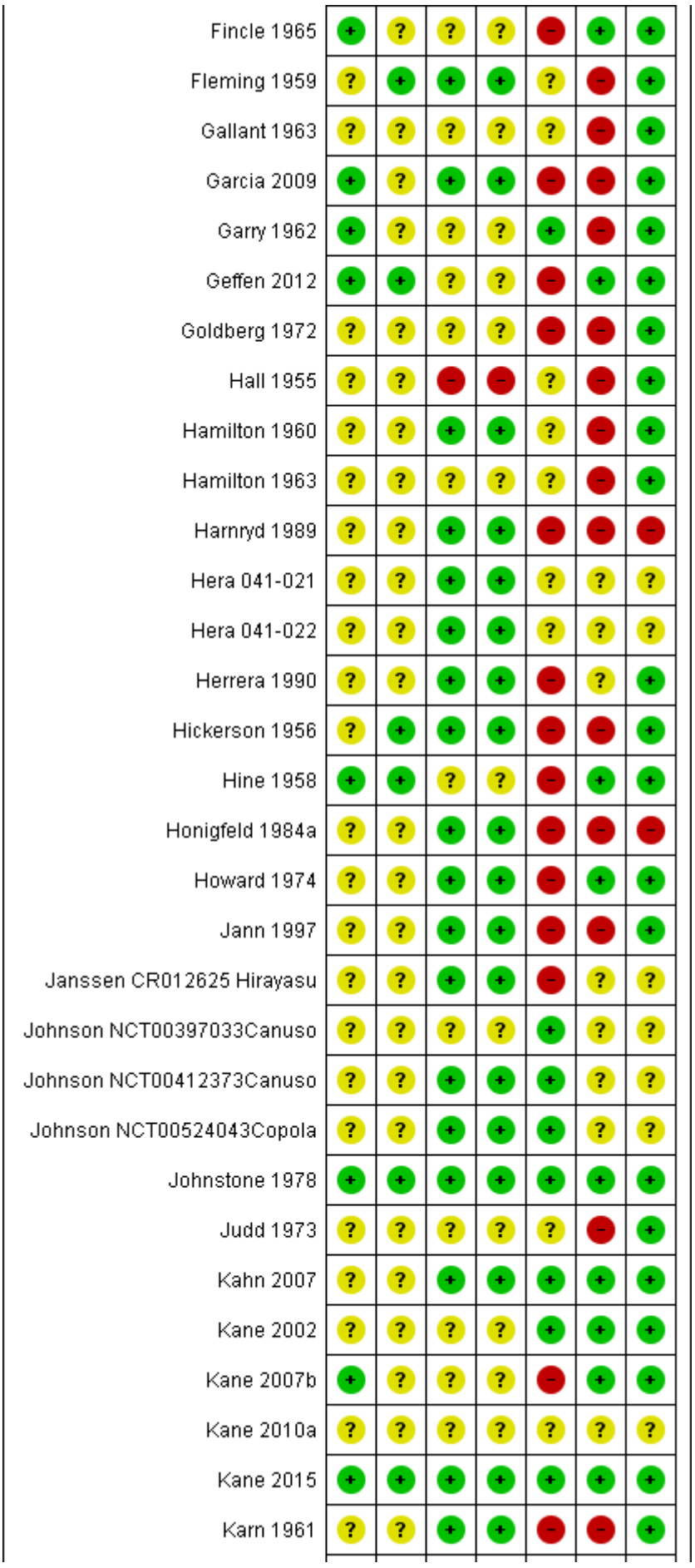
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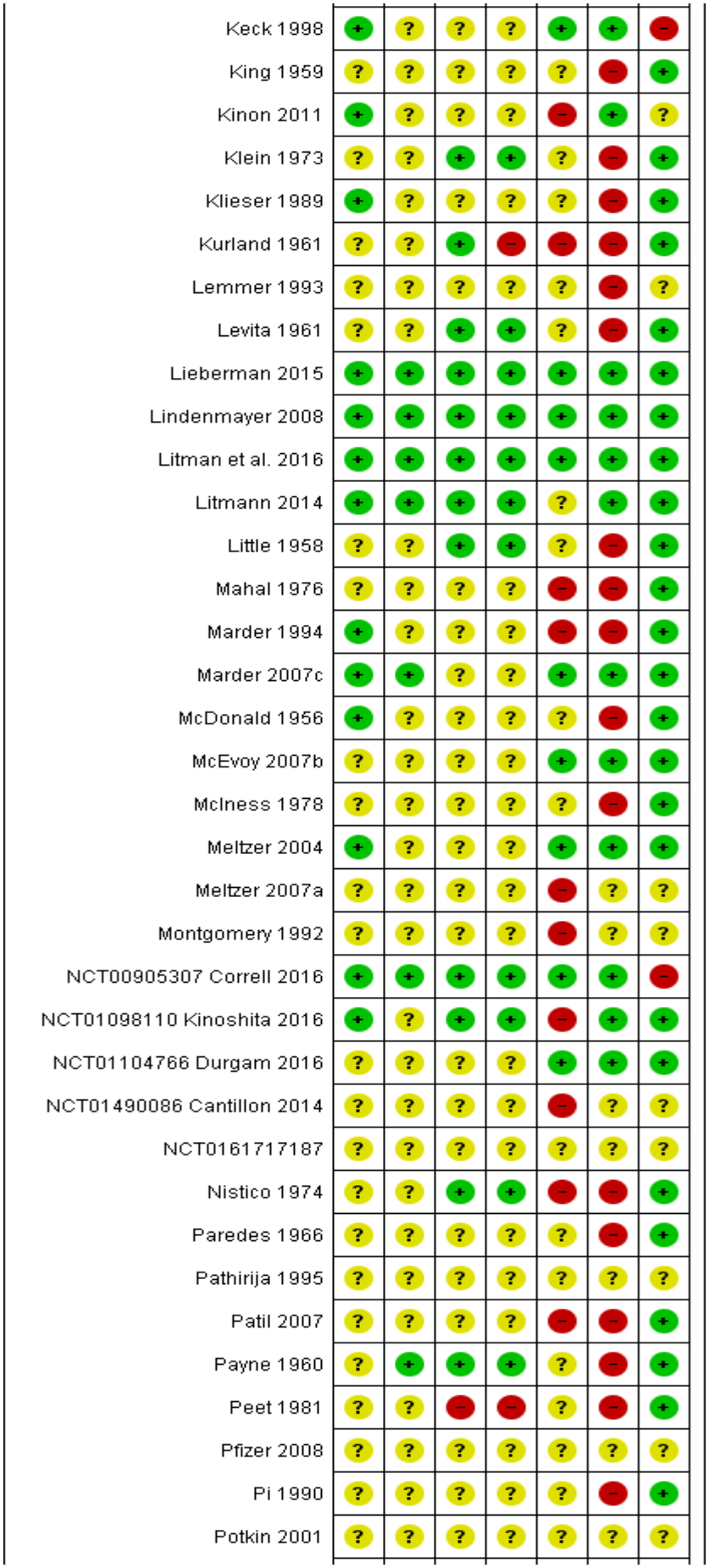
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Marder 1994
Marder 2007c
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McEvoy 2007b
McIness 1978
Meltzer 2004
Meltzer 2007a
Montgomery 1992
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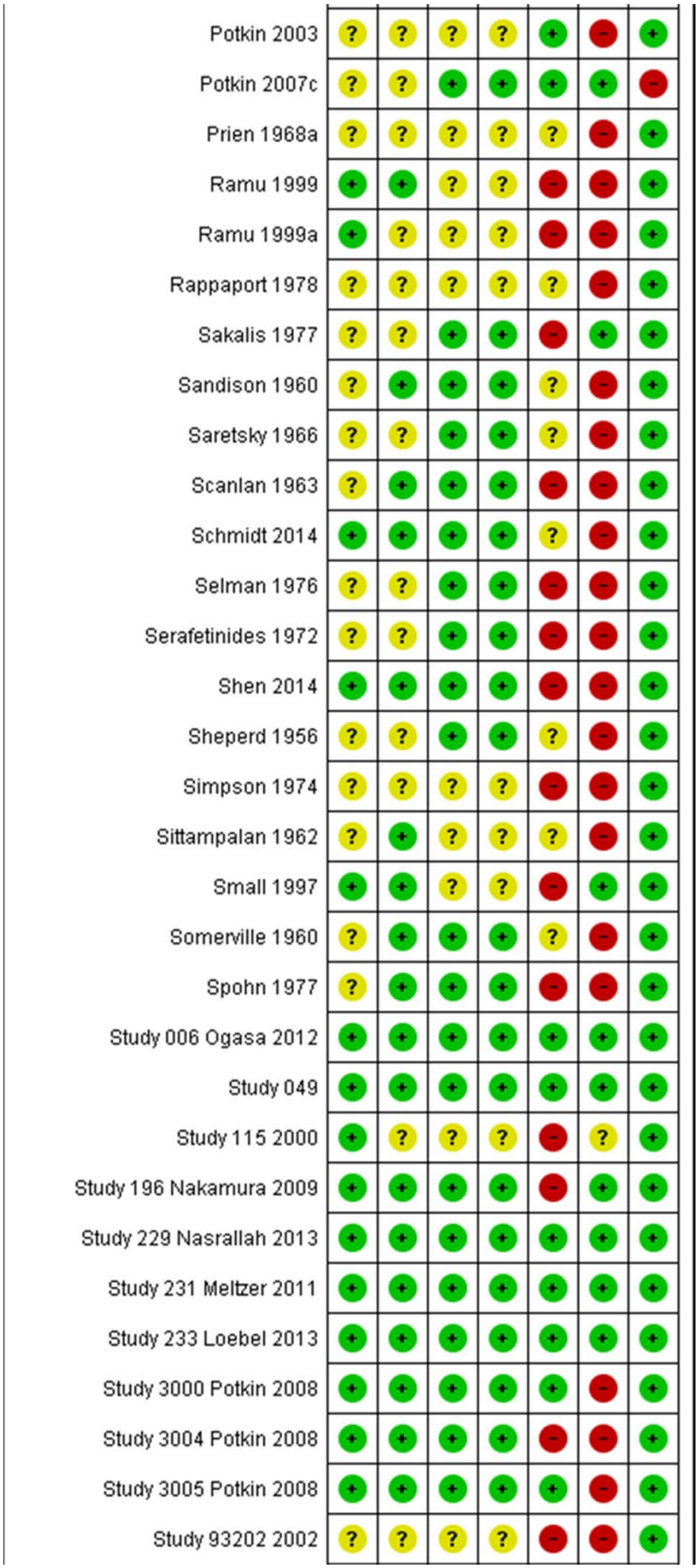
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Study 231 Meltzer 2011
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Study 3005 Potkin 2008
Study 93202 2002

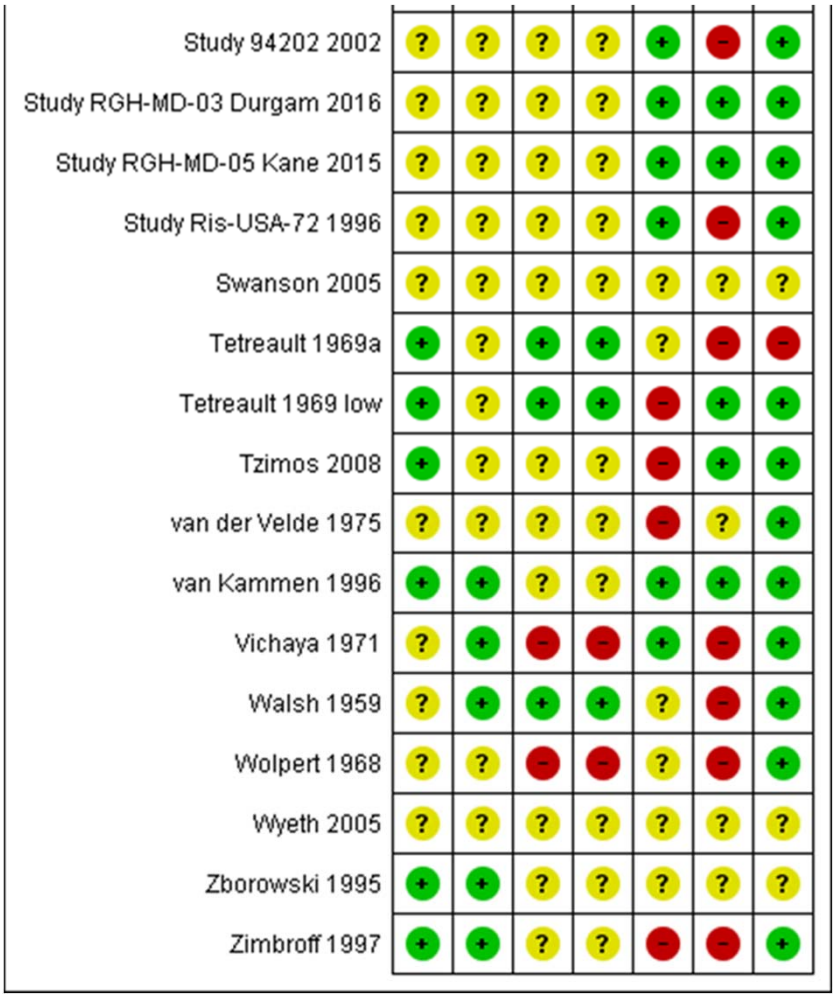
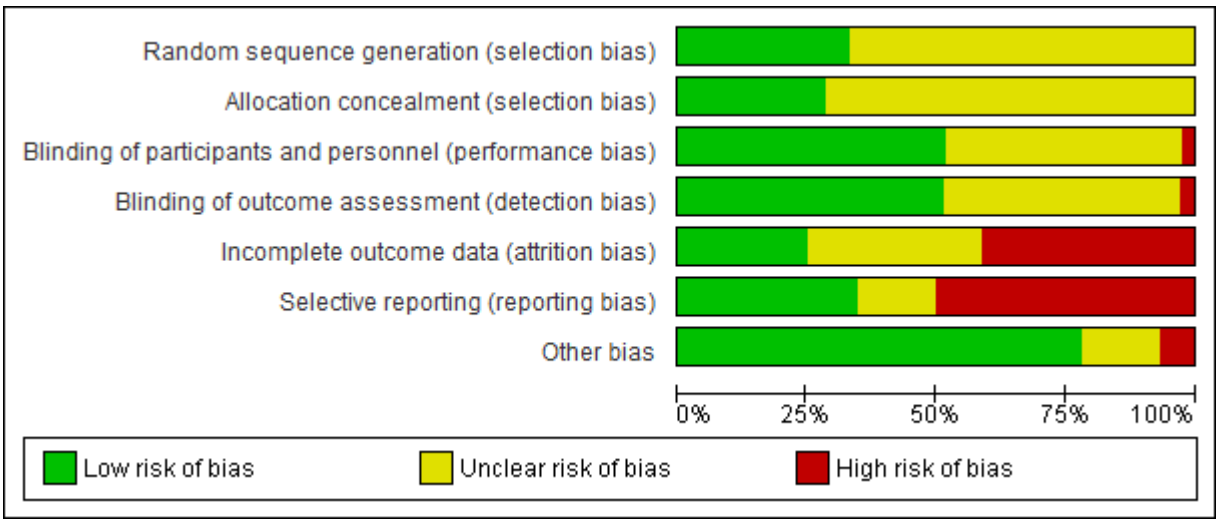


Table S5b: Risk of bias graph: review authors' judgements (Low, Unclear and High) about each risk of bias item presented as percentages across all included studies**.**



Supplementary Table S6

Individual response criteria and Odds Ratios

Table S6a: Combined response criteria

All studies (preferred criterion ≥50% PANSS/BPRS reduction or CGI at least much improved, but authors' criteria were used when not available)			**≥20% PANSS/BPRS reduction or CGI at least minimally better**			**≥50% PANSS/BPRS reduction or CGI at least much improved**		
Drug N n %	PBO N n %	RR/OR/RD/NNT (95% CrI), I^2	Drug N n %	PBO N n %	RR/OR/RD/NNT (95% CrI), I^2	Drug N n %	PBO N n %	RR/OR/RD/NNT (95% CrI), I^2
97 13382 **34%** **(30%,39%)**	97 6780 **19%** **(16%,21%)**	OR: 2.79 (2.40,3.31) RR: 1.94 (1.76,2.18) RD: 0.17 (0.14,0.20) NNT: 6 (5,7) I^2 for OR: 69% (55%,80%)	46 5878 **51%** **(45%,57%)**	46 3040 **30%** **(27%,34%)**	OR: 2.87 (2.43,3.47) RR: 1.75 (1.59,1.97) RD: 0.22 (0.19,0.26) NNT: 5 (4,5) I^2 for OR: 55% (30%,73%)	38 5689 **23%** **(17%,31%)**	38 2714 **13%** **(9%,16%)**	OR: 2.59 (2.06,3.40) RR: 1.96 (1.65,2.44) RD: 0.13 (0.09,0.17) NNT: 8 (6-11) I^2 for OR: 61% (34%,80%)

N= number of studies, n=number of total participants, %=percentage of responders, PANSS = Positive and Negative Syndrome Scale[1], BPRS = Brief Psychiatric Rating Scale[2], CGI = Clinical Global Impression Scale[3], RR = relative risk, OR = odds ratio, RD = absolute risk difference, NNT = number needed to treat (NNTs were calculated as the inverse of the risk differences and rounded up as it is the convention[4])

