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Treatment of people with a first episode of schizophrenia: network meta-analysis of randomised controlled trials and metaregression of response predictors

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Abbreviation

Biosis Biosciences Information Service

BPRS Brief Psychiatry Rating Scale

CGI Clinical Global Impression

CI Confidential Interval

CINeMA Confidence in Network Meta-analysis

DUP Duration of Untreated Psychosis

DSM-IV Diagnostic and Statistical Manual of Mental Disorders

EMBASE Excerpta Medica Database

EPS Extrapyramidal symptom

EUFEST European First-Episode Schizophrenia Trial

FGA First Generation Antipsychotics

GAF Global Assessment of Functioning

GRADE Group Reading Assessment and Diagnostic Evaluation

ICD-10 10th revision of the International Statistical Classification of Diseases and Related Health Problems

MEDLINE Medical Literature Analysis and Retrieval System Online

NIMH National Institute of Mental Health

NMA Network Meta-analysis

OR Odds Ratio

PANSS Positive and Negative Symptom Scale

PSP Personal and Social Performance Scale

PsycINFO Psychology Information (Database of Abstracts of Literature in Psychology)

PubMed Public Medline (Database of references and abstracts on life sciences and Biomedical Topics)

RAISE-ETP Recovery After an Initial Schizophrenia Episode Project's Early Treatment Program

RCT Randomized Clinical Trial

RevMan Review Manager

SANS Scale for the Assessment of Negative Symptom

SAPS Scale for the Assessment of Positive Symptom

SGA Second Generation Antipsychotics

SMD Standardised Mean Difference

SUCRA Surface Under the Cumulative Ranking Curve

SWUN Subjective Well-being Under Neuroleptics Scale

Abstract

The first episode is widely viewed as a pivotal phase of schizophrenia treatment. Many first-episode patients must take antipsychotic drugs for the entire duration of their illnesses. The first step in optimizing their treatment is to choose a suitable drug. However, it is unclear which drug is the best for this population. Multiple randomized controlled trials involving first-episode patients have been conducted, but two systematic reviews using conventional meta-analytic methods found different conclusions. Network meta-analysis is a new method that has the advantage of combining direct and indirect evidence. The first section of this thesis, therefore, compared the efficacy and tolerability of all licensed antipsychotics in the first-episode population using network meta-analysis. A broad search for randomized controlled trials comparing antipsychotic drugs with or without placebo in people with schizophrenia was performed using multiple electronic databases (update search: November, 2016). Nineteen studies with 2,669 participants were identified. The findings of this section indicated the significant superiority of several second-generation antipsychotics as compared to haloperidol, but very few significant differences between second-generation antipsychotics appeared in terms of efficacy and acceptability. The tolerability results were generally compatible with previous findings for the chronic population. There is very little evidence that treatment recommendations can be based on efficacy differences between second-generation antipsychotics. Until clearer efficacy differences are found in future studies, treatment decisions in first-episode patients should be guided by side-effects. One reason why it was difficult to find efficacy differences between compounds in section one was that patients with a first-episode of schizophrenia may respond so well to antipsychotics that there could be ceiling effects. In the second section of the thesis

it was therefore attempted to determine how well first-episode patients respond to antipsychotics because thus far, no systematic review had addressed this. Seventeen studies with 3,156 participants were included. The findings showed that 81.3% and 51.9% of first-episode patients reached at least 20% and 50% PANSS/BPRS reduction from baseline, respectively. These rates are clearly higher than the average response rates in chronic patients. Moreover, female patients, drug-naive patients, more severely ill patients at baseline, and patients with short illness durations had better response rates as compared to their counterparts, which can have implications for the treatment of people experiencing a first episode of schizophrenia.

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1. Introduction

(The contents in the introduction section that are the same as in the two original papers with Yikang Zhu as first author have been marked via the indention of the appropriate paragraphs, as well as a quote from the articles at the end of every such paragraph.)

Schizophrenia is a severe mental illness that causes productivity losses in the affected individuals and creates enormous economic burdens on their families and society. In the US, the economic burden of schizophrenia increased from 62.7 billion US dollars (reported in 2002) to 155.7 billion US dollars in 2013 (Cloutier et al., 2016). Schizophrenia usually begins in adolescence (Keshavan et al., 2014) and lasts for the affected individual's entire life (American Psychiatric Association, 2013). Most individuals with schizophrenia remain chronically ill, while about 20% of patients experience a single psychotic episode and then recover their pre-onset functioning (Alvarez-Jimenez et al., 2011). At present, the most common choice for the treatment of schizophrenia is antipsychotic drugs, which have been studied in at least several thousands RCTs. Numerous studies indicate that treatment response differs substantially among schizophrenics (Gardner and Bostwick, 2012, Lieberman et al., 1996a, Lieberman et al., 1996b). Thus, it is essential to investigate the efficacy and side-effect outcomes in specific subgroups of people with schizophrenia. The classification of these subgroups of schizophrenics, including first-episode patients, child and adolescent patients, treatment-resistant patients, elderly patients, patients with prominent negative symptoms, co-morbid substance abuse patients, and prodromal patients, has been recognized in the field of psychiatry. Systematic reviews of the efficacy and safety of antipsychotic drugs by subgroup can provide recommendations for the individualization of treatment. Furthermore, it can facilitate clinicians in making accurate decisions regarding treatment choice, which may

reduce the consumption of medical resources and the consequent economic burden on patients.

> The first episode of schizophrenia is considered a pivotal phase in treatment. Receiving optimal treatment at this stage can improve long-term outcomes. *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 836 paragraph 1)*

> In general, first-episode patients are characterized by younger age, milder cognitive impairment (McCleery et al., 2014), less negative symptoms (Sanger et al., 1999), and less brain volume loss (Torres et al., 2016) and functional change (Li et al., 2016). *(Zhu et al. 2017 Lancet Psychiatry, page 694 paragraph 2)*

Patients with schizophrenia often grow progressively worse and tend to become more resistant with each relapse (Lieberman et al., 2007). Multiple episodes will aggravate brain function impairment (Dietsche et al., 2017, Li et al., 2016) and deteriorate general functioning (Pukrop et al., 2006). First-episode patients usually have shorter illness durations and less antipsychotic exposure as compared to chronic patients (Crespo-Facorro et al., 2016). The peak age at first-episode onset is the early to mid-20s for males and the late 20s for females (American Psychiatric Association, 2013). This period is a critical period of mental growth and functional recovery. Good control of symptoms during this stage ensures that patients can continue participating in work and studies. However, the heterogeneity of patients with schizophrenia poses a challenge to clinicians when creating appropriate treatment plans.

Treatment response in schizophrenia has received a great deal of attention in this field (Gardner and Bostwick, 2012, Lieberman et al., 1996a, Lieberman et al., 1996b).

An earlier theory suggested that the therapeutic effect of antipsychotic drugs could only be observed after several weeks of antipsychotic use, even though a steady level of drug concentration had already been achieved (Agid et al., 2003). However, recent studies have indicated that the response to antipsychotic drugs may occur much earlier than previously thought (Kapur et al., 2005).

> It has been demonstrated that a substantial amount of treatment effect occurs during the first two weeks (Agid et al., 2003, Leucht et al., 2005a) and response curves often flatten after the third week of treatment (McMahon et al., 2008). *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 841 paragraph 20-21)*

Many researchers have attempted to identify clinically useful predictors of response in schizophrenia. The evidence suggests that several robust factors associated with poor therapeutic outcomes include male sex, earlier disease onset, poor premorbid adjustment, longer illness duration, severe baseline psychopathology, comorbidities (especially substance use disorders), longer duration of untreated psychosis (DUP), and non-adherence to antipsychotics (Carbon and Correll, 2014). A meta-analysis of diagnostic tests also found that a lack of improvement at week 2 predicted later non-response to antipsychotic treatment in patients with acute exacerbation of schizophrenia (Samara et al., 2015). This meta-analysis mainly included studies conducted with chronic patients. However, the response patterns in first-episode patients remain unclear.