Table S6b: Individual response criteria

≥20% PANSS/BPRS reduction			**CGI at least minimally better**			**≥50% PANSS/BPRS reduction**			**CGI at least much better**		
Drug N n %	PBO N n %	RR/OR/RD/NNT (95% CrI), I^2	Drug N n %	PBO N n %	RR/OR/RD/NNT (95% CrI), I^2	Drug N n %	PBO N n %	RR/OR/RD/NNT (95% CrI), I^2	Drug N n %	PBO N n %	RR/OR/RD/NNT (95% CrI), I^2
23 4138 **53%** **(48%,59%)**	23 2168 **34%** **(30%,** **37%)**	OR: 2.44 (2.09,2.89) RR: 1.59 (1.47,1.75) RD: 0.20 (0.17,0.24) NNT: 5 (4-6) I^2 for OR: 41% (5%,71%)	26 2231 **49%** **(39%,** **61%)**	26 1126 **27%** **(21%,** **33%)**	OR: 3.60 (2.65,5.12) RR: 1.99 (1.64,2.50) RD: 0.24 (0.18,0.31) NNT: 4 (3-5) I^2 for OR: 58% (28%,79%)	14 2960 **23%** **(16%,** **32%)**	14 1414 **14%** **(10%,19%)**	OR: 2.09 (1.69,2.60) RR: 1.71 (1.45,2.13) RD: 0.10 (0.07,0.13) NNT: 10 (8-14) I^2 for OR: 13% (0,64%)	23 2707 **22%** **(14%,** **34%)**	23 1280 **11%** **(7%,** **17%)**	OR: 3.10 (2.06,5.22) RR: 2.20 (1.62,3.36) RD: 0.14 (0.08,0.20) NNT: 7 (5-13) I^2 for OR: 72% (44%,89%)

N= number of studies, n=number of total participants, %=percentage of responders, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impression Scale, RR = relative risk, OR = odds ratio, RD = absolute risk difference, NNT = number needed to treat (NNTs were calculated as the inverse of the risk differences and rounded up as it is the convention)

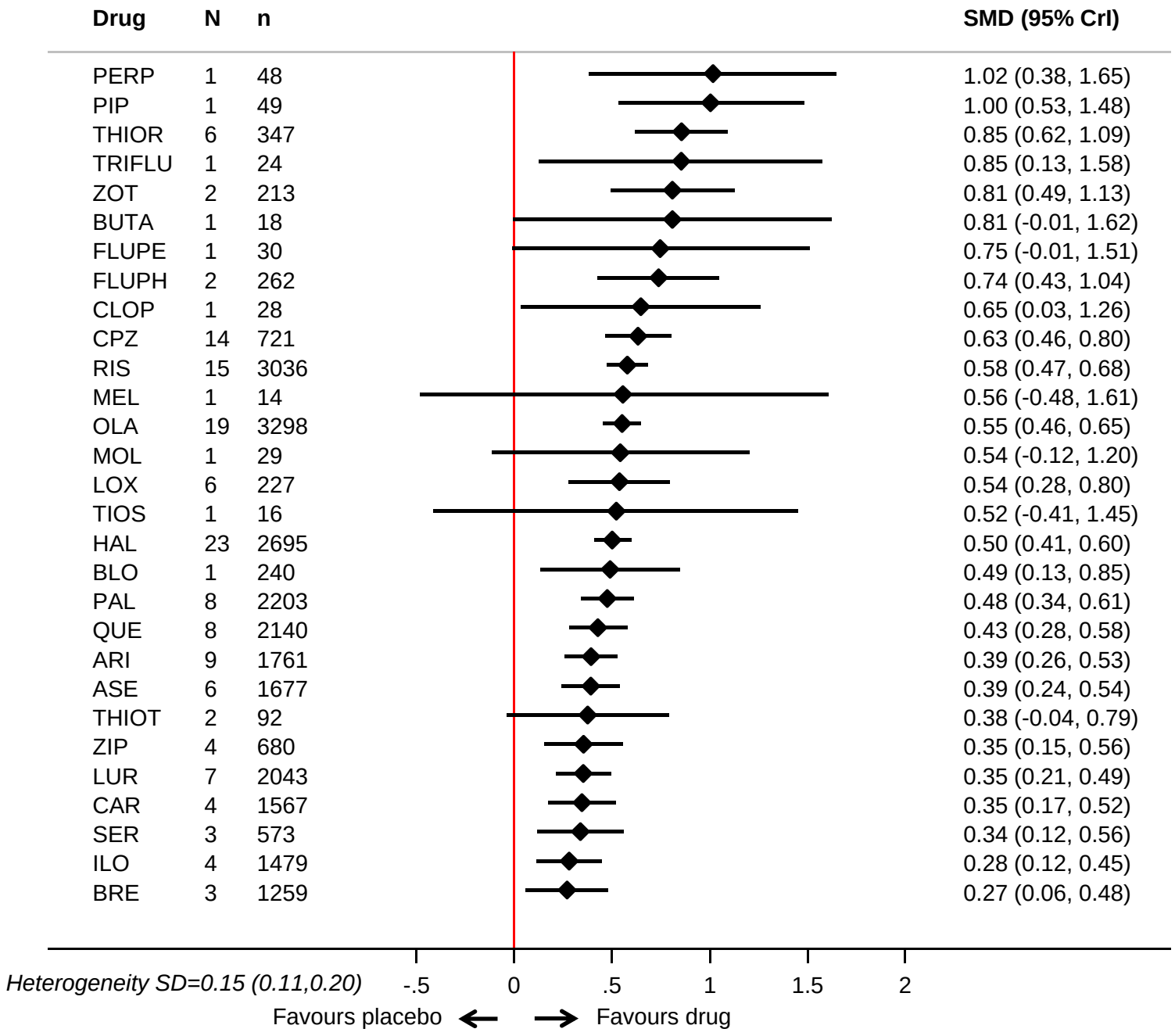
References

1. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. SchizophrBull 1987;13:261-75.
2. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. PsycholRep 1962;10:790-812.
3. Guy W. Clinical Global Impression. In: ECDEU assessment manual for psychopharmacology, revised (DHEW Publ No ADM 76-338). Rockville, MD: National Institute of Mental Health; 1976:218-22.
4. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Chichester, UK: Wiley and Sons; 2011.

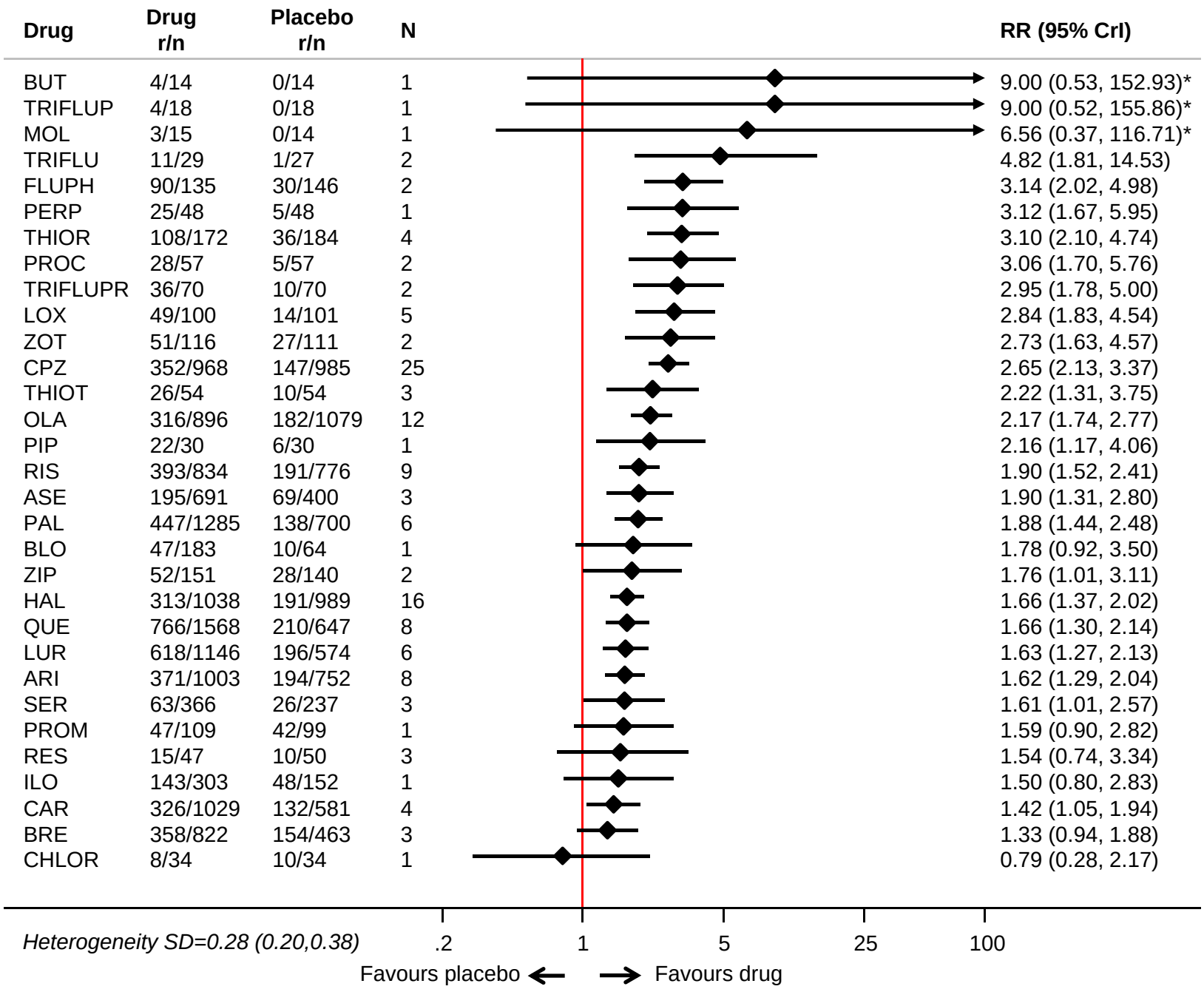
Supplementary Figure S2

Results of the individual drugs in the various outcomes

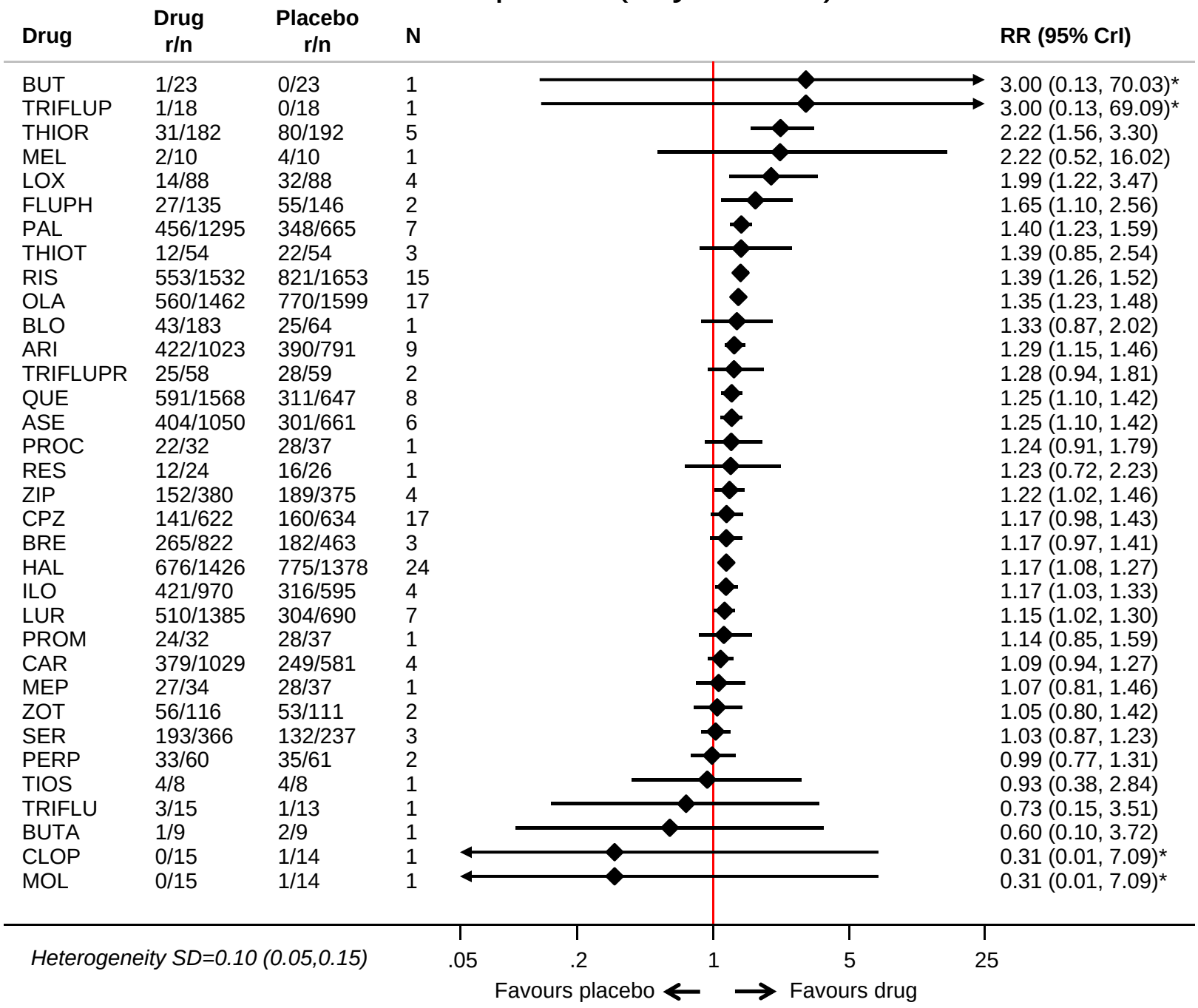
Overall efficacy



Response

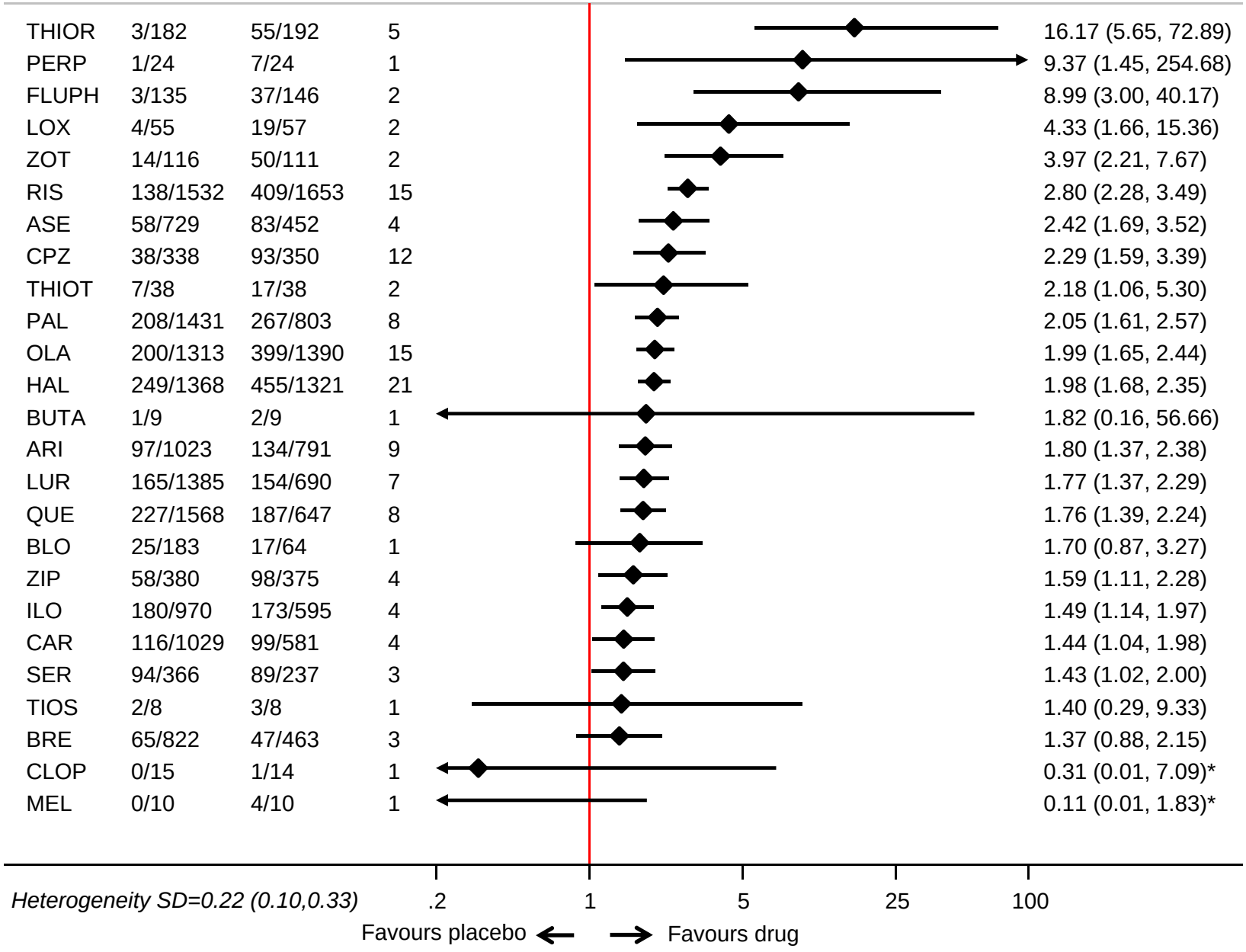

Drug
Drug r/n
Placebo r/n
N
RR (95% CrI)
BUT 4/14 0/14 1 9.00 (0.53, 152.93)*
TRIFLUP 4/18 0/18 1 9.00 (0.52, 155.86)*
MOL 3/15 0/14 1 6.56 (0.37, 116.71)*
TRIFLU 11/29 1/27 2 4.82 (1.81, 14.53)
FLUPH 90/135 30/146 2 3.14 (2.02, 4.98)
PERP 25/48 5/48 1 3.12 (1.67, 5.95)
THIOR 108/172 36/184 4 3.10 (2.10, 4.74)
PROC 28/57 5/57 2 3.06 (1.70, 5.76)
TRIFLUPR 36/70 10/70 2 2.95 (1.78, 5.00)
LOX 49/100 14/101 5 2.84 (1.83, 4.54)
ZOT 51/116 27/111 2 2.73 (1.63, 4.57)
CPZ 352/968 147/985 25 2.65 (2.13, 3.37)
THIOT 26/54 10/54 3 2.22 (1.31, 3.75)
OLA 316/896 182/1079 12 2.17 (1.74, 2.77)
PIP 22/30 6/30 1 2.16 (1.17, 4.06)
RIS 393/834 191/776 9 1.90 (1.52, 2.41)
ASE 195/691 69/400 3 1.90 (1.31, 2.80)
PAL 447/1285 138/700 6 1.88 (1.44, 2.48)
BLO 47/183 10/64 1 1.78 (0.92, 3.50)
ZIP 52/151 28/140 2 1.76 (1.01, 3.11)
HAL 313/1038 191/989 16 1.66 (1.37, 2.02)
QUE 766/1568 210/647 8 1.66 (1.30, 2.14)
LUR 618/1146 196/574 6 1.63 (1.27, 2.13)
ARI 371/1003 194/752 8 1.62 (1.29, 2.04)
SER 63/366 26/237 3 1.61 (1.01, 2.57)
PROM 47/109 42/99 1 1.59 (0.90, 2.82)
RES 15/47 10/50 3 1.54 (0.74, 3.34)
ILO 143/303 48/152 1 1.50 (0.80, 2.83)
CAR 326/1029 132/581 4 1.42 (1.05, 1.94)
BRE 358/822 154/463 3 1.33 (0.94, 1.88)
CHLOR 8/34 10/34 1 0.79 (0.28, 2.17)
Heterogeneity SD=0.28 (0.20,0.38)
.2
1
5
25
100
Favours placebo
Favours drug

Drop-outs (any reason)



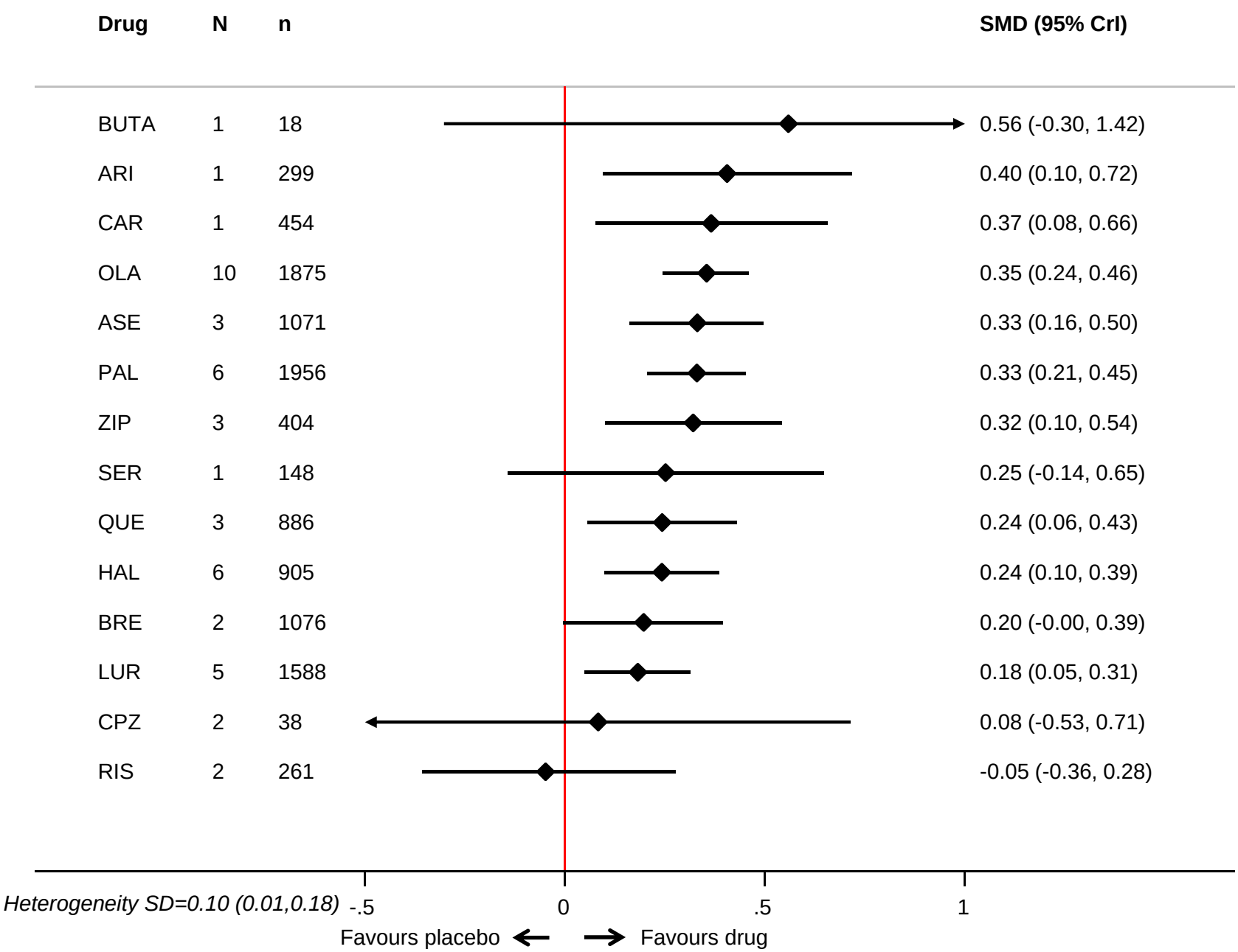
Drop-outs (inefficacy)

Drug	Drug r/n	Placebo r/n	N	RR (95% CrI)
THIOR	3/182	55/192	5	16.17 (5.65, 72.89)
PERP	1/24	7/24	1	9.37 (1.45, 254.68)
FLUPH	3/135	37/146	2	8.99 (3.00, 40.17)
LOX	4/55	19/57	2	4.33 (1.66, 15.36)
ZOT	14/116	50/111	2	3.97 (2.21, 7.67)
RIS	138/1532	409/1653	15	2.80 (2.28, 3.49)
ASE	58/729	83/452	4	2.42 (1.69, 3.52)
CPZ	38/338	93/350	12	2.29 (1.59, 3.39)
THIOT	7/38	17/38	2	2.18 (1.06, 5.30)
PAL	208/1431	267/803	8	2.05 (1.61, 2.57)
OLA	200/1313	399/1390	15	1.99 (1.65, 2.44)
HAL	249/1368	455/1321	21	1.98 (1.68, 2.35)
BUTA	1/9	2/9	1	1.82 (0.16, 56.66)
ARI	97/1023	134/791	9	1.80 (1.37, 2.38)
LUR	165/1385	154/690	7	1.77 (1.37, 2.29)
QUE	227/1568	187/647	8	1.76 (1.39, 2.24)
BLO	25/183	17/64	1	1.70 (0.87, 3.27)
ZIP	58/380	98/375	4	1.59 (1.11, 2.28)
ILO	180/970	173/595	4	1.49 (1.14, 1.97)
CAR	116/1029	99/581	4	1.44 (1.04, 1.98)
SER	94/366	89/237	3	1.43 (1.02, 2.00)
TIOS	2/8	3/8	1	1.40 (0.29, 9.33)
BRE	65/822	47/463	3	1.37 (0.88, 2.15)
CLOP	0/15	1/14	1	0.31 (0.01, 7.09)*
MEL	0/10	4/10	1	0.11 (0.01, 1.83)*

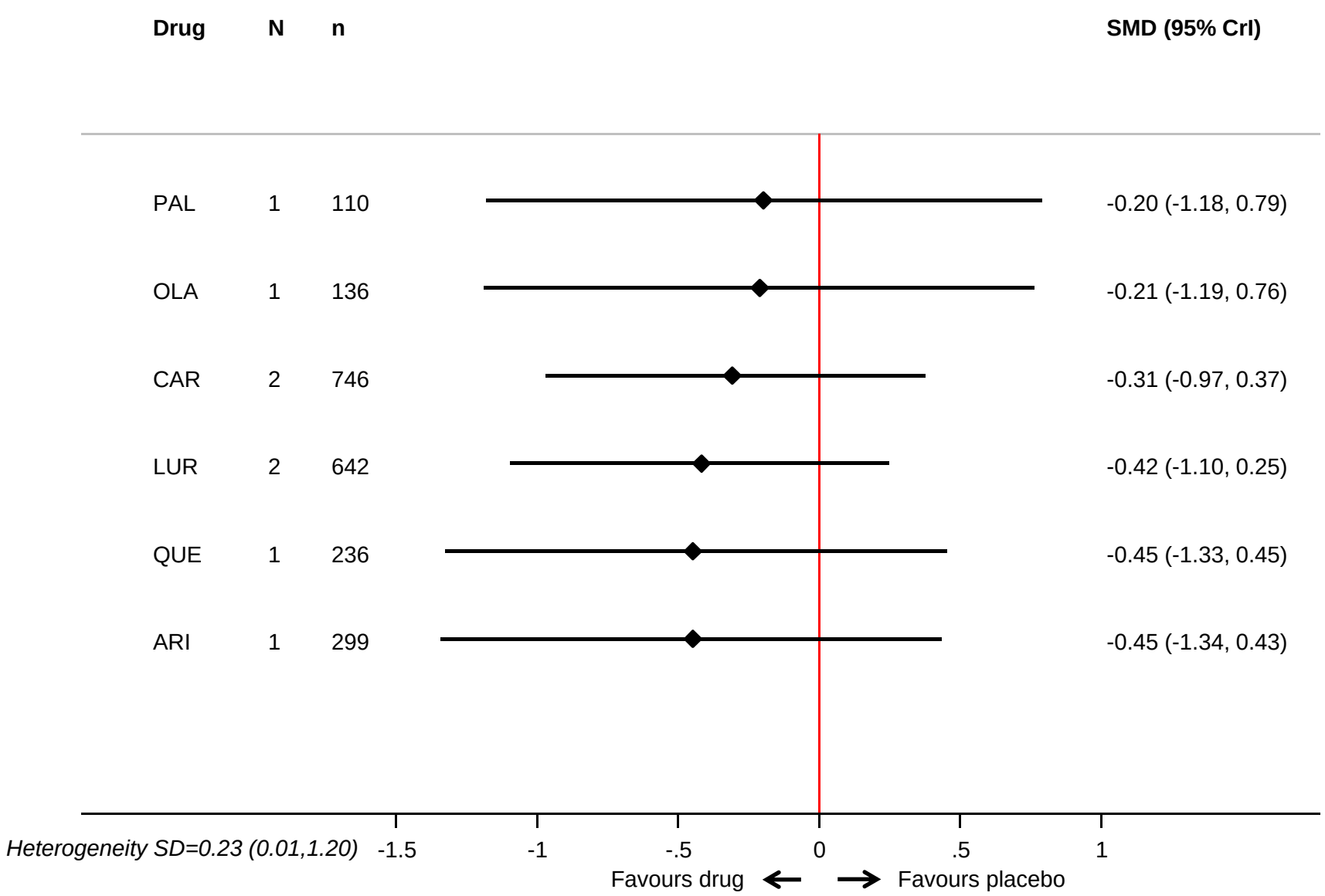


Heterogeneity SD=0.22 (0.10,0.33)

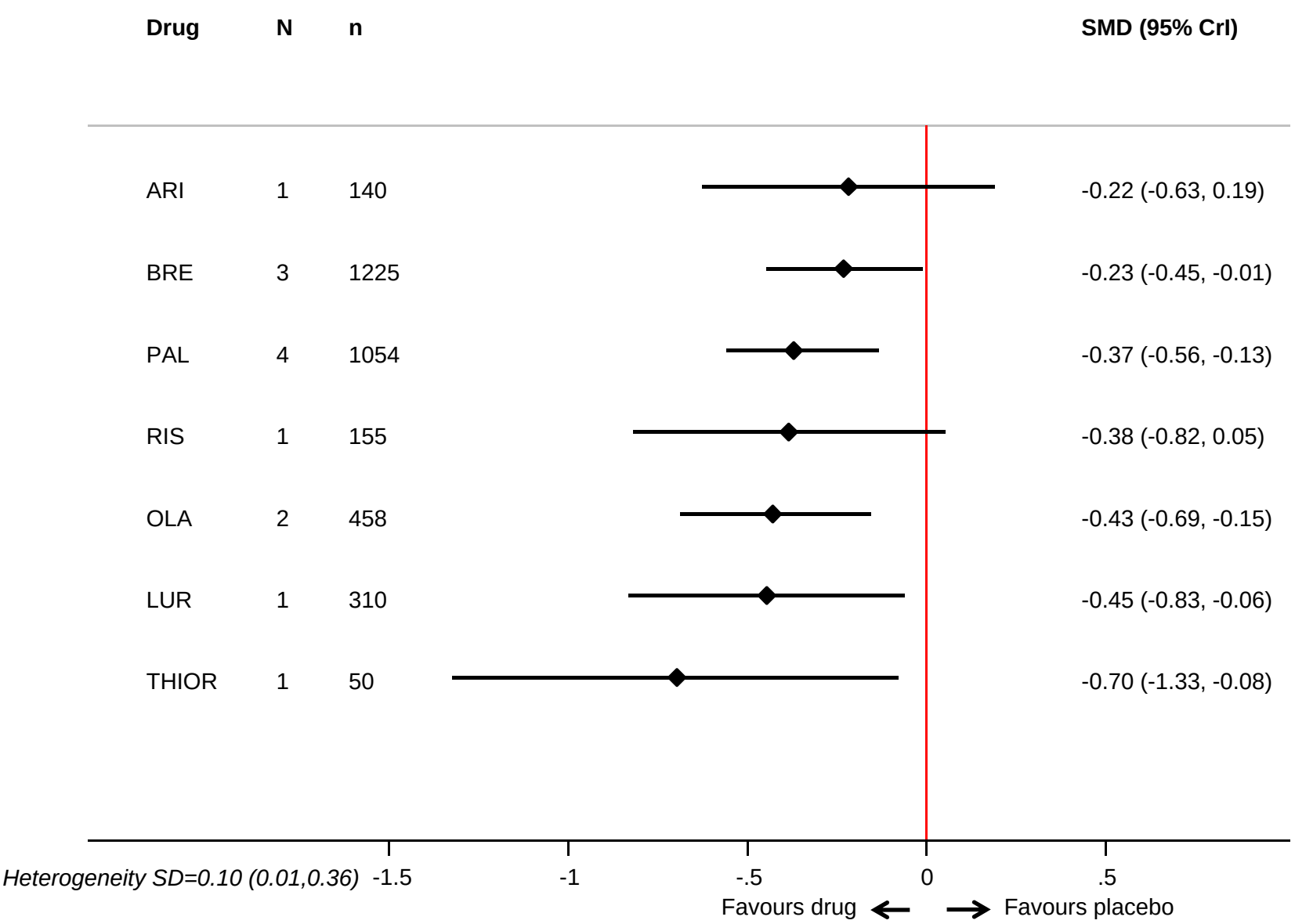
Depression


Drug
N
n
SMD (95% CrI)
BUTA 1 18 0.56 (-0.30, 1.42)
ARI 1 299 0.40 (0.10, 0.72)
CAR 1 454 0.37 (0.08, 0.66)
OLA 10 1875 0.35 (0.24, 0.46)
ASE 3 1071 0.33 (0.16, 0.50)
PAL 6 1956 0.33 (0.21, 0.45)
ZIP 3 404 0.32 (0.10, 0.54)
SER 1 148 0.25 (-0.14, 0.65)
QUE 3 886 0.24 (0.06, 0.43)
HAL 6 905 0.24 (0.10, 0.39)
BRE 2 1076 0.20 (-0.00, 0.39)
LUR 5 1588 0.18 (0.05, 0.31)
CPZ 2 38 0.08 (-0.53, 0.71)
RIS 2 261 -0.05 (-0.36, 0.28)
Heterogeneity SD=0.10 (0.01,0.18)
-.5
0
.5
1
Favours placebo
Favours drug