Over the past decades, many RCTs have been conducted with first-episode schizophrenia patients. The Recovery After an Initial Schizophrenia Episode Project's Early Treatment Program (RAISE-ETP) and the European First-Episode

Schizophrenia Trial (EUFEST) represent the two largest studies addressing the issue of the efficacy and safety of antipsychotic drugs in patients with first-episode schizophrenia. RAISE-ETP, developed by NIMH, was a US-based nationwide effectiveness study conducted at 34 community treatment centers in 21 states among patients with first-episode schizophrenia spectrum disorders (Kane et al., 2015). EUFEST was an open-labeled, 1-year randomized trial comparing haloperidol to multiple SGAs in patients with first-episode schizophrenia (Fleischhacker et al., 2005). In addition to these two large studies, many RCTs have compared the efficacy of various antipsychotics. However, most RCTs had relatively small samples, and thus, their findings must be proven further.

> To my knowledge, there have been two meta-analyses addressing whether SGAs are superior to FGAs in first-episode schizophrenia, but they reached with different conclusions (Crossley et al., 2010, Zhang et al., 2013). The differentiation between SGAs and FGAs has not been emphasized since patent prevention was terminated. *(Zhu et al. 2017 Lancet Psychiatry, page 695 paragraph 4)*

SGAs have generally been believed to be associated with a lower risk of EPS and a higher risk of metabolic side effects as compared to FGAs (Tandon, 2011). Studies (Leucht et al., 2009, Leucht et al., 2013) have also shown that most common SGAs (e.g., olanzapine, risperidone) are better than placebos and FGAs in terms of overall symptom reduction. However, the abovementioned meta-analysis studies (Crossley et al., 2010, Zhang et al., 2013) used conventional pairwise meta-analyses, which can only compare two drugs directly and cannot provide an indirect comparison. They did not determine which drug is best for first-episode patients.

> In this regard, network meta-analysis (also called multiple treatment meta-analysis) can realize the integration of both direct and indirect evidence. *(Zhu et al. 2017 Lancet Psychiatry, page 695 paragraph 4)*
>
> For example, when there are only trials between drug A and drug B or between drug B and drug C but no trials between drug A and drug C, network meta-analysis can fill gaps in the evidence matrix by using direct evidence (A vs B, B vs C) and also indirect evidence (A vs C). *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 13)*

The purpose of the thesis was to compare the efficacy and tolerability of licensed antipsychotics (SGAs and FGAs) in the first-episode population. The thesis consists of two sections: 1) network meta-analysis was used to integrate all the randomised evidence on antipsychotic drugs in this patient group. 2) Another meta-analysis was conducted to find how many first-episode patients respond to antipsychotics according to two response cut-offs. Moreover, a meta-regression was applied to identify factors that predict treatment response in this population.

2. Methods

(The contents in the methods section that are the same as in the two original papers with Yikang Zhu as first author have been marked via the indention of the appropriate paragraphs, as well as a quote from the articles at the end of every such paragraph.)

I. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review, pairwise and network meta-analysis

2.1. Participants and interventions

The participants should satisfy the following inclusion criterion: experiencing first-episode schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders). There was no age limit and no restrictions on setting, gender, or ethnicity. *(Zhu et al. 2017 Lancet Psychiatry, page 695 paragraph 5)*

All definitions of “first-episode” created by the original authors were accepted. *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 836 paragraph 3)*

Studies in which less than 20% of participants were non-first-episode patients or less than 20% were suffering from psychiatric disorders other than schizophrenia (e.g., depression or mental retardation) were acceptable. Studies of treatment-resistant patients, patients with predominantly negative symptoms, patients with concomitant medical or psychiatric illness (e.g., studies in which all patients also had concomitant cannabis abuse), and also studies of stable patients were excluded. *(Zhu et al. 2017 Lancet Psychiatry, page 695 paragraph 5)*

> All trials, irrespective of the diagnostic criteria used, were acceptable, and studies that did not use operationalized criteria, such as ICD-10 or DSM-IV were included in a sensitivity analysis. *(Zhu et al. 2017 Lancet Psychiatry, page 697 paragraph 16)*

> The interventions were antipsychotics (SGAs and FGAs) that were licensed in at least one country and administered via any mode (oral tablets or oral liquid). The considered antipsychotics included amisulpride, aripiprazole, asenapine, benperidol, brexpiprazole, cariprazine, chlorpromazine, clopenthixol, clozapine, flupenthixol, fluphenazine, fluspirilene, haloperidol, iloperidone, levomepromazine, loxapine, lurasidone, molindone, olanzapine, paliperidone, quetiapine, penfluridol, perazine, perphenazine, pimozide, risperidone, sertindole, sulpiride, thioridazine, thiothixene, trifluoperazine, ziprasidone, zotepine, and zuclopenthixol. Depot formulations were excluded because they are mainly used for long-term relapse prevention. According to the International Consensus Study on Antipsychotic dose, the first episode of psychotic illness led to a 25%-30% lower recommended dose than repeatedly acutely psychotic patients (Gardner et al., 2010). *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 6)*

Therefore, lower doses than those recommended for multiple-episode patients in the International Consensus Study were also acceptable.

> All flexible-dose studies were included because these allowed the investigators to titrate to an adequate dose for the individual patient. *(Zhu et al. 2017 Lancet Psychiatry, page 695 paragraph 5)*

2.2. Search strategy and study selection

Multiple database were searched (MEDLINE, EMBASE, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov) for reports published up to November 17, 2016 regarding RCTs that compared antipsychotics with or without placebo in people with schizophrenia, as well as reference lists of previous reviews (Crossley et al., 2010, Leucht et al., 2013, Zhang et al., 2013). The search phrases included terms for schizophrenia and schizophrenia-like disorders, randomization, and all the abovementioned drugs. *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 8)*

Quasi-randomized studies (e.g.,allocation by day of the week) were excluded. Due to the limited number of RCTs involving first-episode schizophrenia, open-label RCTs were included, but these were excluded from the sensitivity analysis of the primary outcome. Cluster-randomized trials were generally excluded. In cross-over trials, only data up to the point of the first cross-over were used to avoid carryover effects (Elbourne et al., 2002). Studies from mainland China were excluded to avoid a systematic bias because serious quality concerns have been raised concerning such studies (www.cfdi.org.cn/resource/news/7713.html). *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 9)*

2.3. Outcomes

2.3.1. Primary outcome

The primary outcome was the overall symptoms of schizophrenia, as measured by rating scales such as PANSS (Kay et al., 1987), BPRS (Overall and Gorham, 1962), or of any other validated scale (e.g., the

Manchester Scale (Hyde, 1989)) for the assessment of overall schizophrenic symptomatology. *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 7)*

The overall symptoms of schizophrenia, as measured by such scales, were the primary outcome in numerous systematic reviews. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 4 paragraph 24)*

Because not all studies used the same scale, the following hierarchy was applied: the mean change in PANSS total score from baseline to endpoint was at the top, followed by the mean change in BPRS score, the mean values at endpoint of the PANSS/BPRS, and finally, other scales. *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 7)*

The results for other rating scales were only used if the instrument has been published in a peer-reviewed journal because it has been shown that invalidated schizophrenia scales exaggerate differences. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 4-5 paragraph 24)*

2.3.2. Secondary outcomes

1. Response to treatment (dichotomous):

   Dichotomous responder data were only secondary outcomes because it must be expected that different criteria were used to define response. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 5 paragraph 25)*

   The definitions used by the original authors were allowed (if available, we preferred 50% PANSS/BPRS reduction and Clinical Global Impression (Guy,

1976) of at least much improved to lower thresholds). *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 7)*

2. Change in the positive symptoms of schizophrenia:

The positive symptoms of schizophrenia were defined according to the positive subscale of PANSS or SAPS or other validated positive symptom scales. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 5 paragraph 25)*

3. Change in the negative symptoms of schizophrenia:

The negative symptoms of schizophrenia were defined according to the negative subscale of PANSS or SANS or other validated negative symptom scales. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 5 paragraph 25)*

4. Dropout for any reason (all-cause discontinuation):

All-cause discontinuation (“dropping out”) for any reason combines efficacy, tolerability, and other factors and is therefore considered a measure of the “acceptability of treatment” (Cipriani et al., 2009). It is being applied more and more frequently in psychiatric trials. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 6 paragraph 25)*

5. Dropout due to the inefficacy of treatment:

Dropout due to the inefficacy of treatment is an additional outcome of the efficacy of treatment that has frequently been considered in other systematic reviews. Dropout due to adverse events was not analyzed. Although, at first

glance, this seems to be a measure of overall tolerability, it is frequently confounded by efficacy-related adverse events such as the “exacerbation of psychosis”. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 6 paragraph 25)*