Quality of life

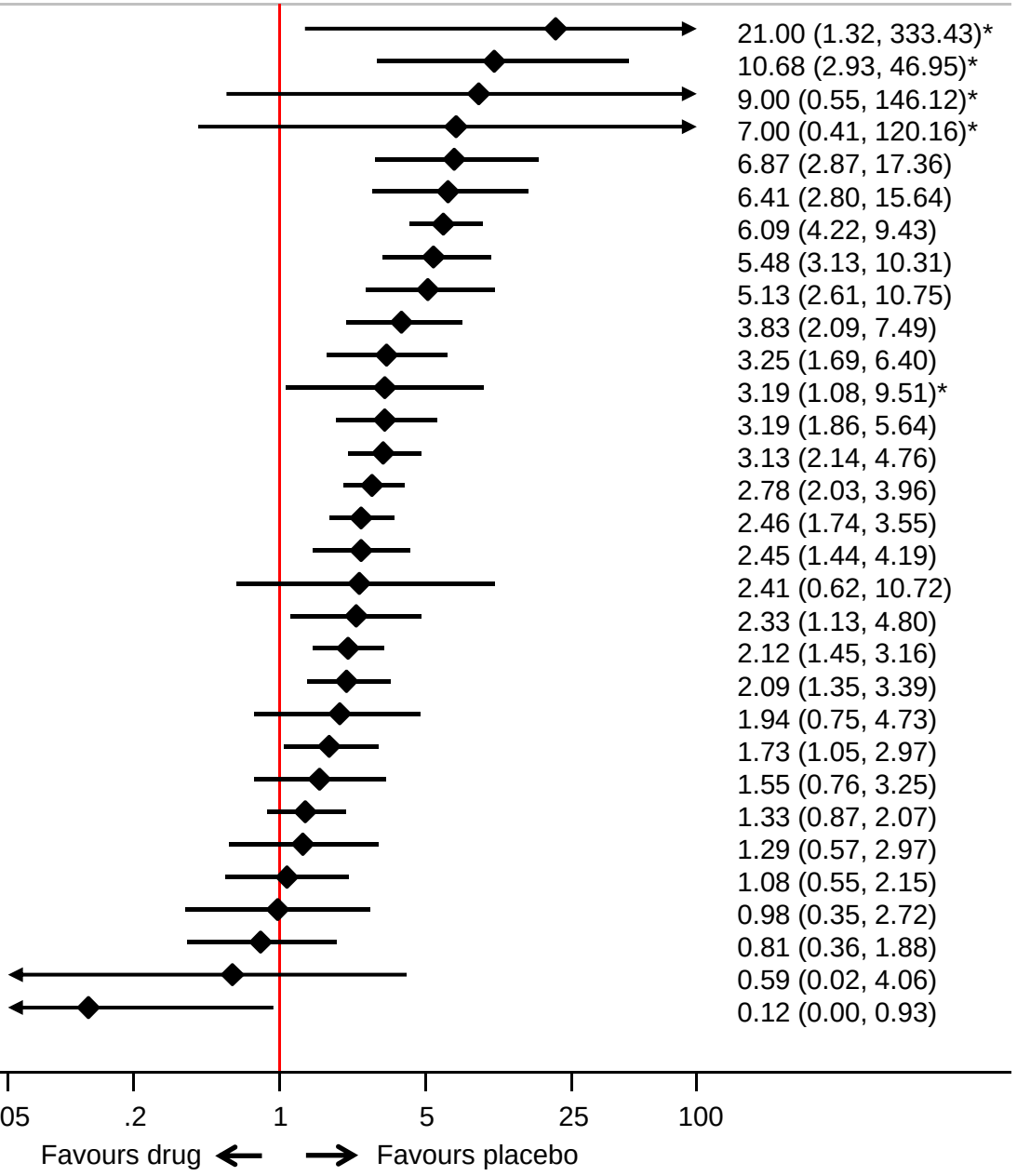


Social functioning



Sedation

Drug	Drug r/n	Placebo r/n	N	RR (95% CrI)
TRIFLUP	10/18	0/18	1	21.00 (1.32, 333.43)*
TRIFLUPR	6/29	0/29	2	10.68 (2.93, 46.95)*
BUTA	4/9	0/9	1	9.00 (0.55, 146.12)*
MEL	3/10	0/10	1	7.00 (0.41, 120.16)*
CLOP	10/15	2/14	1	6.87 (2.87, 17.36)
BUT	17/37	3/37	2	6.41 (2.80, 15.64)
CPZ	258/610	51/639	18	6.09 (4.22, 9.43)
THIOR	62/156	11/184	4	5.48 (3.13, 10.31)
ZOT	44/116	9/111	2	5.13 (2.61, 10.75)
LOX	33/120	7/120	6	3.83 (2.09, 7.49)
FLUPH	37/135	11/146	2	3.25 (1.69, 6.40)
TRIFLU	7/29	0/27	2	3.19 (1.08, 9.51)*
ASE	75/751	16/462	4	3.19 (1.86, 5.64)
QUE	272/1568	46/647	8	3.13 (2.14, 4.76)
OLA	183/1008	64/1179	13	2.78 (2.03, 3.96)
HAL	108/801	49/747	12	2.46 (1.74, 3.55)
ZIP	77/380	26/375	4	2.45 (1.44, 4.19)
BLO	8/183	2/64	1	2.41 (0.62, 10.72)
RES	10/10	4/10	1	2.33 (1.13, 4.80)
RIS	113/989	49/1103	10	2.12 (1.45, 3.16)
LUR	118/1245	24/618	6	2.09 (1.35, 3.39)
THIOT	10/65	6/63	3	1.94 (0.75, 4.73)
ARI	66/776	23/539	6	1.73 (1.05, 2.97)
SER	32/249	16/121	2	1.55 (0.76, 3.25)
PAL	95/1215	36/708	7	1.33 (0.87, 2.07)
ILO	38/303	12/152	1	1.29 (0.57, 2.97)
CAR	36/566	18/281	2	1.08 (0.55, 2.15)
CHLOR	12/52	12/51	1	0.98 (0.35, 2.72)
BRE	19/822	14/463	3	0.81 (0.36, 1.88)
MOL	1/15	1/14	1	0.59 (0.02, 4.06)
PERP	1/24	6/24	1	0.12 (0.00, 0.93)



Heterogeneity SD=0.35 (0.12,0.56)

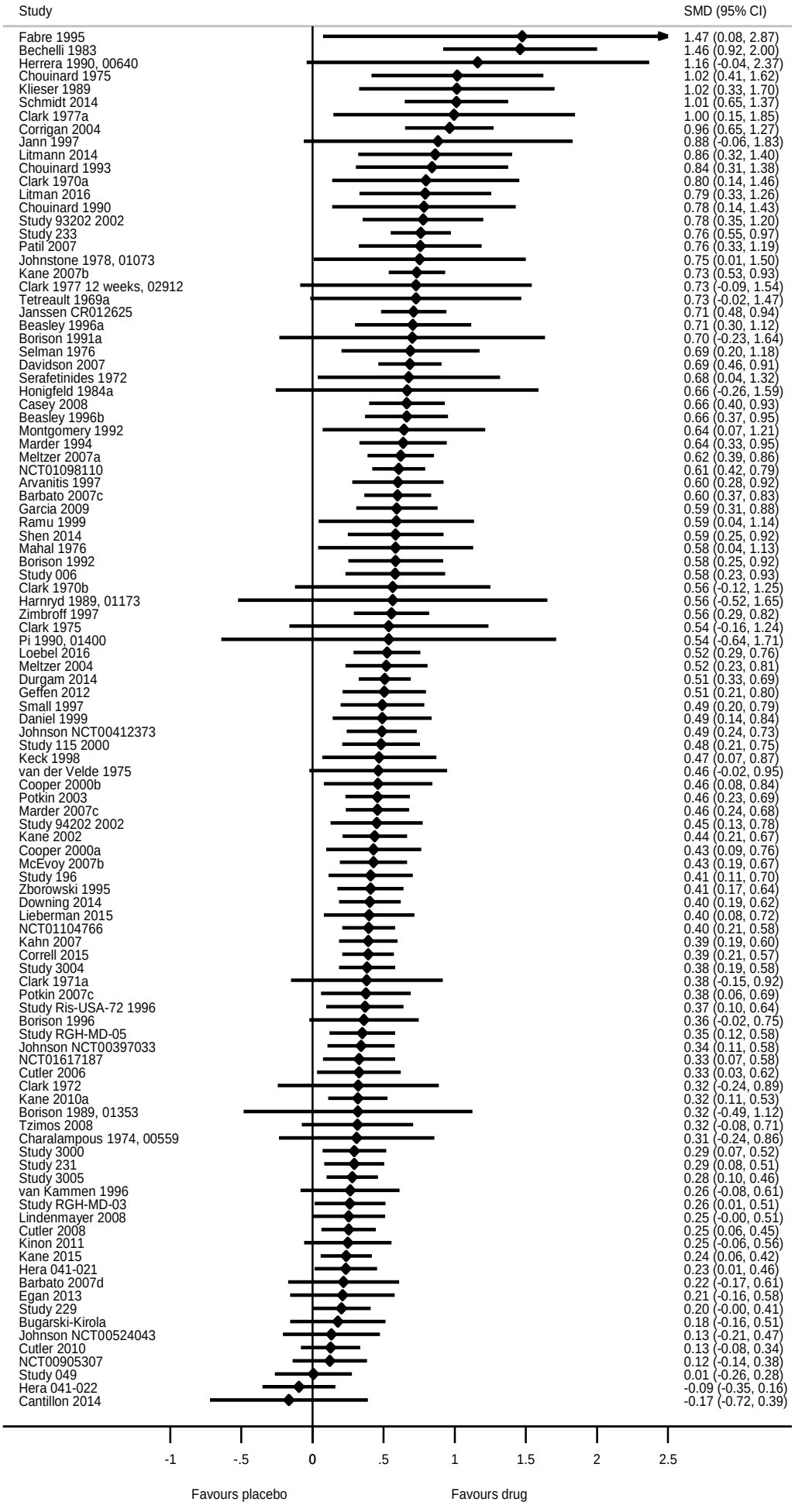
Abbreviations: N = number of trials, n = number of participants, r = number of participants with an event, RR = relative risk, SMD = standardized mean difference, SD = standard deviation, CrI = credible interval, ARI = aripiprazole, ASE = asenapine, BLO = blonanserine, BRE = brexpiprazole, BUTA = butaperazine, CAR = cariprazine, CHLOR = chlorprothixene, CLOP = clopenthixol, CPZ = chlorpromazine, FLUPE = flupenthixol, FLUPH = fluphenazine, HAL = haloperidol, ILO = iloperidone, LOX = loxapine, LUR = lurasidone, MEL = melperone, MOL = molindone, OLA = olanzapine, PAL = paliperidone, PERP = perphenazine, PIP = pipothiazine, QUE = quetiapine, RES = reserpine, RIS = risperidone, SER = sertindole, THIOT = thiothixene, THIOR = thioridazine, TIOS = tiospirone, TRIFLU = trifluperazine, TRIFLUP = trifluperidol, TRIFLUPR = triflupromazine, ZIP = ziprasidone, ZOT = zotepine

* These relative risks were obtained after a continuity correction and from a fixed effect model.

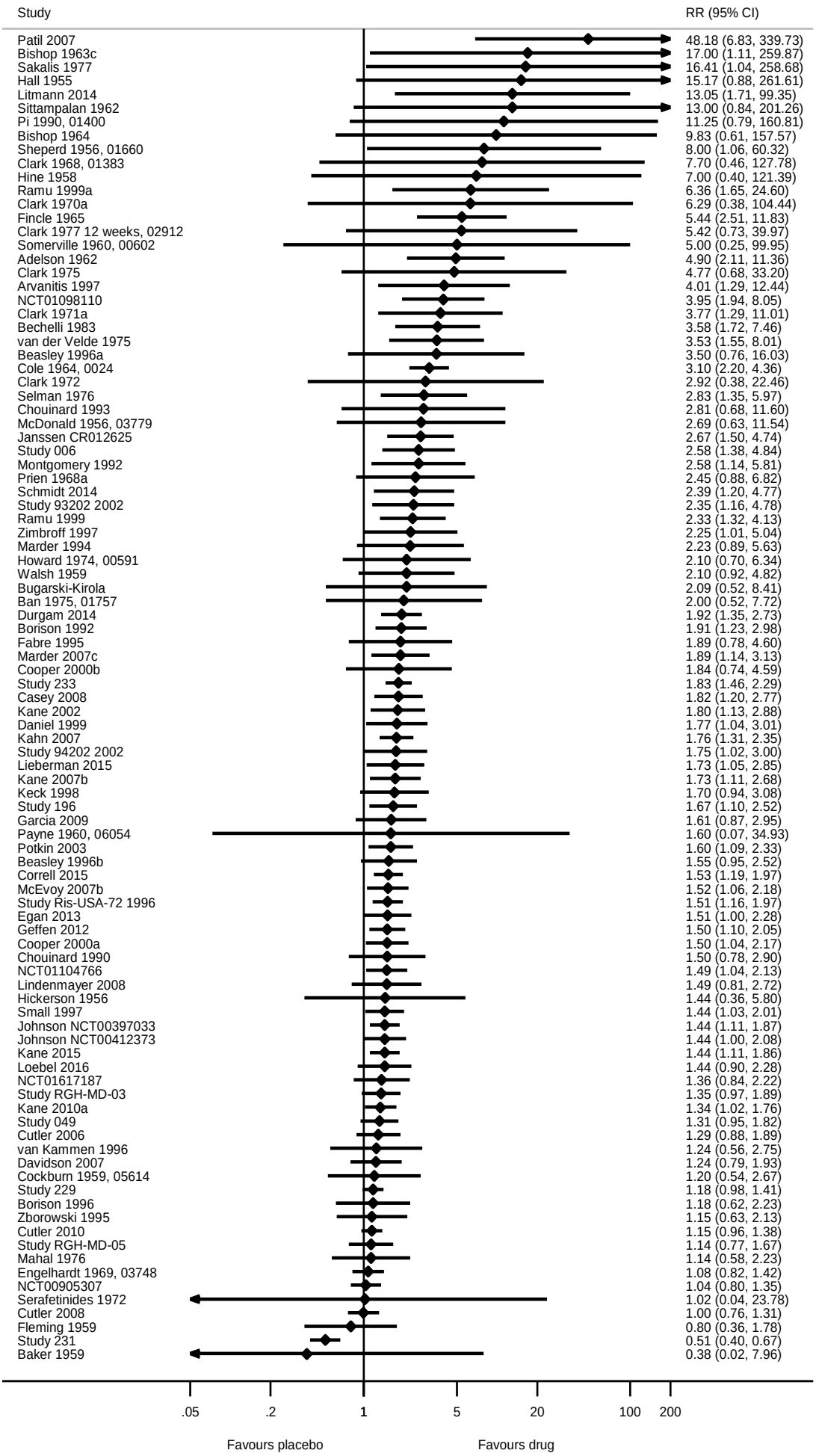
Supplementary Figure S3

Results of the individual studies in the various outcomes

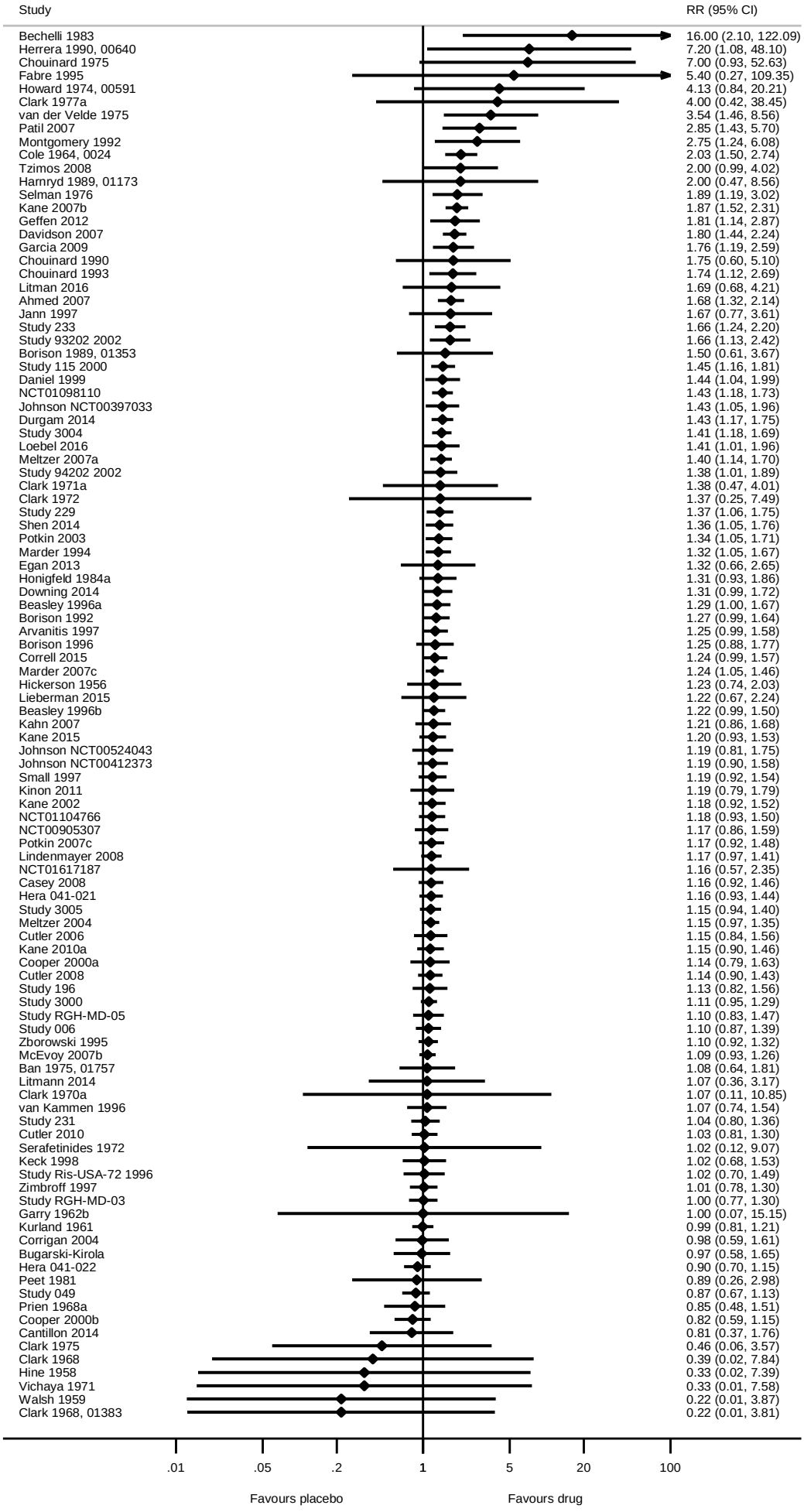
Overall efficacy



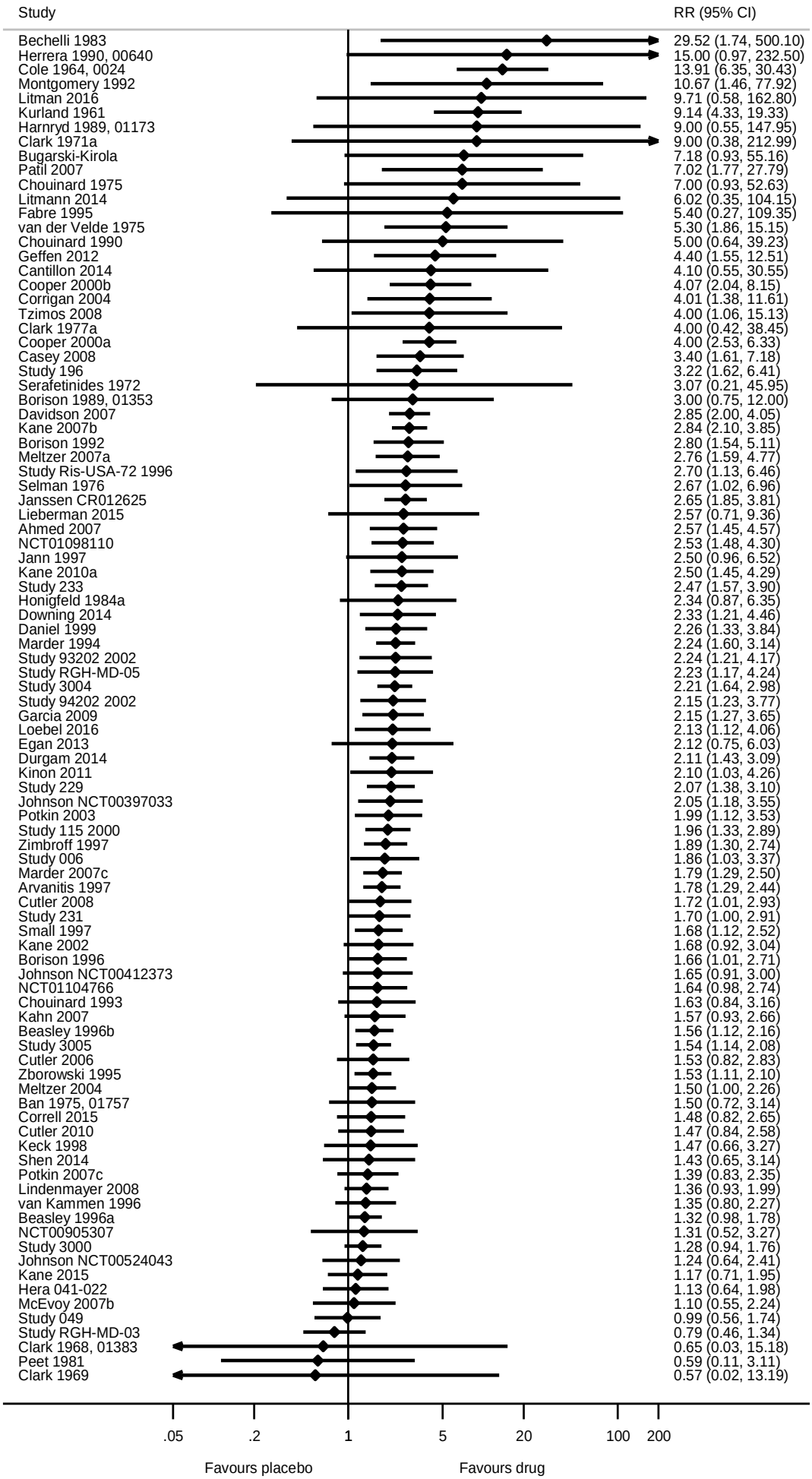
Response


Study
RR (95% CI)
Patil 2007 48.18 (6.83, 339.73)
Bishop 1963c 17.00 (1.11, 259.87)
Sakalis 1977 16.41 (1.04, 258.68)
Hall 1955 15.17 (0.88, 261.61)
Litmann 2014 13.05 (1.71, 99.35)
Sittampalan 1962 13.00 (0.84, 201.26)
Pi 1990, 01400 11.25 (0.79, 160.81)
Bishop 1964 9.83 (0.61, 157.57)
Sheperd 1956, 01660 8.00 (1.06, 60.32)
Clark 1968, 01383 7.70 (0.46, 127.78)
Hine 1958 7.00 (0.40, 121.39)
Ramu 1999a 6.36 (1.65, 24.60)
Clark 1970a 6.29 (0.38, 104.44)
Fincle 1965 5.44 (2.51, 11.83)
Clark 1977 12 weeks, 02912 5.42 (0.73, 39.97)
Somerville 1960, 00602 5.00 (0.25, 99.95)
Adelson 1962 4.90 (2.11, 11.36)
Clark 1975 4.77 (0.68, 33.20)
Arvanitis 1997 4.01 (1.29, 12.44)
NCT01098110 3.95 (1.94, 8.05)
Clark 1971a 3.77 (1.29, 11.01)
Bechelli 1983 3.58 (1.72, 7.46)
van der Velde 1975 3.53 (1.55, 8.01)
Beasley 1996a 3.50 (0.76, 16.03)
Cole 1964, 0024 3.10 (2.20, 4.36)
Clark 1972 2.92 (0.38, 22.46)
Selman 1976 2.83 (1.35, 5.97)
Chouinard 1993 2.81 (0.68, 11.60)
McDonald 1956, 03779 2.69 (0.63, 11.54)
Janssen CR012625 2.67 (1.50, 4.74)
Study 006 2.58 (1.38, 4.84)
Montgomery 1992 2.58 (1.14, 5.81)
Prien 1968a 2.45 (0.88, 6.82)
Schmidt 2014 2.39 (1.20, 4.77)
Study 93202 2002 2.35 (1.16, 4.78)
Ramu 1999 2.33 (1.32, 4.13)
Zimbroff 1997 2.25 (1.01, 5.04)
Marder 1994 2.23 (0.89, 5.63)
Howard 1974, 00591 2.10 (0.70, 6.34)
Walsh 1959 2.10 (0.92, 4.82)
Bugarski-Kirola 2.09 (0.52, 8.41)
Ban 1975, 01757 2.00 (0.52, 7.72)
Durgam 2014 1.92 (1.35, 2.73)
Borison 1992 1.91 (1.23, 2.98)
Fabre 1995 1.89 (0.78, 4.60)
Marder 2007c 1.89 (1.14, 3.13)
Cooper 2000b 1.84 (0.74, 4.59)
Study 233 1.83 (1.46, 2.29)
Casey 2008 1.82 (1.20, 2.77)
Kane 2002 1.80 (1.13, 2.88)
Daniel 1999 1.77 (1.04, 3.01)
Kahn 2007 1.76 (1.31, 2.35)
Study 94202 2002 1.75 (1.02, 3.00)
Lieberman 2015 1.73 (1.05, 2.85)
Kane 2007b 1.73 (1.11, 2.68)
Keck 1998 1.70 (0.94, 3.08)
Study 196 1.67 (1.10, 2.52)
Garcia 2009 1.61 (0.87, 2.95)
Payne 1960, 06054 1.60 (0.07, 34.93)
Potkin 2003 1.60 (1.09, 2.33)
Beasley 1996b 1.55 (0.95, 2.52)
Correll 2015 1.53 (1.19, 1.97)
McEvoy 2007b 1.52 (1.06, 2.18)
Study Ris-USA-72 1996 1.51 (1.16, 1.97)
Egan 2013 1.51 (1.00, 2.28)
Geffen 2012 1.50 (1.10, 2.05)
Cooper 2000a 1.50 (1.04, 2.17)
Chouinard 1990 1.50 (0.78, 2.90)
NCT01104766 1.49 (1.04, 2.13)
Lindenmayer 2008 1.49 (0.81, 2.72)
Hickerson 1956 1.44 (0.36, 5.80)
Small 1997 1.44 (1.03, 2.01)
Johnson NCT00397033 1.44 (1.11, 1.87)
Johnson NCT00412373 1.44 (1.00, 2.08)
Kane 2015 1.44 (1.11, 1.86)
Loebel 2016 1.44 (0.90, 2.28)
NCT01617187 1.36 (0.84, 2.22)
Study RGH-MD-03 1.35 (0.97, 1.89)
Kane 2010a 1.34 (1.02, 1.76)
Study 049 1.31 (0.95, 1.82)
Cutler 2006 1.29 (0.88, 1.89)
van Kammen 1996 1.24 (0.56, 2.75)
Davidson 2007 1.24 (0.79, 1.93)
Cockburn 1959, 05614 1.20 (0.54, 2.67)
Study 229 1.18 (0.98, 1.41)
Borison 1996 1.18 (0.62, 2.23)
Zborowski 1995 1.15 (0.63, 2.13)
Cutler 2010 1.15 (0.96, 1.38)
Study RGH-MD-05 1.14 (0.77, 1.67)
Mahal 1976 1.14 (0.58, 2.23)
Engelhardt 1969, 03748 1.08 (0.82, 1.42)
NCT00905307 1.04 (0.80, 1.35)
Serafetinides 1972 1.02 (0.04, 23.78)
Cutler 2008 1.00 (0.76, 1.31)
Fleming 1959 0.80 (0.36, 1.78)
Study 231 0.51 (0.40, 0.67)
Baker 1959 0.38 (0.02, 7.96)
.05
.2
1
5
20
100
200
Favours placebo
Favours drug

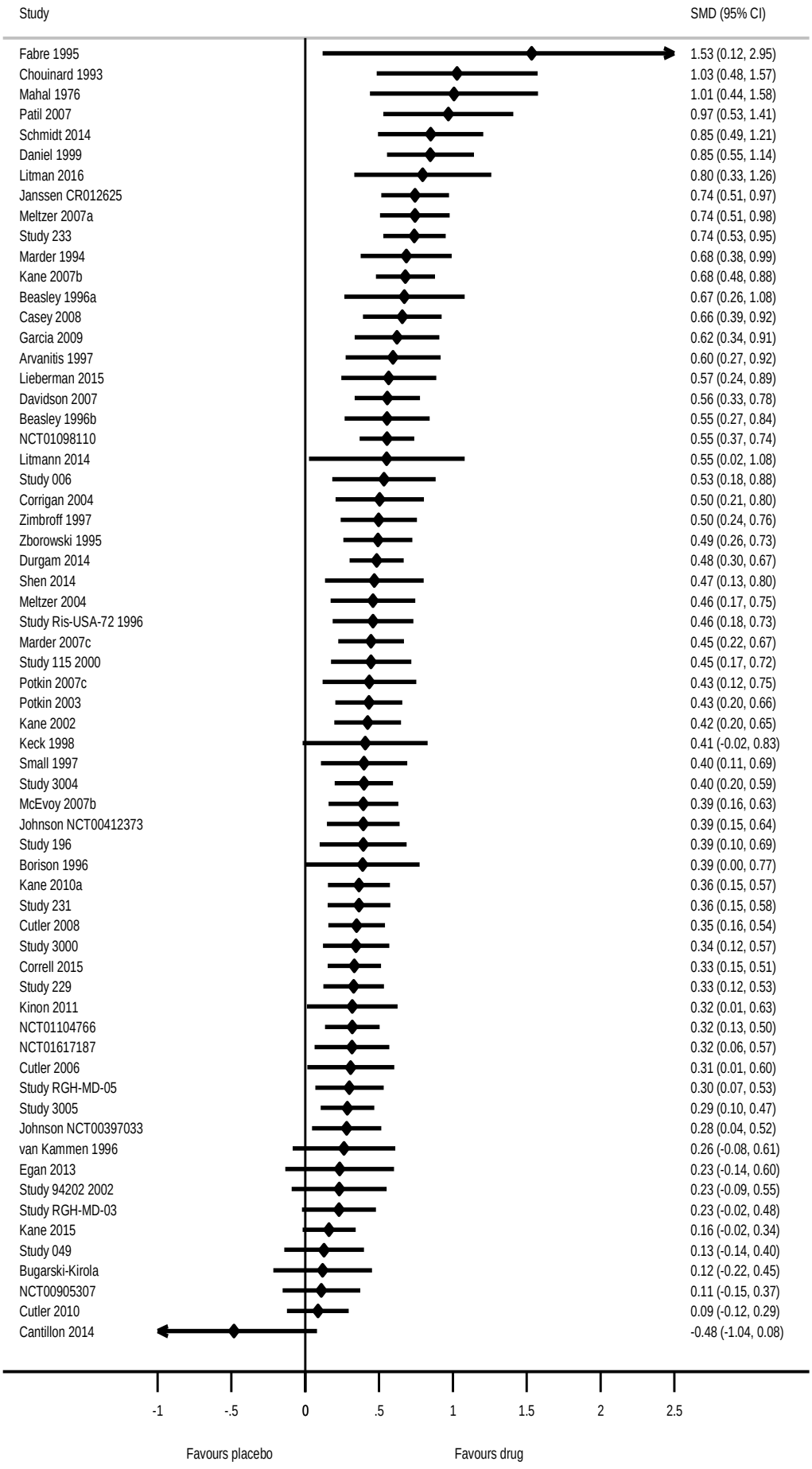
Dropouts (any reason)



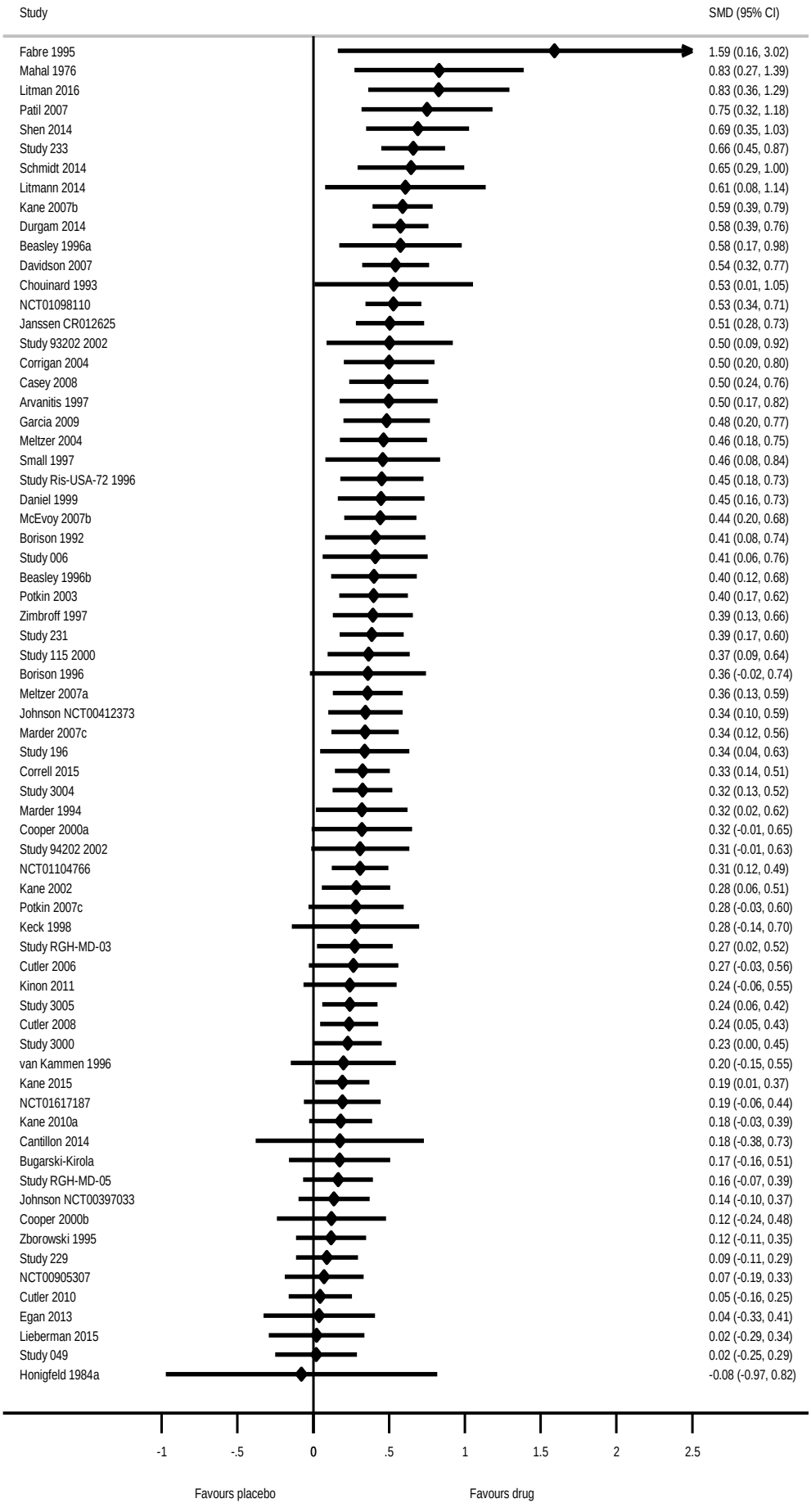
Dropouts (inefficacy)