6. Adverse events:

Antipsychotics are associated with a wide variety of side-effects. The following selection covers the most important domains that are usually mentioned in the side-effect tables of the relevant guidelines: a) EPS: The use of anti-Parkinson medication is an objective, global measure of EPS, such as parkinsonism, akinesia, or dystonia. b) Akathisia: This movement disorder probably has a different mechanism of action than other EPS and therefore seems to be quite frequent with SGAs such as aripiprazole or amisulpride, which are otherwise relatively benign in terms of EPS (Leucht et al., 2013); the treatment of akathisia is also different, in part, from that of other EPS (e.g., beta-blockers are recommended), so it cannot be fully alleviated via the use of anti-Parkinson medication. c) Weight gain (mean change and number of participants with significant weight gain): this is the most important side effect of many SGAs (Leucht et al., 2013), and it is correlated with increases in glucose, cholesterol, and triglycerides. The additional analysis of these metabolic effects was not considered because it is unlikely that they were frequently analyzed in old RCTs. d) Prolactin levels (mean change and number of participants with significant increases): this objective measure can cause sexual side-effects and osteoporosis. e) Sedation/somnolence. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 6 paragraph 25)*

7. Patients' subjective well-being and quality of life:

For many patients, overall quality of life may be more important than the mere reduction of schizophrenic symptoms. This outcome was measured by the mean values of these concepts on various rating scales (e.g., "Subjective well-being under neuroleptics scale" (SWUN)) *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 6 paragraph 25)*

8. Overall functioning:

The consideration of the outcomes of social participation has increasingly been called for. Functioning will be measured by rating scales such as GAF or PSP. *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 6 paragraph 25)*

2.4. Data extraction and risk-of-bias assessment

Two reviewers independently inspected all abstracts identified in the searches. Disagreements were resolved via discussion, and where doubt still remained, the full article was acquired for further inspection. Once the full articles were obtained, two reviewers independently determined whether the studies met the inclusion criteria. If disagreements could not be resolved, these two reviewers discussed the situation with the team leader and also contacted the authors via e-mail to seek further information. Again, two reviewers independently reviewed the full text and extracted the relevant data from the included trials. *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 10-11)*

In addition, the extracted data from all included studies were double-checked by the author for consistency.

> The quality of studies was assessed in terms of sequence generation, allocation concealment, blinding, the completeness of the outcome data, selective reporting, and other biases using the Cochrane risk-of-bias tool (Higgins and Green, 2011). The global risk-of-bias rating for each study was assessed based on the criteria applied in a network meta-analysis of antidepressants (Furukawa et al., 2016). *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 11)*

2.5. Statistical analysis

> First, random-effects, pairwise meta-analyses were conducted with RevMan (Version 5.3). The SMD was used as the effect size for continuous outcomes and the OR was used as the effect size for dichotomous outcomes. Both types of effect size were reported along with their 95% CI. The heterogeneity in each pairwise comparison was assessed with the I^2 statistic (I^2 > 50% indicated considerable heterogeneity). *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 12)*
>
> Second, random-effects network meta-analyses were conducted within a frequentist framework in Stata (Version 14.0), using the *network* package (White, 2015) to estimate summary effect sizes, which were also presented as SMDs or ORs along with their 95% CI. A common heterogeneity estimate was assessed for all treatment comparisons. *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 13)*

Meta-analytic figures were produced with the *network graphs* Stata package (Chaimani and Salanti, 2015).

Network meta-analysis synthesizes both direct and indirect evidence, allows the comparison of the relative effectiveness of a pair of antipsychotics that have not been compared previously in any of the included trials, and provides a hierarchy of treatments according to any outcome being considered (Salanti, 2012). The surface under the cumulative ranking curve (SUCRA) was used to provide a hierarchy of the competing treatments (Salanti et al., 2011). *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 7-8 paragraph 28)*

The SUCRA is a simple transformation of the mean rank and it ranged from 0 to 1. The SUCRA value will be 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst (Salanti et al., 2011). *(Zhu et al. 2017 Lancet Psychiatry, page 696 paragraph 13)*

The main assumption of network meta-analysis is that of transitivity, meaning that the distribution of effect modifiers remains the same across treatment comparisons (Salanti, 2012). *(Zhu et al. 2017 Lancet Psychiatry, Supplementary Appendix, page 7 paragraph 28)*

To assess the transitivity assumption before performing our network meta-analysis, the similarity of populations was ensured within and across treatment comparisons by using relatively narrow inclusion criteria. To statistically evaluate transitivity, the author considered whether the potential effect modifiers were distributed similarly across direct comparisons. *(Zhu et al. 2017 Lancet Psychiatry, page 697 paragraph 14)*

The heterogeneity of the network meta-analyses was assessed using the between-studies variance tau square for each outcome by referring to the empirical distributions of heterogeneity values typically found in meta-analyses (Rhodes et al., 2015, Turner et al., 2012). Inconsistency (disagreements between direct and indirect evidence) was tested using several approaches: a) the loop-specific method, which tests inconsistency in every closed loop of evidence (Bucher et al., 1997); b) the side-splitting approach, which tests discrepancies between the direct and indirect evidence obtained via the entire network for each comparison (Dias et al., 2010); and c) the design-by-treatment interaction model, which tests inconsistency from all possible sources within the network jointly (Higgins et al., 2012). *(Zhu et al. 2017 Lancet Psychiatry, page 697 paragraph 15)*

Two planned sensitivity analyses on the primary outcome were conducted *a priori* to evaluate the robustness of the estimates derived from the primary analysis: the exclusion of open-label RCTs and the exclusion of studies that did not use operationalized criteria, such as the ICD-10 or DSM-IV. A *post-hoc* sensitivity analysis was also performed, in which we included the study by Robinson et al. (Robinson et al., 2006). The definition of “short term” adopted was the standard of the Cochrane Schizophrenia Group, which defines periods up to 3 months as short term. This study was originally excluded because its duration (16 weeks) exceeded our *a-priori*-defined maximum (13 weeks). *(Zhu et al. 2017 Lancet Psychiatry, page 697 paragraph 16)*

To explore the reasons for heterogeneity, the planned meta-regression analyses (continuous moderators) and subgroup analyses (dichotomous

moderators) of the primary outcome were conducted using the following variables: drug naivety, the severity of illness at baseline, the duration of untreated psychosis (DUP) and the gender ratio. A *post-hoc* subgroup analysis was performed based on haloperidol dose and using overall symptom change and use of anti-Parkinson medication as the outcomes. Moreover, subgroup analyses of the effects of haloperidol and risperidone dose were also conducted via simple pairwise meta-analyses of these outcomes. The dose cutoffs for the subgroup analyses were more than or equal to 4 mg/day versus less than 4mg/day. Lower thresholds could not be examined, because the lowest haloperidol and risperidone doses were 3 and 2.4 mg/day, respectively. Haloperidol/risperidone was compared with all other antipsychotics as a group in the latter subgroup analyses. *(Zhu et al. 2017 Lancet Psychiatry, page 697 paragraph 17)*

The potential small-trial effects and publication bias of the primary outcome were assessed with a comparison-adjusted funnel plot (Chaimani et al., 2013). The author assumed that more recently introduced drugs were potentially favored in small trials. Standard funnel plots of single comparisons (e.g., olanzapine vs haloperidol) were planned if at least ten relevant studies were available. *(Zhu et al. 2017 Lancet Psychiatry, page 697 paragraph 18)*

Finally, the quality of evidence was assessed regarding the primary outcome and the most important secondary outcome (the use of anti-Parkinson medication at least once) based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is in line with the framework suggested by Salanti et al. (Salanti et al., 2014). The

author assessed the following five domains to determine the level of confidence in a specific pairwise effect and treatment ranking as estimated via network meta-analysis: study limitations, indirectness, inconsistency, imprecision, and publication bias. The author applied an under-development online tool known as CINeMA (http://ec2-35-156-97-18.eu-central-1.compute.amazonaws.com:8004/ocpu/library/contribution/www/#welcome) for the assessment of study limitations. *(Zhu et al. 2017 Lancet Psychiatry, page 697 paragraph 18)*

II. How well do patients with a first episode of schizophrenia respond to antipsychotics: a systematic review and meta-analysis

2.6. Definitions of response

PANSS and BPRS are the most frequently used instruments in assessing psychopathology in schizophrenia trials. In most antipsychotic drug trials, the PANSS/BPRS mean endpoint score or the mean change from the baseline score is used as the primary outcome (Leucht et al., 2005b, Leucht et al., 2005c). However, one problem is that a highly statistically significant difference between interventions could result in a difference of only a few scale points (Leucht et al., 2007). Interpreting the results from a clinical perspective is thus a thorny issue. To solve this problem, the PANSS/BPRS-defined response rate is a useful measure that can be understood more intuitively than a mean difference in scale points (Leucht et al., 2007). However, a further problem is that various definitions of response have been used in clinical trials and there is no consensus regarding which cutoff is the most appropriate.