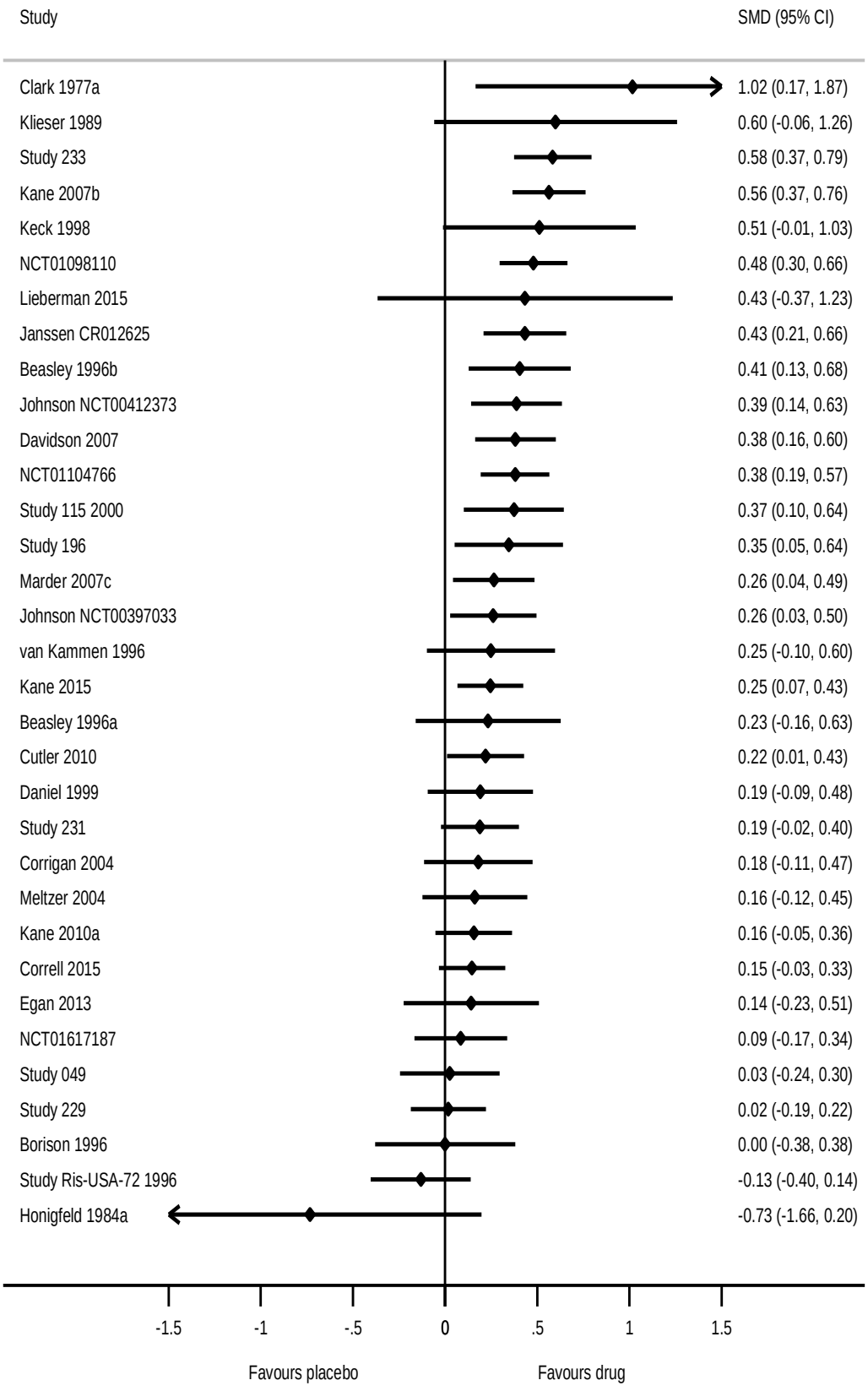
Positive symptoms



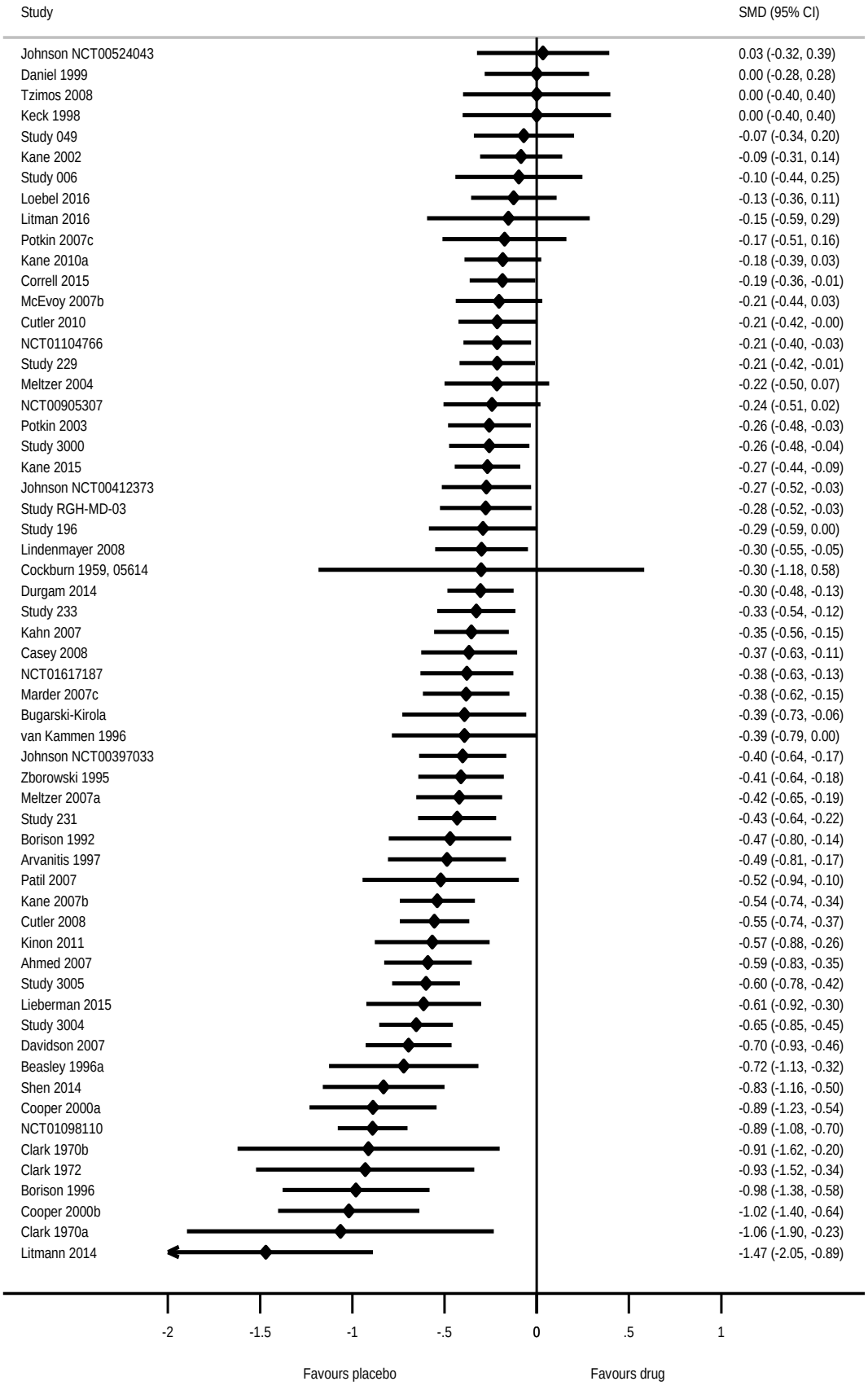
Negative symptoms



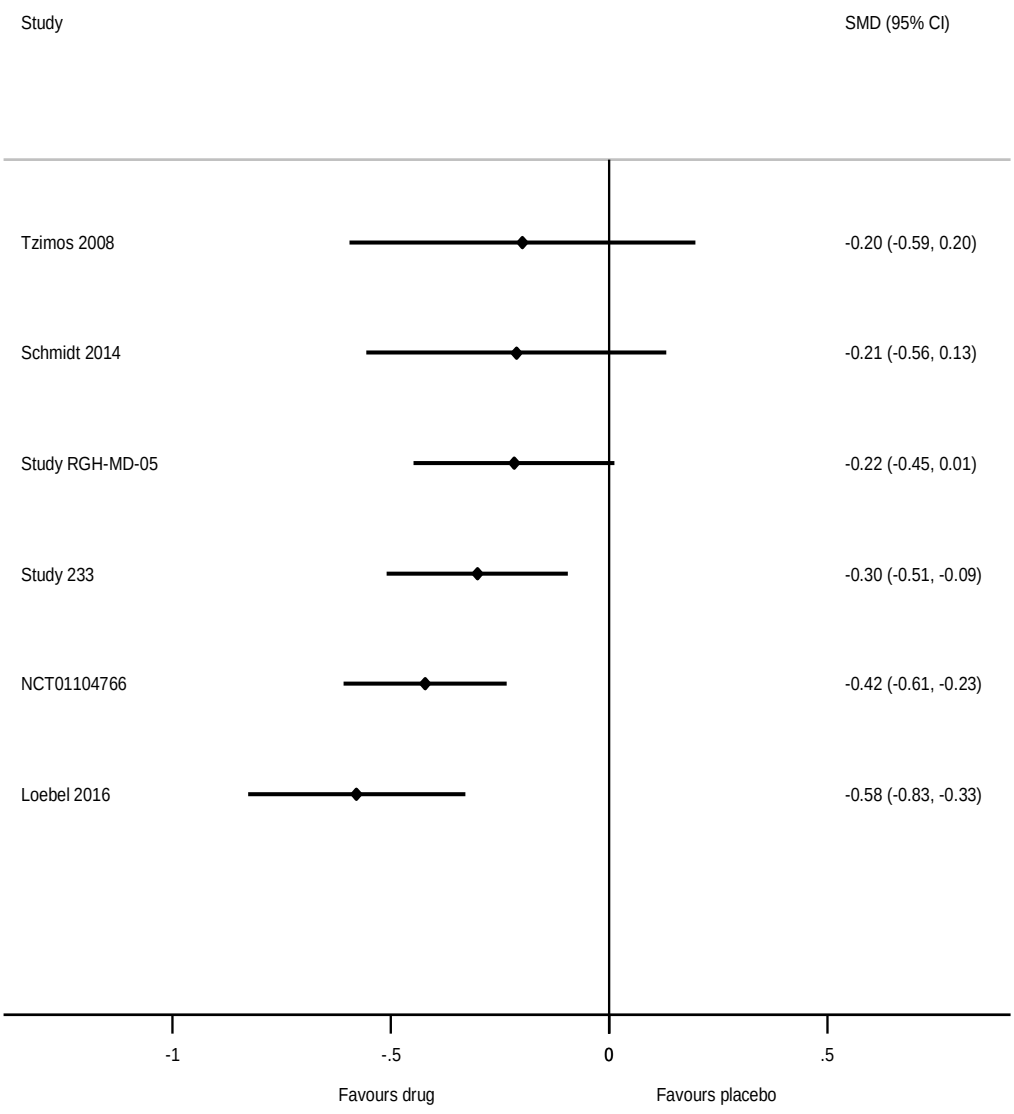
Depressive symptoms



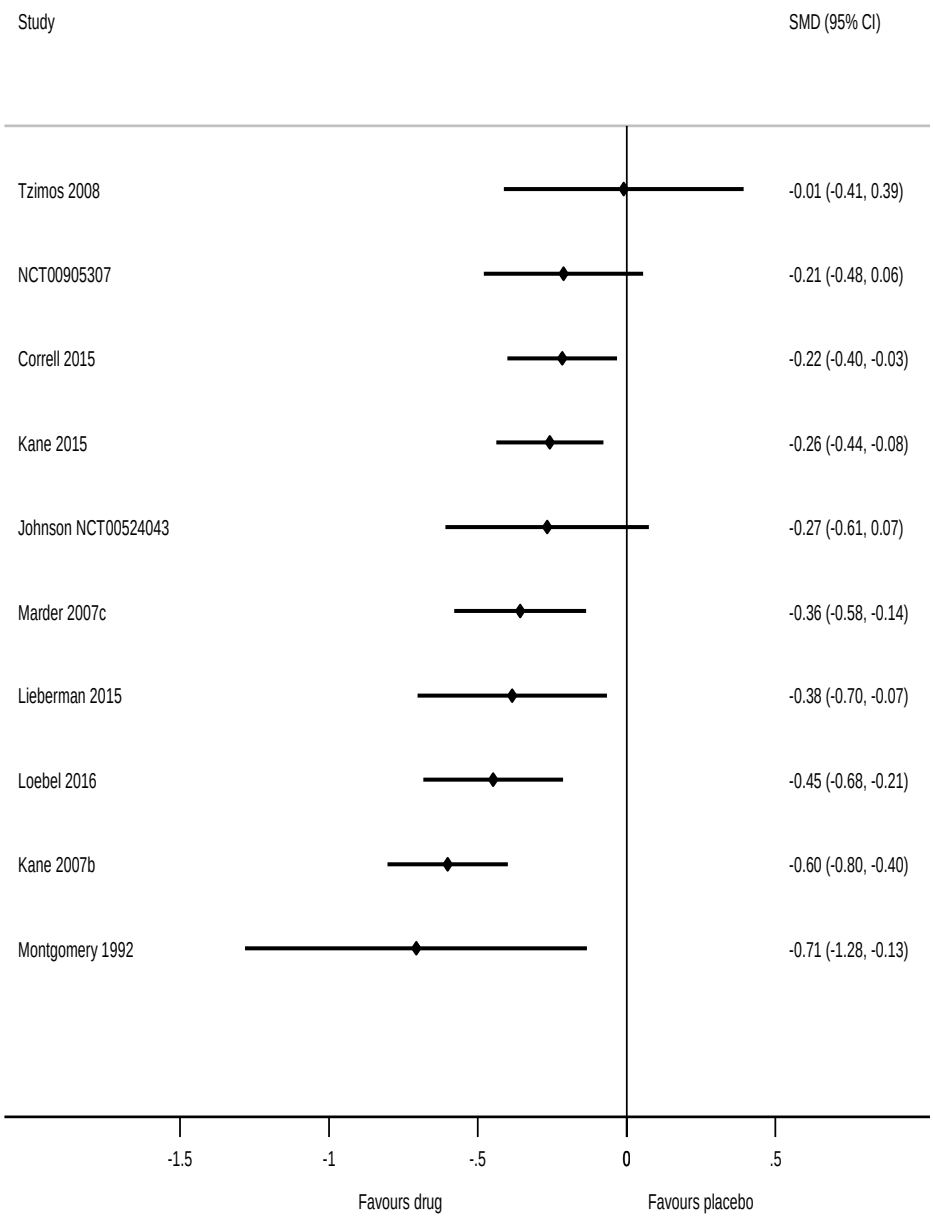
Weight gain


Study
SMD (95% CI)
Johnson NCT00524043 0.03 (-0.32, 0.39)
Daniel 1999 0.00 (-0.28, 0.28)
Tzimos 2008 0.00 (-0.40, 0.40)
Keck 1998 0.00 (-0.40, 0.40)
Study 049 -0.07 (-0.34, 0.20)
Kane 2002 -0.09 (-0.31, 0.14)
Study 006 -0.10 (-0.44, 0.25)
Loebel 2016 -0.13 (-0.36, 0.11)
Litman 2016 -0.15 (-0.59, 0.29)
Potkin 2007c -0.17 (-0.51, 0.16)
Kane 2010a -0.18 (-0.39, 0.03)
Correll 2015 -0.19 (-0.36, -0.01)
McEvoy 2007b -0.21 (-0.44, 0.03)
Cutler 2010 -0.21 (-0.42, -0.00)
NCT01104766 -0.21 (-0.40, -0.03)
Study 229 -0.21 (-0.42, -0.01)
Meltzer 2004 -0.22 (-0.50, 0.07)
NCT00905307 -0.24 (-0.51, 0.02)
Potkin 2003 -0.26 (-0.48, -0.03)
Study 3000 -0.26 (-0.48, -0.04)
Kane 2015 -0.27 (-0.44, -0.09)
Johnson NCT00412373 -0.27 (-0.52, -0.03)
Study RGH-MD-03 -0.28 (-0.52, -0.03)
Study 196 -0.29 (-0.59, 0.00)
Lindenmayer 2008 -0.30 (-0.55, -0.05)
Cockburn 1959, 05614 -0.30 (-1.18, 0.58)
Durgam 2014 -0.30 (-0.48, -0.13)
Study 233 -0.33 (-0.54, -0.12)
Kahn 2007 -0.35 (-0.56, -0.15)
Casey 2008 -0.37 (-0.63, -0.11)
NCT01617187 -0.38 (-0.63, -0.13)
Marder 2007c -0.38 (-0.62, -0.15)
Bugarski-Kirola -0.39 (-0.73, -0.06)
van Kammen 1996 -0.39 (-0.79, 0.00)
Johnson NCT00397033 -0.40 (-0.64, -0.17)
Zborowski 1995 -0.41 (-0.64, -0.18)
Meltzer 2007a -0.42 (-0.65, -0.19)
Study 231 -0.43 (-0.64, -0.22)
Borison 1992 -0.47 (-0.80, -0.14)
Arvanitis 1997 -0.49 (-0.81, -0.17)
Patil 2007 -0.52 (-0.94, -0.10)
Kane 2007b -0.54 (-0.74, -0.34)
Cutler 2008 -0.55 (-0.74, -0.37)
Kinon 2011 -0.57 (-0.88, -0.26)
Ahmed 2007 -0.59 (-0.83, -0.35)
Study 3005 -0.60 (-0.78, -0.42)
Lieberman 2015 -0.61 (-0.92, -0.30)
Study 3004 -0.65 (-0.85, -0.45)
Davidson 2007 -0.70 (-0.93, -0.46)
Beasley 1996a -0.72 (-1.13, -0.32)
Shen 2014 -0.83 (-1.16, -0.50)
Cooper 2000a -0.89 (-1.23, -0.54)
NCT01098110 -0.89 (-1.08, -0.70)
Clark 1970b -0.91 (-1.62, -0.20)
Clark 1972 -0.93 (-1.52, -0.34)
Borison 1996 -0.98 (-1.38, -0.58)
Cooper 2000b -1.02 (-1.40, -0.64)
Clark 1970a -1.06 (-1.90, -0.23)
Litmann 2014 -1.47 (-2.05, -0.89)
-2
-1.5
-1
-.5
0
.5
1
Favours placebo
Favours drug