Equipercentile linking studies comparing PANSS/BPRS ratings with simultaneous CGI ratings (Guy, 1976) have shown that at least 20% cutoff, which has been most frequently used, does not even mean minimally improved according to the CGI of the raters, whereas the 50% cutoff roughly corresponds to much improved according to the CGI (Leucht et al., 2005b, Leucht et al., 2005c, Schennach-Wolff et al., 2010, Levine et al., 2008). Therefore, the results were presented for both 50% and 20% cutoffs, but 50% was the primary cutoff value based on the assumption of high response rates among first-episode patients. When results based on other cutoffs were reported (e.g., 30% or 40%) or when no response rates were presented, the author used an imputation method first proposed by Furukawa et al. (Furukawa et al., 2005) and then replicated by Samara et al. (Samara et al., 2013) to estimate at least 20% and 50% cutoffs by converting the means and standard deviations of the PANSS/BPRS scores at endpoint or the change in scores from baseline. Another fundamental problem is that the PANSS/BPRS-defined response rate is often calculated incorrectly (Obermeier et al., 2011), because the minimum score of 30/18 is not subtracted when a 1-7 scoring system is used, which leads to the underestimation of the response rate (Leucht et al., 2007, Obermeier et al., 2010). Accordingly, the minimum score of 30/18 was subtracted when estimating the percentage of PANSS/BPRS rating reduction (Leucht et al., 2005b, Leucht et al., 2005c, Schennach-Wolff et al., 2010). *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 837 paragraph 5)*

2.7. Statistical analysis

> A single-group summary meta-analysis was conducted with Comprehensive Meta-Analysis software (Version 2.0) (Biostat, Inc., Englewood, NJ. USA) for both at least 20% and 50% cutoffs. This single-group summary meta-analysis was performed to obtain an average of all included studies in one group instead of a between-group difference, but the essence of the calculation is same as that described above (Borenstein et al., 2009). *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 837 paragraph 6)*

The response rate among first-episode patients was examined by pooling the response rates of the individual arms.

> To determine whether the results were robust, a sensitivity analysis was performed to first combine the arms of each study and then pool the studies. Because the imputation method tended to introduce bias into the results of the estimation by centralizing the distribution of the lower and higher values, the author performed another sensitivity analysis, excluding the imputed response rates (Samara et al., 2013). Heterogeneity was evaluated using the I-square statistic (>50% indicated considerable heterogeneity) (Higgins et al., 2003). To explore which factors explained heterogeneity, the author performed subgroup (binary outcomes) and meta-regression (continuous outcomes) analyses for the 50%-cutoff data using a random-effects model. The subgroup analyses were used to compare various study designs (blinded vs open-label) and various types of participants (drug-naive vs pre-treated). The moderators for the meta-regression analyses were chosen *a priori* and included gender ratio, mean age, study duration, the duration of illness, the baseline severity of illness, and the dose of antipsychotics in olanzapine equivalents (Gardner et al., 2010). The small-study effects were

assessed via a visual examination of funnel plots. *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 837-838 paragraph 6)*

3. Discussion

(The contents in the discussion section that are the same as in the two original papers with Yikang Zhu as first author has been marked via the indention of the appropriate paragraphs, as well as a quote from the articles at the end of every such paragraph.)

I. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review, pairwise and network meta-analysis

> Both pairwise and network meta-analyses were used to integrate the currently available randomized evidence in the domains of the efficacy, acceptability, and tolerability of antipsychotics in the acute treatment of first-episode schizophrenia. Overall, the significant superiority of several SGAs as compared to haloperidol was found, but very few significant differences between SGAs in terms of efficacy and acceptability emerged. The results regarding tolerability were generally compatible with previous findings in the chronic population (Leucht et al., 2013). *(Zhu et al. 2017 Lancet Psychiatry, page 701 paragraph 32)*
>
> Regarding the primary outcome, the significant superiority of amisulpride, olanzapine, ziprasidone and risperidone compared to haloperidol was found, as was that of amisulpride as compared to quetiapine. When excluding open-label trials in a sensitivity analysis of the primary outcome, the only significant difference was the superiority of olanzapine over haloperidol and quetiapine. Much like an earlier conventional meta-analysis performed by Zhang et al. (Zhang et al., 2013), this result also shows that several SGAs were better than haloperidol in terms of efficacy, whereas very few significant differences between SGAs were found. This suggests that there

> is very little evidence that treatment recommendations can be made based on efficacy differences between SGAs. *(Zhu et al. 2017 Lancet Psychiatry, page 701 paragraph 33)*
>
> Because first-episode patients, in general, respond better than chronic patients, the ceiling effects of antipsychotic response in the first-episode population could be responsible for these results. For instance, a recent meta-analysis (Leucht et al., 2017) performed by our team found that only 51% and 23% of chronic patients achieved an at least a 20% and 50% PANSS/BPRS reduction from baseline, respectively, although it must be noted that these were placebo-controlled trials, while no placebo-controlled trial was found for the current analysis. In contrast, it has been reported that the remission rates of first-episode patients are 87% by 1 year (Robinson et al., 1999) and 90% by 2 years (Lieberman et al., 2003). The remission rates in first-episode patients are so high that measuring efficacy differences between SGAs becomes difficult. *(Zhu et al. 2017 Lancet Psychiatry, page 702 paragraph 34)*

This hypothesis is explored in the second section of this thesis.

> All-cause discontinuation is often considered a measure of the acceptability of treatments (Cipriani et al., 2009) because it is composed of dropouts due to inefficacy and adverse events. In the NMA, aripiprazole, quetiapine, risperidone, and olanzapine were better than haloperidol, which indicates that compared to the only analyzed FGA (haloperidol), SGAs should be preferred in first-episode patients. *(Zhu et al. 2017 Lancet Psychiatry, page 702 paragraph 35)*

> The tolerability results generally corresponded to those of chronic patients (Leucht et al., 2013). In terms of broad measures of movement disorders, olanzapine was associated with the less frequent use of anti-Parkinson medication as compared to haloperidol, zuclopenthixol, and risperidone, and quetiapine was associated with the less frequent use of anti-Parkinson medication as compared to haloperidol and zuclopenthixol. Quetiapine and olanzapine produced less akathisia than haloperidol, risperidone, and aripiprazole. This demonstrates the low risk of movement disorders due to olanzapine and quetiapine in first-episode patients. *(Zhu et al. 2017 Lancet Psychiatry, page 702 paragraph 36)*

Weight gain is regarded as the most problematic side effect of most SGAs.

> Olanzapine produced statistically significantly more weight gain than all the other SGAs in our analysis. Thus, olanzapine is not recommended as the first-line treatment for first-episode patients in some guidelines (Buchanan et al., 2010, De Hert et al., 2012). *(Zhu et al. 2017 Lancet Psychiatry, page 702 paragraph 37)*

Severe weight gain can be associated with high cardiovascular risk and hepatic toxicity. Some reviews recommend that monitoring likely weight and metabolic changes across time is mandatory in first-episode patients who have just started antipsychotic treatment (Crespo-Facorro et al., 2016).

Prolactin increase is another major side effect of antipsychotics.

> Molindone, aripiprazole, olanzapine, and haloperidol produced less prolactin increase than risperidone, while no data were available for amisulpride and

> paliperidone, two other prolactin-elevating antipsychotics. *(Zhu et al. 2017 Lancet Psychiatry, page 702 paragraph 37)*

Prolactin increases with antipsychotics have been proven to be dose-dependent (Peuskens et al., 2014), and sustained prolactin increases can be associated with amenorrhoea, galactorrhea, hirsutism, gynecomastia, impotence, and osteoporosis (Byerly et al., 2009, Trives et al., 2013).

> In contrast, the finding that quetiapine produced less sedation than risperidone and aripiprazole could be artifactual because a large NMA study in chronic patients indicated that quetiapine was more sedating than risperidone and aripiprazole (Leucht et al., 2013). Furthermore, this outcome was statistically significantly inconsistent; thus, the result is not reliable. *(Zhu et al. 2017 Lancet Psychiatry, page 702 paragraph 37)*

> Dose effects were addressed in several analyses of the primary outcome (overall reduction in symptoms) and secondary outcome (the use of anti-Parkinson medication), because these outcomes may be the most relevant to dose effects. *(Zhu et al. 2017 Lancet Psychiatry, page 702 paragraph 38)*

However, due to the limited number of trials for each drug, these post-hoc subgroup analyses had to be restricted to haloperidol dose and risperidone dose. The dose cutoffs for were higher than and equal to 4 mg/day versus lower than 4 mg/day for both drugs.

> Higher haloperidol doses were found to be associated with significantly more frequent use of anti-Parkinson medication as compared to lower doses, while no dose effects of risperidone were found for this outcome, and no

> subgroup differences in the overall reduction of symptoms were found for either haloperidol or risperidone. *(Zhu et al. 2017 Lancet Psychiatry, page 700 paragraph 29)*
>
> In line with some (Leucht et al., 2013, Davis et al., 2003), but not all (Geddes et al., 2000) earlier meta-analyses of chronic patients, dose effects on efficacy were not found. Because haloperidol is associated with a particularly high risk of movement disorders and it was the only FGAs with several trials available, these results cannot be generalized to most other FGAs. Furthermore, a 2 mg/day dose of haloperidol may be sufficient in first-episode patients (Oosthuizen et al., 2004), but most included haloperidol trials used doses higher than 2 mg/day. This should be taken into account when interpreting the results. *(Zhu et al. 2017 Lancet Psychiatry, page 702-703 paragraph 38)*

Consistency is a central assumption of NMA (Salanti, 2012). Three methods were used to test for inconsistency.

> The results indicated that there was no important inconsistency for the primary outcome, but the loop-specific and side-splitting tests showed some inconsistency for the secondary outcomes (positive symptoms, negative symptoms, and sedation). The design-by-treatment interaction model suggested some inconsistency regarding sedation and prolactin as well. *(Zhu et al. 2017 Lancet Psychiatry, page 700 paragraph 28)*
>
> Additionally, we assessed the quality of evidence contributing to each network estimate using the GRADE framework in terms of study limitations, imprecision, inconsistency, indirectness and publication bias for the primary

outcome (overall reduction in symptoms) and secondary outcome (the use of anti-Parkinson medication). The quality of evidence for both outcomes was assessed as being between very low and moderate for the individual comparison and as low for the rankings. *(Zhu et al. 2017 Lancet Psychiatry, page 700 paragraph 31)*

Several limitations should be considered. Firstly, though nineteen RCTs with 2,669 participants were included, only haloperidol, olanzapine, risperidone, and quetiapine had several trials available. The results for most of the other antipsychotics were derived from indirect evidence in the network because the evidence regarding these antipsychotics was limited to a single trial. Secondly, haloperidol was the only FGA with several trials available, and for the newly marketed SGAs brexpiprazole, cariprazine, iloperidone, lurasidone, and paliperidone, there was not even a single trial. Therefore, no conclusions can be drawn regarding their effects in first-episode patients. Again, due to the dearth of available data, the network meta-regression analyses that had been planned for severity of illness at baseline, duration of untreated psychosis (DUP) (Perkins et al., 2005), and gender ratio were not feasible. Nevertheless, the author found dose effects of haloperidol on the use of anti-Parkinson medication based on a subgroup analysis of pairwise meta-analyses. Moreover, only short-term studies (up to 13 weeks) were included. There are some long-term studies, but most of these were open-label studies. Considering their heterogeneity, short-term and long-term studies were not combined in the NMA. Quality of life and overall functioning are viewed as important measures in assessing the effects of antipsychotics, but very few studies provided data regarding these outcomes. Future studies

should focus on them. Finally, the quality of evidence for the overall reduction of symptoms and the use of anti-Parkinson medication, as assessed via GRADE approach (Salanti et al., 2014), was between very low and moderate, which limits the confidence in these findings. *(Zhu et al. 2017 Lancet Psychiatry, page 703 paragraph 39)*

II. How well do patients with a first episode of schizophrenia respond to antipsychotics: a systematic review and meta-analysis

The main findings were that 81.3% and 51.9% of first-episode patients reached at least a 20% and 50% PANSS/BPRS score reduction from baseline, respectively, while a meta-analysis of chronic patients showed that only 53% and 23% of such patients reached 20% and 50% PANSS/BPRS score reduction from baseline (Leucht et al., 2017). *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 841 paragraph 19)*

The determinants of response were age, gender, baseline severity, drug naivety, and illness duration (patient characteristics), as well as the blindness of the study (methodological factor). The response rates in drug-naive first-episode patients were higher as compared to studies that allowed some pre-treatment. One potential explanation is that pre-treated patients already had decreased symptoms, so their leeway for response was lower than that of drug-naive patients. This could also explain why more baseline-severe patients had a higher response rate than less severe patients, which has also been proven in chronic patients (Furukawa et al., 2015, Rabinowitz et al., 2014). The meta-regression results revealed better treatment response in female patients and patients with shorter illness durations,

which is also consistent with the findings of Rabinowitz et al. (Rabinowitz et al., 2014). Although it has been hypothesized in the literature that female patients have better outcomes than males (Angermeyer et al., 1989), the reasons for this remain unclear. An increased response rate in patients with shorter illness durations may be associated with the duration of untreated psychosis (DUP). However, DUP could not be analyzed as a separate factor because it was rarely reported. One reason for the better response seen in older patients could be that the early onset of schizophrenia is typically associated with increased illness severity and a less treatable form of illness. Onset during youth may also be associated with co-morbidities, which places large demands on treatment. Regarding the higher response rates in open-label studies as compared to blinded RCTs, the author speculates that efficacy may be overestimated in open studies because raters know which treatment is assigned to the patients. In contrast, study duration was not correlated with treatment response. It has been demonstrated in previous studies that a substantial amount of treatment effect occurs during the first two weeks (Agid et al., 2003, Leucht et al., 2005a) and response curves often flatten after the third week of treatment (McMahon et al., 2008). Longer study duration, therefore, is not related to a better response. Finally, there was no significant correlation between antipsychotic dosage and response rates. This may be attributable to the conversion to olanzapine equivalents because each method of dose equivalent calculation has its own limitations (Leucht et al., 2016, Leucht et al., 2015, Leucht et al., 2014). *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 841 paragraph 20)*

Several limitations should be taken into account. Firstly, many included studies did not report the response rates for the two cutoffs. Therefore, the categorical response was estimated from the mean PANSS/BPRS scores and standard deviations using an imputation method. However, it has been proven that the imputation method tends to centralize the distribution of lower and higher values (Samara et al., 2013). For this reason, a sensitivity analysis excluding the imputed values was conducted, but this left only five studies. Thus, the results were not very useful. Secondly, due to the various definitions of “first-episode” used in the studies, it may be difficult to diagnose patients during the early stage of schizophrenia, which means that some first-episode patients may actually be suffering from mental illnesses other than schizophrenia. Moreover, not a single placebo-controlled first-episode study was identified. Because recent trials in chronic patients have shown a substantial placebo effect, it would be valuable to know the degree to which such effects explain the high response rates seen in first-episode trials. This would also have implications for future studies. Studies in the first-episode population may provide better sensitivity detection than trials involving chronic patients if placebo response in this population is not very high. For example, a previous large NIMH trial showed that there was a substantial difference between antipsychotic drugs and placebo (61% versus 22% for at least much improved on CGI), and about 50% of the sample in this study was first-episode or drug-naive (Cole, 1964). Similarly, a recent study by Rabinowitz et al. (Rabinowitz et al., 2014) revealed that drug-placebo differences were larger in patients with shorter illness durations. Emsley et al. (Emsley et al., 2013) also reported that the time to remission

was considerably longer during the second episode as compared to the first episode. However, due to ethical concerns, the benefits of conducting a placebo-controlled trial in first-episode patients should be carefully weighed against the risks. *(Zhu et al. 2017 Eur Neuropsychopharmacol, page 841 paragraph 21)*

3.1. Links between the two sections

The two sections of this thesis were framed around the general questions as to how effective antipsychotic drugs are for people with a first episode of schizophrenia, and whether there are efficacy differences between compounds. Antipsychotics are the only effective monotherapeutic approach in the treatment of first-episode schizophrenia, but two conventional meta-analyses could not determine which individual antipsychotic medication is the one best in important clinical domains of efficacy, acceptability and tolerability (Crossley et al., 2010, Zhang et al., 2013). Providing rankings of the different drugs in various domains with network meta-analysis has the potential to assist clinicians to set up more rational treatment plans.