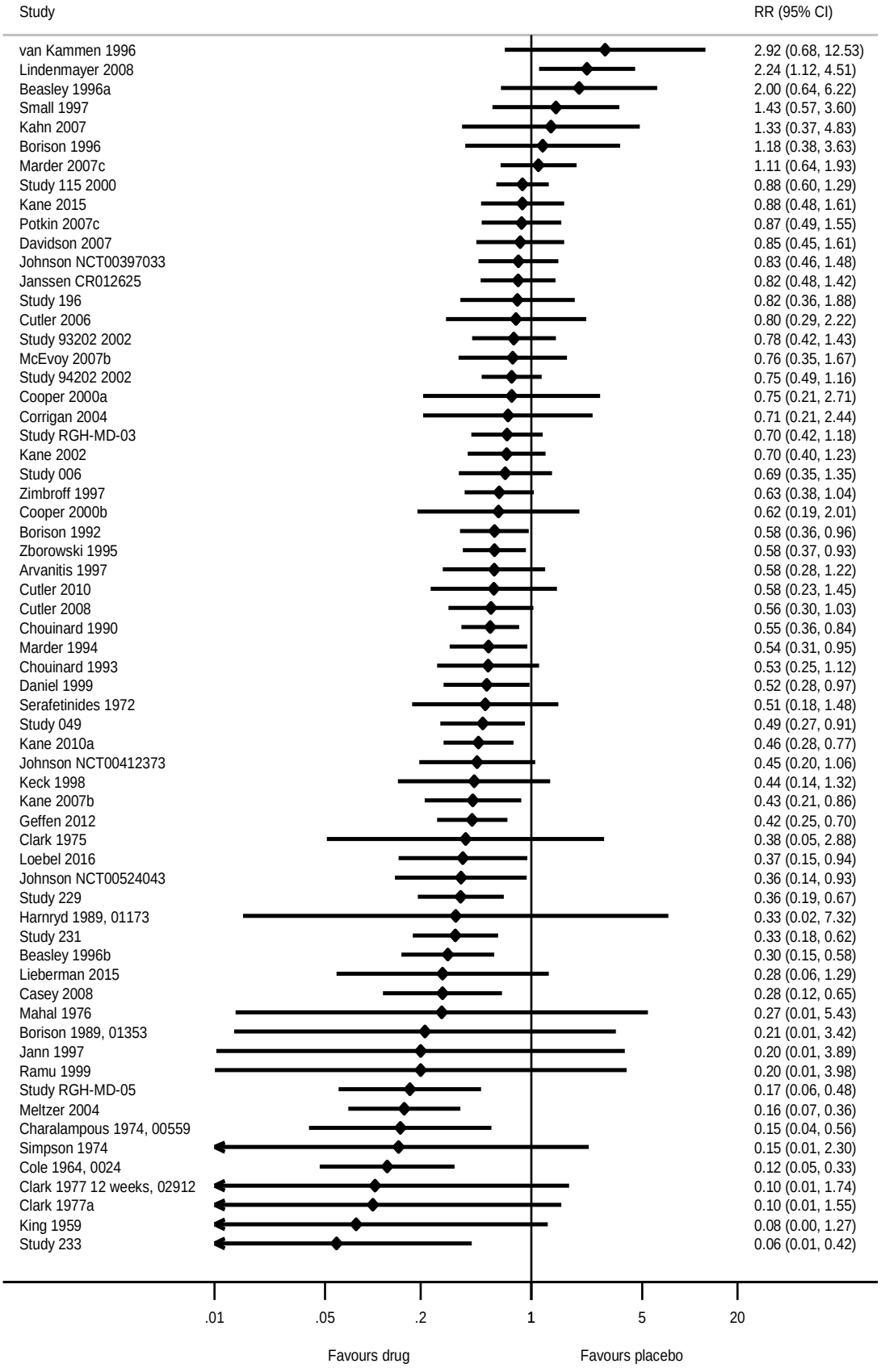
Quality of life



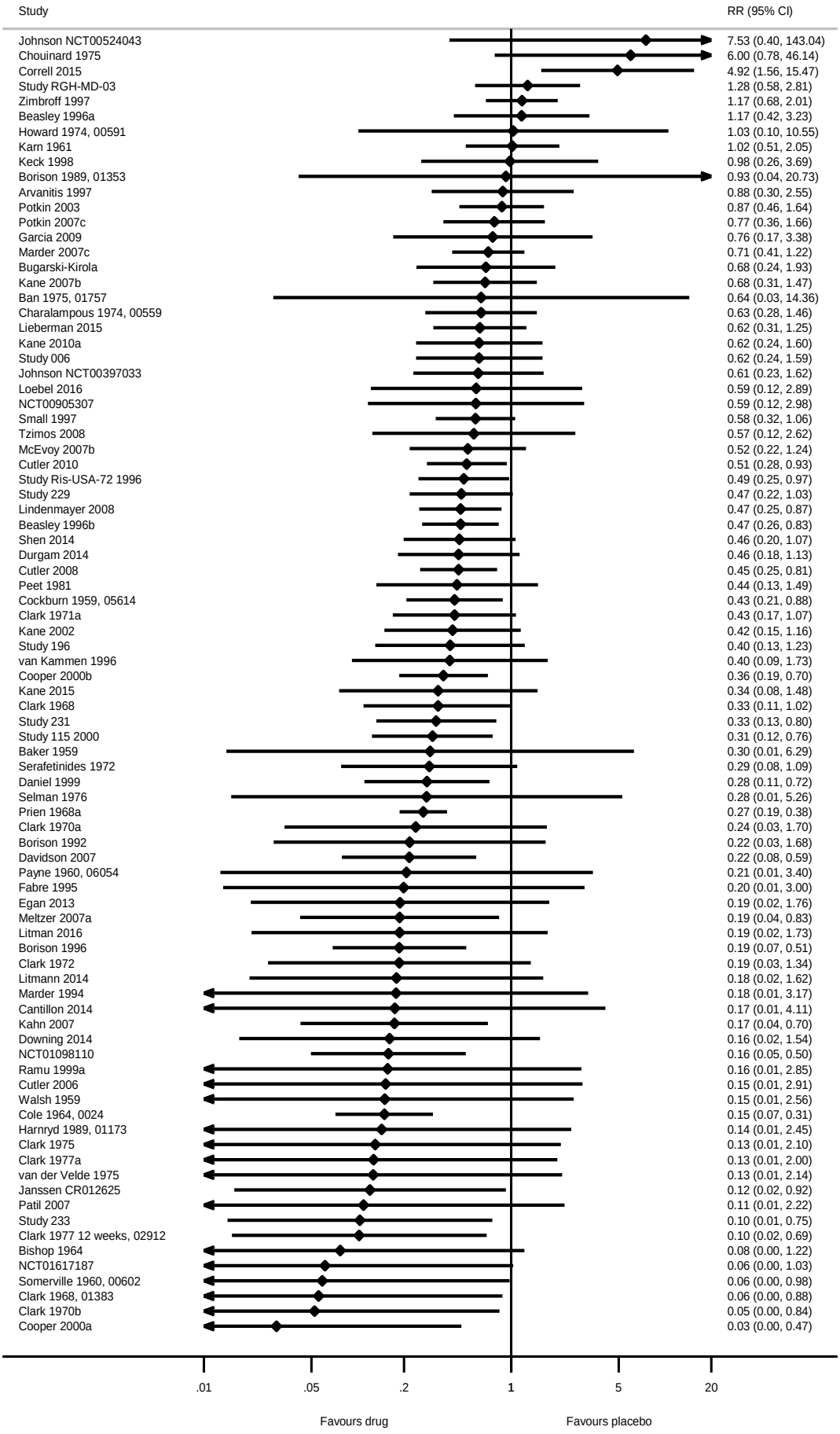
Social functioning



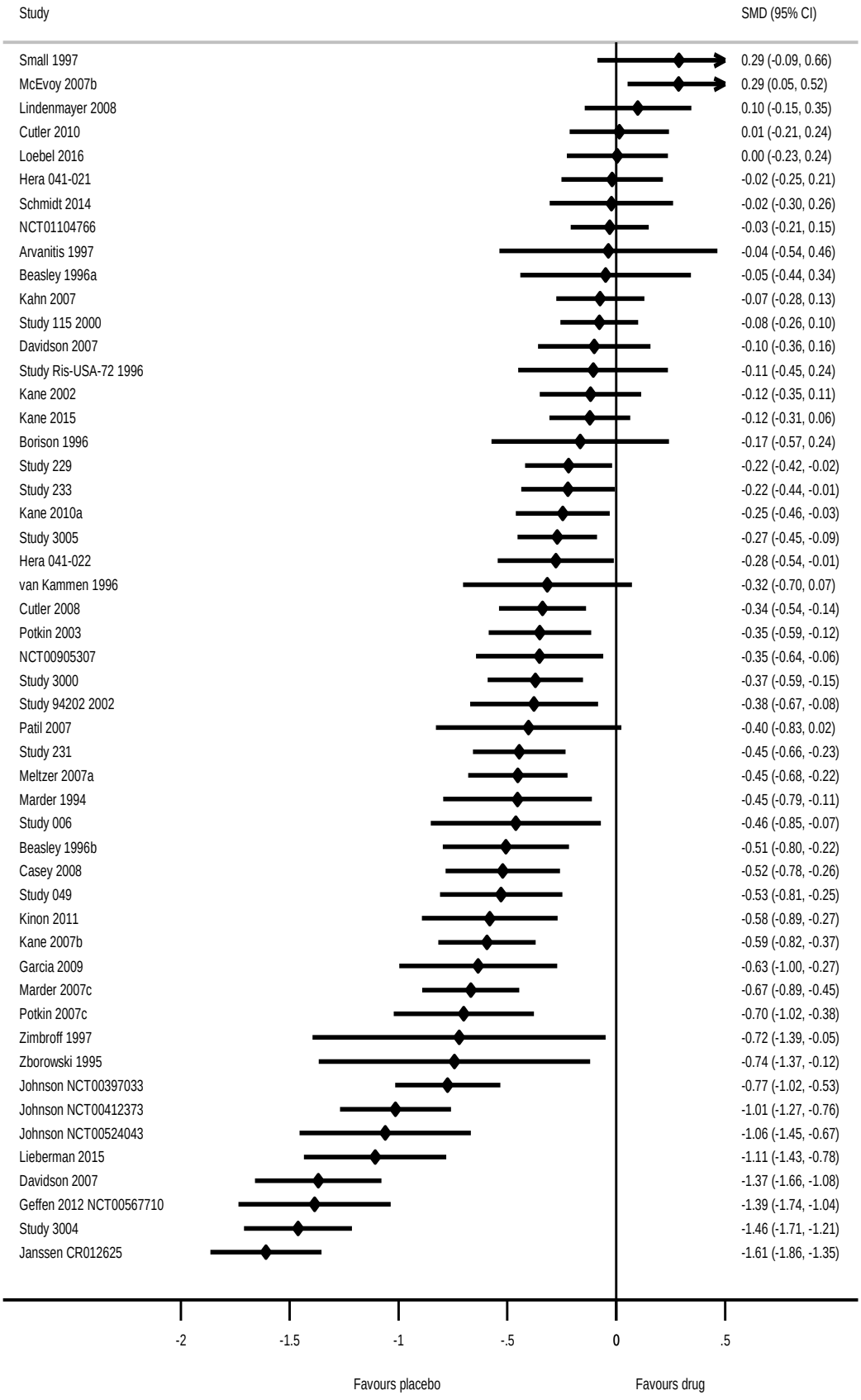
Antiparkinson medication



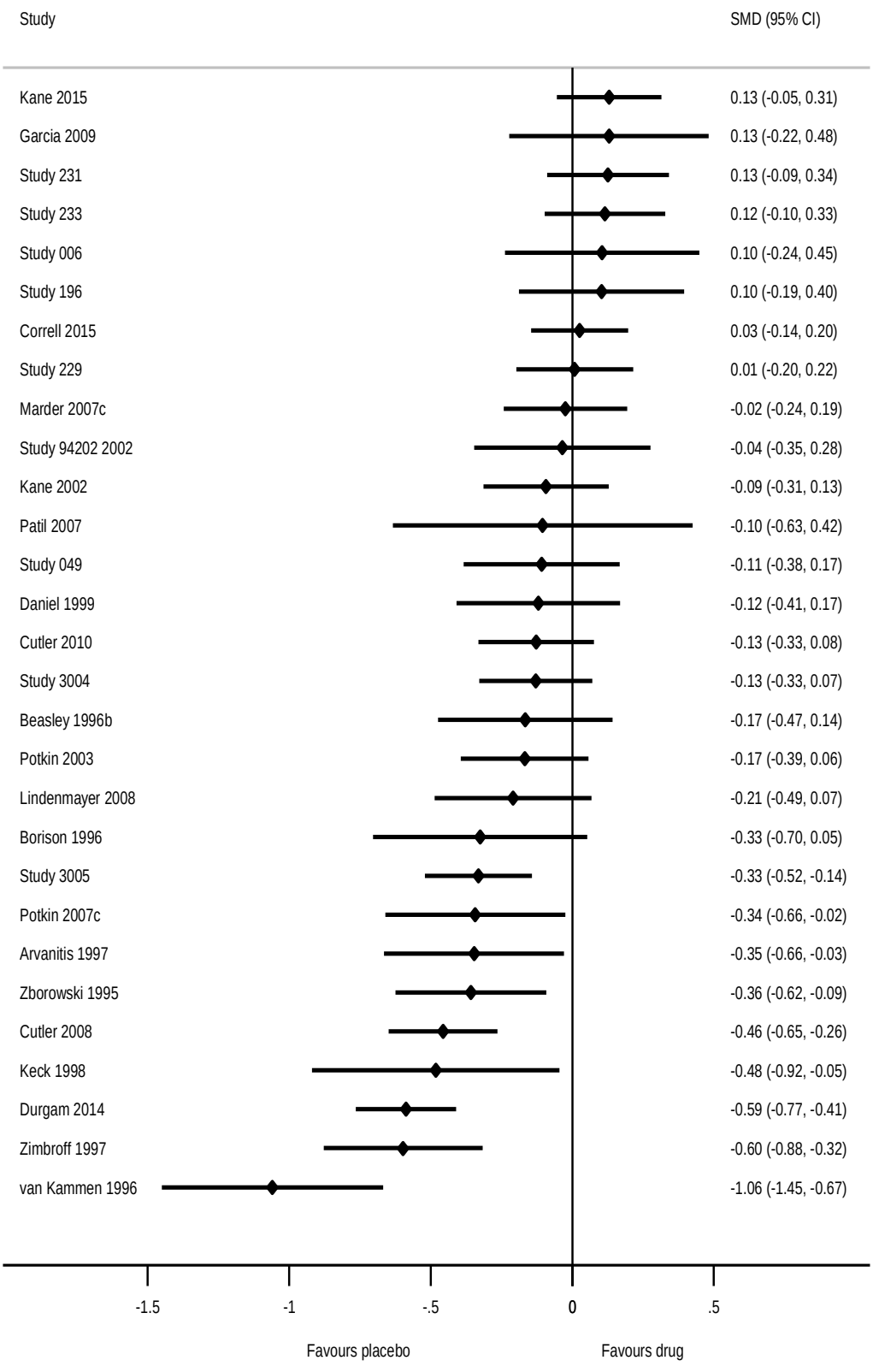
Depression


Study
RR (95% CI)
Johnson NCT00524043 7.53 (0.40, 143.04)
Chouinard 1975 6.00 (0.78, 46.14)
Correll 2015 4.92 (1.56, 15.47)
Study RGH-MD-03 1.28 (0.58, 2.81)
Zimbroff 1997 1.17 (0.68, 2.01)
Beasley 1996a 1.17 (0.42, 3.23)
Howard 1974, 00591 1.03 (0.10, 10.55)
Karn 1961 1.02 (0.51, 2.05)
Keck 1998 0.98 (0.26, 3.69)
Borison 1989, 01353 0.93 (0.04, 20.73)
Arvanitis 1997 0.88 (0.30, 2.55)
Potkin 2003 0.87 (0.46, 1.64)
Potkin 2007c 0.77 (0.36, 1.66)
Garcia 2009 0.76 (0.17, 3.38)
Marder 2007c 0.71 (0.41, 1.22)
Bugarski-Kirola 0.68 (0.24, 1.93)
Kane 2007b 0.68 (0.31, 1.47)
Ban 1975, 01757 0.64 (0.03, 14.36)
Charalampous 1974, 00559 0.63 (0.28, 1.46)
Lieberman 2015 0.62 (0.31, 1.25)
Kane 2010a 0.62 (0.24, 1.60)
Study 006 0.62 (0.24, 1.59)
Johnson NCT00397033 0.61 (0.23, 1.62)
Loebel 2016 0.59 (0.12, 2.89)
NCT00905307 0.59 (0.12, 2.98)
Small 1997 0.58 (0.32, 1.06)
Tzimos 2008 0.57 (0.12, 2.62)
McEvoy 2007b 0.52 (0.22, 1.24)
Cutler 2010 0.51 (0.28, 0.93)
Study Ris-USA-72 1996 0.49 (0.25, 0.97)
Study 229 0.47 (0.22, 1.03)
Lindenmayer 2008 0.47 (0.25, 0.87)
Beasley 1996b 0.47 (0.26, 0.83)
Shen 2014 0.46 (0.20, 1.07)
Durgam 2014 0.46 (0.18, 1.13)
Cutler 2008 0.45 (0.25, 0.81)
Peet 1981 0.44 (0.13, 1.49)
Cockburn 1959, 05614 0.43 (0.21, 0.88)
Clark 1971a 0.43 (0.17, 1.07)
Kane 2002 0.42 (0.15, 1.16)
Study 196 0.40 (0.13, 1.23)
van Kammen 1996 0.40 (0.09, 1.73)
Cooper 2000b 0.36 (0.19, 0.70)
Kane 2015 0.34 (0.08, 1.48)
Clark 1968 0.33 (0.11, 1.02)
Study 231 0.33 (0.13, 0.80)
Study 115 2000 0.31 (0.12, 0.76)
Baker 1959 0.30 (0.01, 6.29)
Serafetinides 1972 0.29 (0.08, 1.09)
Daniel 1999 0.28 (0.11, 0.72)
Selman 1976 0.28 (0.01, 5.26)
Prien 1968a 0.27 (0.19, 0.38)
Clark 1970a 0.24 (0.03, 1.70)
Borison 1992 0.22 (0.03, 1.68)
Davidson 2007 0.22 (0.08, 0.59)
Payne 1960, 06054 0.21 (0.01, 3.40)
Fabre 1995 0.20 (0.01, 3.00)
Egan 2013 0.19 (0.02, 1.76)
Meltzer 2007a 0.19 (0.04, 0.83)
Litman 2016 0.19 (0.02, 1.73)
Borison 1996 0.19 (0.07, 0.51)
Clark 1972 0.19 (0.03, 1.34)
Litmann 2014 0.18 (0.02, 1.62)
Marder 1994 0.18 (0.01, 3.17)
Cantillon 2014 0.17 (0.01, 4.11)
Kahn 2007 0.17 (0.04, 0.70)
Downing 2014 0.16 (0.02, 1.54)
NCT01098110 0.16 (0.05, 0.50)
Ramu 1999a 0.16 (0.01, 2.85)
Cutler 2006 0.15 (0.01, 2.91)
Walsh 1959 0.15 (0.01, 2.56)
Cole 1964, 0024 0.15 (0.07, 0.31)
Harnryd 1989, 01173 0.14 (0.01, 2.45)
Clark 1975 0.13 (0.01, 2.10)
Clark 1977a 0.13 (0.01, 2.00)
van der Velde 1975 0.13 (0.01, 2.14)
Janssen CR012625 0.12 (0.02, 0.92)
Patil 2007 0.11 (0.01, 2.22)
Study 233 0.10 (0.01, 0.75)
Clark 1977 12 weeks, 02912 0.10 (0.02, 0.69)
Bishop 1964 0.08 (0.00, 1.22)
NCT01617187 0.06 (0.00, 1.03)
Somerville 1960, 00602 0.06 (0.00, 0.98)
Clark 1968, 01383 0.06 (0.00, 0.88)
Clark 1970b 0.05 (0.00, 0.84)
Cooper 2000a 0.03 (0.00, 0.47)
.01
.05
.2
1
5
20
Favours drug
Favours placebo

Prolactin increase



QTc prolongation



Supplementary Table S7

Multivariable meta-regression sensitivity analyses including all moderators that were significant in univariate analyses and excluding pharmaceutical sponsorship

Meta-regression model combining all moderators that were significant in univariate analyses