In section 1, the differences in side-effects between compounds overall paralleled previous findings in chronic patients (Leucht et al., 2013). However, the results in the first section also showed that there is very little evidence for efficacy differences between second generation antipsychotics, which are now the mainstay of treatment. Overall, only the first generation antipsychotic haloperidol appeared to be inferior to some newer compounds. This situation is not satisfactory, because there is a clinical impression that the various antipsychotic drugs differ in efficacy, but this impression has not been documented by the currently available trials in first-episode patients. There were two major potential reasons: First, the number of studies available for

each compound was small restricting statistical power. Second, it had been reported in the literature that first-episode patients could respond so well to antipsychotic drugs in general that there may be “ceiling effects” (Baker, 2004). If people with a first episode of schizophrenia responded generally well to antipsychotics, it may as a consequence be difficult to demonstrate efficacy differences between drugs, and very large studies would be necessary for such proof.

This hypothesis was the major motivation to carry out the second analysis in which it was attempted to find out the average response rates to antipsychotic drugs in randomised-controlled trials, and to identify moderators of their efficacy. Such a systematic review and meta-analysis on the responder rates of first-episode patients had not been available. Two response criteria were applied: at least 50% PANSS/BPRS total score reduction from baseline, roughly corresponding to much improved according to the CGI of raters, and at least 20% PANSS/BPRS total score reduction from baseline, roughly corresponding to minimally improved according to the CGI (Leucht et al., 2005b, Leucht et al., 2005c, Schennach-Wolff et al., 2010, Levine et al., 2008).

As usually only results based on one response cutoff are presented in such publications, both criteria were calculated for all included studies via an imputation method originally proposed by Furukawa et al. (Furukawa et al., 2005) and replicated by Samara et al. (Samara et al., 2013). This imputation method allows to estimate response rates based on any percentage cutoff between 1% and 100% reduction of the PANSS/BPRS total score from baseline. (Samara et al., 2013) had shown that the results estimated with this imputation method agree with observed (true) values to a reasonable degree. In this thesis this methodology was systematically applied in

a meta-analysis in schizophrenia for the first time, which was an important novel aspect of the thesis.

This second section of the thesis indeed confirmed the high response rates in first-episode patients. Over half of first-episode patients reached an at least 50% PANSS/BPRS total score reduction from baseline. These high response rates were in so far surprising as the 50% PANSS/BPRS total score reduction from baseline is a stringent cutoff which is rarely reached by chronic patients (in approximately 15% of the participants in a recent meta-analysis) (Leucht et al., 2017). Nevertheless, this cutoff had been recommended for trials in acutely ill patients, because “much improvement” may more appropriately meet the expectations of patients and clinicians than the often used cutoff at least 20% PANSS/BPRS total score reduction from baseline (Leucht et al., 2005b, Leucht et al., 2005c, Schennach-Wolff et al., 2010, Levine et al., 2008, Leucht et al., 2007). The 20% cutoff was also applied and reached by over 80% of the included patients. As 20% PANSS/BPRS total reduction approximately means “minimally improved” according to the CGI, this finding suggests that more than 4/5 of people with a first episode of schizophrenia respond at least somewhat to antipsychotic drugs. Moreover, female patients, drug-naive patients, more severely ill patients at baseline, and patients with shorter illness durations had significantly better response rates than their counterparts. These were important predictors of response.

The methodological and clinical implications of section 2 were that as first-episode patients have a generally great therapeutic sensitivity to antipsychotic drugs, differences between compounds may be difficult to demonstrate in clinical trials. Thus, following the conclusions of section 1 drug choice may mainly be guided by the side-effect profiles of the various compounds. Moreover, as first-episode patients

generally respond well, they may need lower doses and they may benefit even less from increasing to high doses of antipsychotics than chronic patients. However, as even in the first episode many patients will not fully respond (somewhat fewer than 50% of such patients according to the at least 50% PANSS/BPRS reduction from baseline cutoff), one consequence for research is that we need more investment in drug development on the one hand. On the other hand, an early intervention with other treatments, for example, repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) could be effective in the first-episode population, but they have not been sufficiently tested in RCTs. Another question is how many first-episode patients do not need antipsychotics, because they remit spontaneously. This question could not be answered, because there were no placebo-controlled trials.

The treatment during the first episode may be fundamental for the long-term outcome. Individualized treatment, which has also been emphasized in clinical guidelines such as NICE (https://www.nice.org.uk/guidance/cg178/chapter/ 1-Recommendations#subsequent-acute-episodes-of-psychosis-or-schizophrenia-and-referral-in-crisis-2), should mainly consider side-effects such as weight gain, metabolic disorders, prolactin increase, and movement disorders (section 1). These side effects can seriously affect patients' quality of life and medication compliance. Moreover, clinicians should focus on establishing a good doctor-patient trust with patients in an early stage, encourage patients to participate in the formulation of treatment plan as early as possible, help patients to prevent potential treatment risks as early as possible, and encourage patients to restore their social function with the help of drugs and other treatments.

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Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses

Yikang Zhu, Marc Krause, Maximilian Huhn, Philipp Rothe, Johannes Schneider-Thoma, Anna Chaimani, Chunbo Li, John M Davis, Stefan Leucht

Summary

Background **The first episode of schizophrenia is a pivotal phase of this debilitating illness. Which drug to use remains controversial without a summary of all direct or indirect comparisons of drugs. We did a systematic review with pairwise and network meta-analyses of efficacy and tolerability.**

Methods **We searched MEDLINE, Embase, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov for randomised controlled trials of antipsychotics for the acute treatment of first-episode schizophrenia, published up to Nov 17, 2016. Our primary outcome was overall change in symptoms. Secondary outcomes were change in positive and negative symptoms, categorical response to treatment, study dropout for any reason and for inefficacy of treatment, use of drugs to treat parkinsonian symptoms, weight gain, sedation, increase in prolactin release, overall functioning, and quality of life. We did the meta-analyses with a random-effects model to calculate standardised mean differences (SMDs) or odds ratios (ORs) with 95% CIs.**

Findings **We identified 19 relevant randomised controlled trials of 12 antipsychotic drugs that involved 2669 participants. 13 of the studies presented data on the primary outcome. For overall reduction of symptoms, amisulpride (SMD –0·37, 95% CI –0·61 to –0·14), olanzapine (–0·25, –0·39 to –0·12), ziprasidone (–0·25, –0·48 to –0·01), and risperidone (–0·14, –0·27 to –0·01) were significantly more efficacious than haloperidol, but the evidence was very low to moderate quality. Amisulpride was superior for reduction of symptoms to quetiapine (SMD –0·25, 95% CI –0·50 to –0·01). Olanzapine was superior to haloperidol and risperidone for reduction of negative symptoms. Several second-generation antipsychotics were superior to haloperidol in terms of all-cause discontinuation. Olanzapine was associated with at least one use of drugs to treat parkinsonian symptoms and quetiapine with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine, but, again, evidence was very low to low quality. Molindone was superior to risperidone, haloperidol, and olanzapine in terms of weight gain, and superior to risperidone in terms of increase in prolactin release.**

Interpreation **Haloperidol seems to be a suboptimum treatment option for acute treatment of first-episode schizophrenia, but we found little difference between second-generation antipsychotics. The evidence was generally of low quality and the numbers of patients for each drug were small. Thus, the choice of treatment should be guided primarily by side-effects.**

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Introduction

Schizophrenia is a severe mental disorder that affects more than 21 million people worldwide. WHO has ranked the disorder the eighth leading cause of disability among all illnesses worldwide in the age group 15–44 years.[1] According to the 2015 Global Burden of Disease Study, the total number of disability-adjusted life-years associated with schizophrenia has risen by more than 17% since 2005.[2]

The first episode of schizophrenia is particularly important for several reasons. Characteristics of patients differ from those of patients with chronic disease in various ways. First episodes generally occur in people aged 15–25 years and are associated with less pronounced negative symptoms than chronic schizophrenia.[3] Some cognitive domains, such as working memory and social cognition, are more preserved than in chronic disease.[4] Neuroimaging studies suggest that brain volume loss[5] and functional connectivity alterations[6] are less in the first episode than later in the disease course.

The duration of untreated psychosis is negatively associated with long-term outcomes.[7,8] People presenting with a first episode of schizophrenia usually respond very well to antipsychotic drugs.[9–12] By contrast, the effects of antipsychotics in chronic patients can be unsatisfactory, although a good response is seen again in some patients when relapse happens. Meta-analyses of treatment in chronic patients have shown moderate differences in efficacy for different antipsychotics compared with placebo (median standardised mean difference [SMD] 0·44, range 0·33–0·88)[13] and that only 23% of patients treated with antipsychotics versus 14% receiving placebo achieved at least 50% reduction in Positive and Negative Syndrome Scale score (PANSS) or the Brief Psychiatric Rating Scale (BPRS) from baseline or a Clinical Global Impression Rating of at least much

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Research in context

Evidence before this study

The first episode of schizophrenia is a pivotal phase of this illness, but the choice of which drug to use is controversial. We searched MEDLINE and the Cochrane Library for analyses of drugs comparisons and found two conventional pairwise meta-analyses, one showing no difference between first-generation and second-generation antipsychotics, and one showing significant superiority of individual second-generation antipsychotics for specific factors. We found no systematic reviews that compared later-introduced antipsychotics with each other or that used a network meta-analytic approach. We searched MEDLINE, Embase, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov for all randomised controlled trials published up to Nov 17, 2016, that compared antipsychotic drugs with each other or with placebo, from which we extracted data on first-episode patients.

Added value of this study

We used network meta-analysis to compare all antipsychotics with data available from randomised controlled trials on the acute treatment of first-episode schizophrenia in various domains of efficacy and tolerability. We included 19 randomised controlled trials involving 2669 participants, published between 1987 and 2015. Several second-generation antipsychotics were superior to haloperidol in terms of efficacy, acceptability, and some aspects of tolerability, whereas we found few and inconsistent, differences between individual second-generation antipsychotics. Tolerability overall was similar to that in patients receiving chronic treatment.

Implications of all the available evidence

Second-generation antipsychotics are the mainstay of treatment in developed countries, and we found little evidence on which to base drug choice in terms of efficacy in patients presenting with first-episode schizophrenia. Therefore, treatment decisions in this population should be guided by side-effects.

improved.[14] Therefore, optimum treatment of the first episode might improve the long-term prognosis.

In the past few decades, multiple randomised controlled trials of treatments for patients having a first episode of schizophrenia have been done. Two conventional pairwise meta-analyses have assessed whether second-generation antipsychotics are better than first-generation compounds to treat first episodes, but they came to different conclusions,[15,16] possibly because different approaches were used. The first compared first-generation and second-generation antipsychotics as groups and found no difference in efficacy between them, whereas the second compared each second-generation antipsychotics individually and found that several were superior to first-generation drugs. Many second-generation antipsychotics have lost patent protection and, therefore, increased cost no longer plays a major part in the choice of drug. Thus, comparisons of first-generation with second-generation antipsychotics have lessened, and it has even been suggested that they be merged into one class.[17] This strategy has been adopted by some international bodies, such as the European and American Colleges of Neuropsychopharmacology, which now use Neuroscience based Nomenclature[18] to classify antipsychotics by primary mechanism of action. Consequently, differences between individual antipsychotics have become more important than whether they are first or second generation. Because so many antipsychotics are available, however, conventional pairwise meta-analyses, which can compare only two drugs at a time, do not yield robust data on which to base recommendations. Network meta-analysis might be particularly helpful in this regard, because it allows analysis of all the evidence simultaneously. Moreover, by using indirect and direct evidence, gaps in the evidence matrix can be filled.[19] We used this method to assess which antipsychotics are most suitable to treat first-episode schizophrenia in various domains of efficacy and tolerability.

For the **study protocol** see www.crd.york.ac.uk/prospero

See Online for appendix

For the **Cochrane Schizophrenia Group** see http://schizophrenia.cochrane.org

Methods

Study design and participants

The study protocol is registered at PROSPERO, number CRD42015025111 (appendix pp 2–10), and followed the PRISMA extension for network meta-analysis.[20,21] We included individuals presenting with a first episode of schizophrenia or related disorders (eg, schizophreniform or schizoaffective disorders), using the definitions of first episode made by the study authors. We placed no restrictions on age, setting, sex, or ethnicity. To meet the assumptions of the analyses, we optimised homogeneity of studies within and across treatment comparisons by excluding those in treatment-resistant patients, in people with predominantly negative symptoms or concomitant medical or psychiatric illnesses (eg, studies in which all patients also had concomitant cannabis misuse), and in stable patients (ie, mainly relapse-prevention studies). We accepted studies in which less than 20% of participants had psychiatric disorders other than schizophrenia (eg, depression or mental retardation) or less than 20% of participants were not having a first episode. Following the rules of the Cochrane Schizophrenia Group, we included the trials irrespective of the diagnostic criteria used.

Antipsychotics

We considered the following antipsychotic drugs: amisulpride, aripiprazole, asenapine, benperidol, brexpiprazole, cariprazine, chlorpromazine, clozapine, flupenthixol, fluphenazine, fluspirilene, haloperidol,

iloperidone, levomepromazine, loxapine, lurasidone, molindone, olanzapine, paliperidone, quetiapine, penfluridol, perazine, perphenazine, pimozide, risperidone, sertindole, sulpiride, thioridazine, tiotixene, trifluoperazine, ziprasidone, zotepine, and zuclopenthixol (also known as clopenthixol). In fixed-dose studies, we followed the International Consensus Study of Antipsychotic dosing,[22] which recommends 25–30% lower doses for first-episode patients than for chronic patients. We included all flexible-dose studies because these allow the investigators to titrate the dose to that adequate for the individual patient. We excluded studies of depot formulations because these are mainly used for long-term prevention of relapse, which is not addressed in this review.

Outcomes

The primary outcome was overall change in symptoms of schizophrenia as measured by rating scales, such as the PANSS,[23] the BPRS,[24] or any other validated scale (eg, the Manchester Scale[25]). As not all studies used the same scale, we applied the following hierarchy: first, mean change in the PANSS total score from baseline to endpoint; if unavailable, mean change in BPRS score; if change in PANSS or BPRS were unavailable, the mean scores for either at the endpoint; then other scales. Secondary outcomes were response (as defined in the study; if available, we preferred 50% reduction in PANSS or BPRS and Clinical Global Impression of at least much improved to lower thresholds[26]), change in positive symptoms of schizophrenia, change in negative symptoms of schizophrenia, study dropout for any reason (all-cause discontinuation), dropout because of inefficacy of treatment, use of drugs to treat parkinsonian symptoms, akathisia, weight gain (we extracted data on mean weight gain and weight gain for at least 7%, although in this study we analyse only mean change), increased prolactin release (we extracted data on mean change and number of participants with substantial increases, but analyse only mean change here), sedation, overall functioning, and quality of life. Because this review is on acute treatment, we only included the studies that provided short-term data (≤13 weeks).

Search strategy and selection criteria

We searched MEDLINE, Embase, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov for randomised controlled trials published up to Nov 17, 2016, that compared antipsychotic drugs with each other or with placebo in people with schizophrenia. We also searched the reference lists of previous reviews.[13,15,16] The search terms included those related to schizophrenia and schizophrenia-like disorders, randomisation, and all aforementioned drugs (appendix pp 11–22). As this review is part of a project that involves several subgroups of schizophrenia patients, we did not set the search terms to find only first-episode patients.