	Coefficient (95% CrI)	Interpretation	Proba-bility*
Placebo response [10-unit increase]	-0.11 (-0.20,-0.02)	A 10 PANSS points higher mean change score in the placebo arm would reduce the SMD on average by 0.11 units	94.2%
Industry sponsored or not	-0.20 (-0.37,-0.02)	The SMD for studies including at least one sponsored drug would be on average 0.20 units smaller than non-sponsored studies	78.4%
Publication year [ten-year increase]	-0.06 (-0.17,0.05)	A 10 years later published study would have an on average 0.06 units smaller SMD	28.8%
Sample size [100 participants increase]	0.00 (-0.04,0.04)	A 100 participants larger study would have an on average the same SMD	9.3%
Number of sites [10-site increase]	0.02 (-0.02,0.06)	The SMD of a study with 10 more sites would be on average 0.02 units larger	18.0%
Mean dose [100 CPZ units increase]	0.01 (-0.02,0.05)	A 100 CPZ units higher mean dose would increase the SMD on average by 0.01 units	9.3%
Number of medications	0.02 (-0.09,0.14)	The SMD for a study with 1 more medication would be on average 0.02 units larger	42.4%
Coefficient for operationalized or not	-0.02 (-0.46,0.42)	The SMD for studies without operationalized criteria would be on average 0.02 units smaller than studies with operationalized	35.8%
Baseline severity entry minimum score	-0.05 (-0.28,0.18)	The SMD for studies having a minimum baseline severity entry score would on average 0.05 units smaller that with studies without a minimum baseline severity entry score.	36.8%
Scale	0.01 (-0.23,0.22)	The SMD of a study using BPRS would be on average 0.01 units larger compared to a study using PANSS	39.8%
Drug mechanism			
M2 vs M1	-0.05 (-0.24,0.15)	The SMD of a study with a drug of mechanism 2 would be on average 0.05 units smaller than of a study with a drug of mechanism 1	32.2%
M3 vs M1	-0.04 (-0.29,0.20)	The SMD of a study with a drug of mechanism 3 would be on average 0.03 units smaller than of a study with a drug of mechanism 1	30.8%

M4 vs M1	-0.06 (-0.28,0.17)	The SMD of a study with a drug of mechanism 4 would be on average 0.06 units smaller than of a study with a drug of mechanism 1	36.8%
M5 vs M1	-0.03 (-0.31,0.26)	The SMD of a study with a drug of mechanism 5 would be on average 0.03 units smaller than of a study with a drug of mechanism 1	40.5%
Summary of the above model (72 studies, 17710 participants)			
Heterogeneity SD	0.13 (0.08,0.18)	18.8% of the heterogeneity explained	

*Probability that each moderator should be included in the model, FGA = first generation antipsychotic, SGA = second generation antipsychotic, SMD = standardized mean difference, M1 – M5 are drug mechanisms of action according to the "Neuroscience-based Nomenclature" (84): M1 = receptor antagonist (D2); M2 = receptor antagonist (D2, 5-HT2), M3 = receptor partial agonist (D2, 5-HT1A), M4= receptor antagonist (D2, 5-HT2, NE alpha2), M5= receptor antagonist (D2, 5-HT2) and reuptake inhibitor (NET)

Meta-regression model excluding the moderator for sponsorship

	Coefficient (95% CrI)	Interpretation	Proba-bility*
Placebo response [10-unit increase]	-0.10 (-0.18,-0.03)	A 10 PANSS points higher mean change score in the placebo arm would reduce the SMD on average by 0.10 units	90.8%
Publication year [ten-year increase]	-0.02 (-0.07,0.07)	A 10 years later published study would have an on average 0.02 units smaller SMD	25.9%
Sample size [100 participants increase]	-0.02 (-0.04,0.01)	A 100 participants larger study would have an on average 0.02 units smaller SMD	9.4%
Mean dose [100 CPZ units increase]	0.01 (-0.02,0.04)	A 100 CPZ units higher mean dose would increase the SMD on average by 0.01 units	9.0%
Baseline severity entry minimum score	-0.05 (-0.22,0.11)	The SMD for studies having a minimum baseline severity entry score would be on average 0.05 units smaller than studies without a minimum baseline severity entry score.	42.2%
Summary of the above model (83 studies, 19300 participants)			
Heterogeneity SD	0.13 (0.09,0.18)	18.8% of the heterogeneity explained	

Supplementary Table S8

Replication of the analysis by Rutherford et al. 2014 (1)

Background

A major finding in the analysis of Rutherford et al. 2014 (1) was that in addition to increasing placebo-response over time, drug-response has decreased. In our analysis, however, drug-response remained rather constant over the years. The major difference between Rutherford et al. (1) and our analysis was that they did not only use the drug groups from the placebo-controlled trials, but also from trials that compared two antipsychotics with each other, without a placebo group. Such trials have different characteristics, for example, the drop-out rates are much higher in placebo-controlled trials. We, therefore, analyzed the drug groups only from the placebo-controlled studies found by Rutherford et al. (1) to see whether the decrease in drug-response over the years could also be found in them.

Method

We identified the placebo-controlled studies (1-33) in the table of included studies of Rutherford et al. 2014 (1) (note that one publication included three studies (26)). A few studies that we had not included due to other inclusion criteria (mainly depot studies) were extracted independently by at least two researchers.

We conducted three analyses:

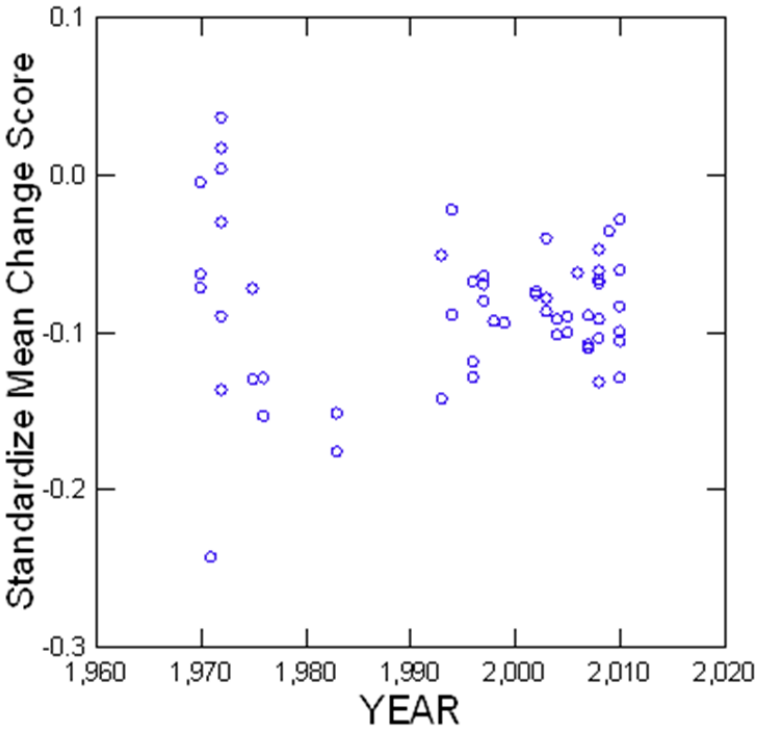
1. A simple Spearman correlation of drug response and publication year which uses all study arms without a correction. As some studies used the BPRS and others the PANSS, we converted the BPRS/PANSS change in a standardized change score with the same method used by Rutherford et al. (1)
2. A random-effects meta-regression of drug-response with publication year as a moderator with Comprehensive meta-analysis version 2 (34). Again, the BPRS/PANSS change was converted to a standardized mean change score as in Rutherford et al. (1). If there are several active study arms, they are combined in a meta-regression, therefore the numbers are lower than in analysis 1.
3. A random effects, meta-regression of drug-response with publication year as a moderator with Comprehensive meta-analysis version 2. In studies that used the BPRS, the BPRS was converted to the PANSS using a validated conversion method as in our main analysis (Leucht et al. 2013 (35)). If there are several active study arms, they are combined in a meta-regression, therefore the numbers are lower than in analysis 1.

Results

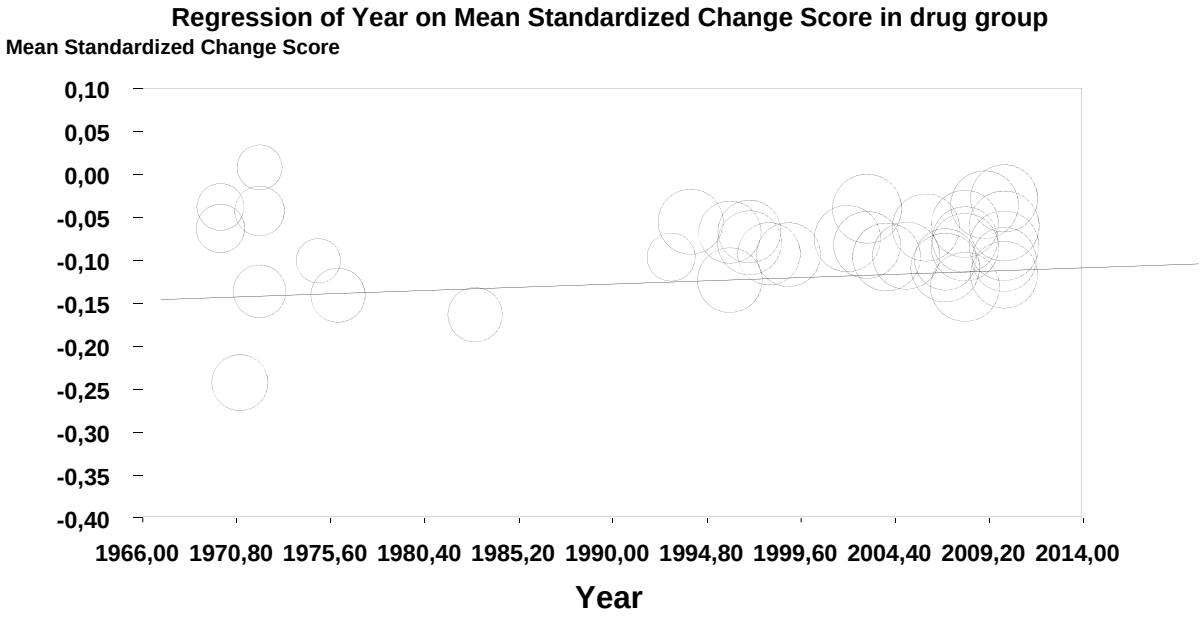
We did not find a significant decrease or increase of drug-reponse over the years in any of the three analyses. Moreover, it should be noted that in our more than two times larger main analysis (see Figure 4 and Table 2 in the main manuscript), drug response did not increase over the years).

1. Spearman correlation of drug-response (standardized mean change score) and publication year

Spearman correlation coefficient R = -0.029, p = 0.83, 56 study arms

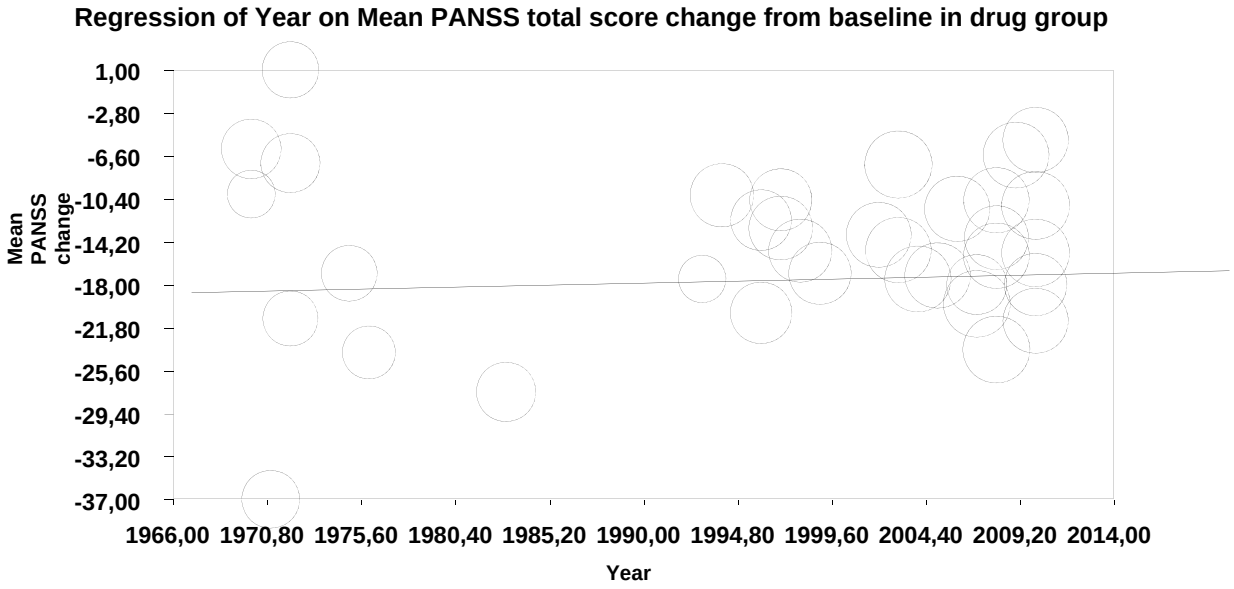


2. Meta-regression of drug-response (standardized mean change score) and publication year



Slope = 0.00078, 95% confidence interval -0.00018 to 0.00175, p-value = 0.11

3. Meta-regression of drug-response (mean PANSS total score change from baseline) and publication year



Slope = 0.03648, 95% confidence interval -0.12528 to 0.19823, p-value = 0.66

Discussion

We could not replicate the finding of decreasing drug-response over time by Rutherford et al.(1) As in our analysis, drug-response remained stable over the year, it is only the response in the placebo groups which has gone up. This is in line with an analysis of a database available to the Food and Drug Administration.(36) As explained above, the most likely explanation is that Rutherford et al.(1) did not only use the drug groups from the placebo-controlled trials, but also from trials that compared two antipsychotics with each other, without a placebo group. Excluding the head-to-head trials from the analysis, no decreasing drug-response can be found. As a limitation, it is possible that we did not always extract the data in exactly the same way as Rutherford et al.(1) For example, in contrast to the current analysis, they also included subtherapeutic doses. Such doses are nowadays used either in dose-finding studies or as pseudo-placebos (e.g. olanzapine 1mg/day). The approach can have reduced effect sizes of recent years artificially because both dose-finding studies and studies using pseudo-placebo doses became widespread only in the 1990s. But we believe that the major difference is the inclusion of a

different type of studies in the analysis. This finding is important for the understanding of what explains the decreasing effect sizes over time.

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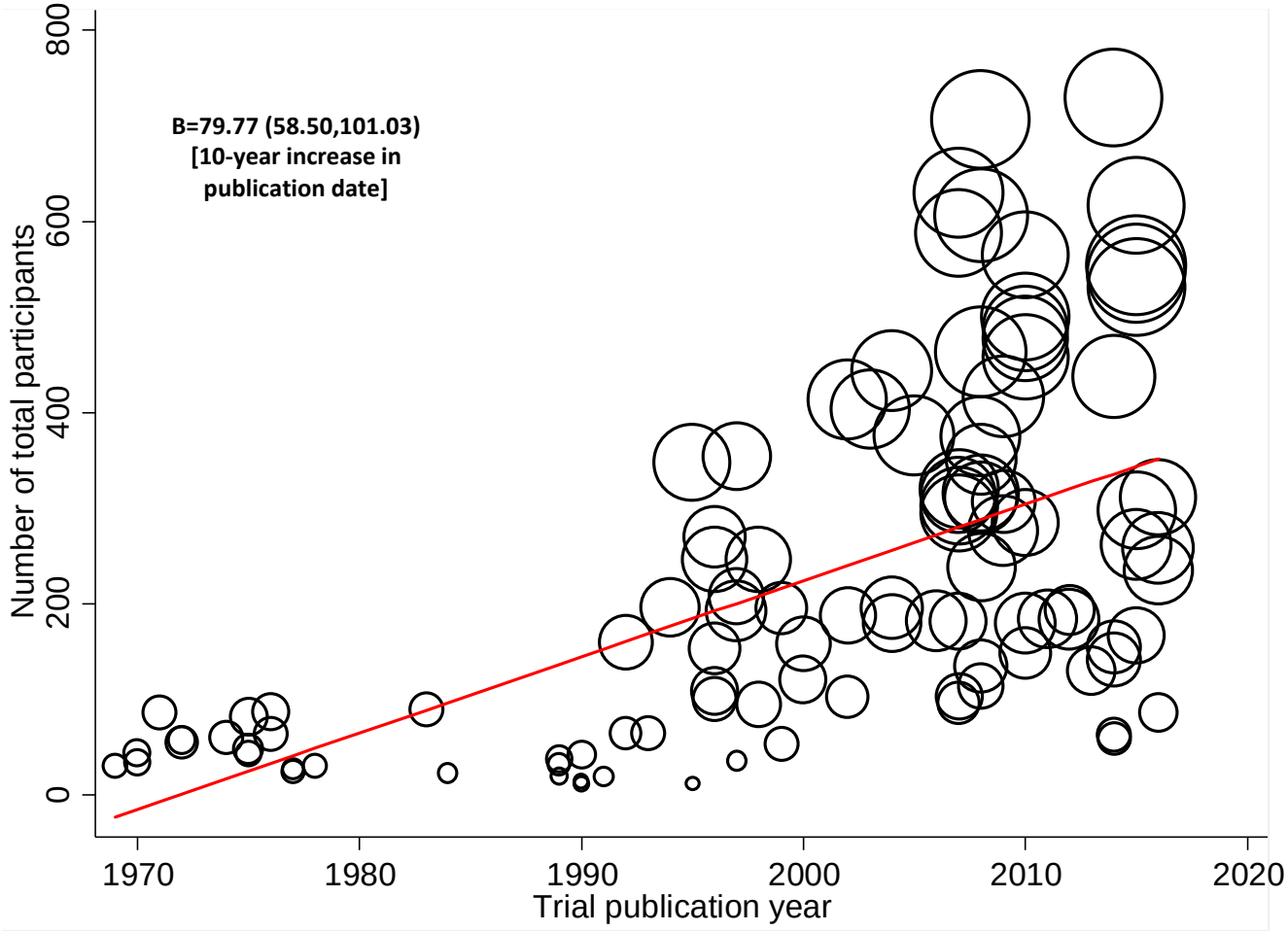
Supplementary Figure S4

Association between publication year and sample size


B=79.77 (58.50,101.03)
[10-year increase in
publication date]
Number of total participants
0
200
400
600
800
1970
1980
1990
2000
2010
2020
Trial publication year