We included all randomised controlled trials, but excluded quasi-randomised studies (eg, allocation by day of the week). Because the number of randomised controlled trials of treatment for first-episode schizophrenia was small, we also included open-label studies. In crossover trials, we only included data up to the point of the first crossover to avoid carry-over effects.[27] Cluster-randomised trials were excluded. We excluded studies from mainland China to avoid a systematic bias because many did not use appropriate randomisation procedures or report the details of their methods.[28] Moreover, the China Food and Drug Administration has reported that many of the published reports are not reliable.[29]

Data extraction and risk of bias assessment

All abstracts identified in the searches were reviewed independently by two of YZ, MK, MH, and an independent analyst. Disagreements were resolved by discussion. If doubt remained, the full paper was obtained for further assessment. Once eligible papers had been selected, the full reports were obtained for all papers, which were again independently reviewed by at least two of the same assessment group. Disagreements about eligibility were discussed with SL and the original authors were contacted by email to ask for further information.

Two of YZ, PR, and SL and an independent analyst reviewed the main reports and supplementary materials, extracted the relevant data and entered the information into electronic forms, and assessed risk of bias in terms of sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other biases, with the Cochrane risk of bias tool.[30] We also assessed a global risk of bias rating for each study based on the criteria applied in a network meta-analysis of antidepressants.[31]

Statistical analysis

First, we did random-effects conventional pairwise meta-analyses with RevMan (version 5.3). We calculated SMDs for continuous outcomes and odds ratios (ORs) for binary outcomes, with 95% CIs. In line with Cohen's guideline for magnitude of effect, we took SMDs of –0·2 to be small, –0·50 to be medium, and –0·8 to be large.[32] The heterogeneity in each pairwise comparison was assessed with the I^2 statistic (I^2 >50% taken to indicate substantial heterogeneity).

Second, we did a random-effects network meta-analysis in Stata (version 14.0), using the network package to estimate summary effect sizes that were again presented as SMDs or ORs with 95% CIs.[33,34] Network meta-analysis integrates direct evidence (direct comparisons of two or more interventions) and indirect evidence (drawn from two interventions that have separately been compared with one or more common comparators) for every treatment contrast. For instance,

if there are trials that directly compare risperidone with aripiprazole and trials that compare risperidone with quetiapine, but none compares aripiprazole with quetiapine, network meta-analysis enables indirect estimation of the effect of aripiprazole versus quetiapine from the other comparisons. Moreover, network meta-analysis can create a hierarchy of treatments based on the surface under the cumulative ranking curve (SUCRA).[35] This is a simple transformation of the mean rank and ranges from 0 to 1, with 1 indicating that a treatment is certain to be the best and 0 that a treatment is certain to be the worst.

Before we did the network meta-analysis, we attempted to assess the transitivity assumption.[36] This assumption implies that studies comparing different sets of interventions are sufficiently similar to provide valid indirect inferences, which we hoped to ensure by applying narrow inclusion criteria, making populations similar within and across treatment comparisons. We also considered whether the potential effect modifiers were distributed similarly across the available direct comparisons.

We assumed a common heterogeneity estimate for all treatment comparisons. We presented the between-study variance τ^2 for each outcome and assessed heterogeneity by referring to empirical distributions of heterogeneity values typically found in meta-analyses.[37,38] Statistical inconsistency (disagreements between direct and indirect evidence) was tested with three different approaches: the loop-specific approach that tests inconsistency in every closed loop of evidence;[39] the side-splitting method that tests for each comparison discrepancies between direct and indirect evidence obtained by the entire network;[40] and the design-by-treatment interaction model that tests inconsistency from all possible sources in the network jointly.[41]

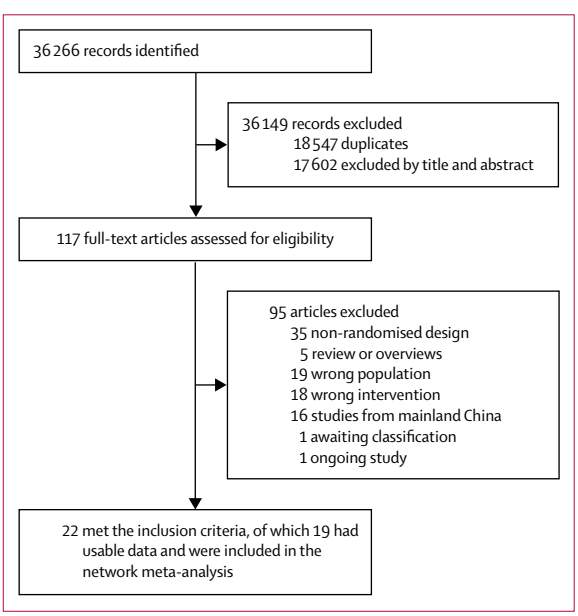

Figure 1: **Selection of studies**

For **CINeMA** see http://ec2-35-156-97-18.eu-central-1.compute.amazonaws.com:8004/ocpu/library/contribution/www/#welcome

We planned a priori two sensitivity analyses on the primary outcome, intended to assess the robustness of the estimates from the primary analysis. In one we excluded open-label randomised controlled trials, and in the other we excluded studies that did not use operationalised criteria, such as ICD-10 or DSM-IV. In response to peer review, we also did a post-hoc sensitivity analysis in which we included the study by Robinson and colleagues,[42] which was originally excluded because its duration (16 weeks) exceeded our predefined maximum of 13 weeks. Usable data in that study were available only for response and weight gain and, therefore, we analysed these instead of our primary outcome.

To explore reasons for heterogeneity, we planned meta-regression analyses (continuous moderators) and subgroup analyses (dichotomous moderators) of the primary outcome according to the following variables: antipsychotic naive, severity of illness at baseline, duration of untreated psychosis, and the ratio of male to female participants. In response to peer review, we also did a post-hoc subgroup analysis of overall symptom change and use of drugs to treat parkinsonian symptoms based on haloperidol dose (≥4 *vs* <4 mg per day). We did pairwise subgroup meta-analyses of different doses of haloperidol and risperidone (≥4 *vs* <4 mg per day) versus all other antipsychotics on these outcomes. Lower thresholds could not be assessed, because the lowest doses for haloperidol and risperidone, respectively, were 3·0 mg per day and 2·4 mg per day.

We investigated potential effects from small trials and publication bias for the primary outcome with a comparison-adjusted funnel plot.[43] We assumed that drugs introduced to the market later would be potentially favoured by small trials. We also planned to create standard funnel plots of single comparisons (eg, olanzapine *vs* haloperidol) if at least ten studies were available.

Finally, we assessed the quality of evidence for the primary outcome and the secondary outcome at least one use of drugs to treat parkinsonian symptoms with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, following the framework suggested by Salanti and colleagues.[19] We used the online tool, CINeMA, to assess study limitations in the following five domains for all relative effects and for treatment ranking estimated by network meta-analysis: study limitations, indirectness, inconsistency, imprecision, and publication bias.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 36 266 potentially relevant citations, from which 117 were left after removal of duplicates and the titles and abstracts were reviewed (figure 1). After checking the full-text articles, we identified 19 randomised controlled trials involving 2669 participants that had us able data (table).[3,44–62] The reports were published between 1987 and 2015, and provided comparisons of 12 antipsychotic drugs that were included in the network meta-analysis. 11 studies were of haloperidol, 13 of risperidone, seven of olanzapine, four of quetiapine, and one each of ziprasidone, zuclopenthixol, molindone, flupenthixol, pimozide, aripiprazole, amisulpride, and sertindole. The mean sample size was 140 participants (range 8–498), the mean duration of illness was 1·5 years (SD 1·8), and the mean age of trial participants was 23·9 years (SD 9·7). Sex was indicated for 2598 patients, of whom 1710 (66%) were men. The median duration of trial was 8 weeks (range 4–13). The overall risk of bias findings are shown in the appendix (pp 23–25). Few details were reported about randomisation procedures and concealment of treatment allocation. 12 (63%) studies were double blind, three (16%) were single blind (those assessing outcomes were blinded), and four (21%) studies were open label. We judged five (26%) and two (11%) of the studies to have a high risk of bias in terms of attrition and selective reporting, respectively, and that only a few other studies had clear methodological problems, such as imbalance of groups at baseline. Nine (47%) studies were funded by pharmaceutical companies.

The mean antipsychotic dose was 12 mg per day in olanzapine equivalents.[22] The network of comparators for the primary outcome is shown in figure 2, and those for secondary outcomes are presented in the appendix (pp 26–37). The results of simple pairwise and network meta-analyses were generally consistent, except that, as expected, network meta-analysis produced more

	Study treatments (number of patients)	Trial duration (weeks)	Mean dose (DDD, MED, CMD, IC; mg per day)	Diagnosis	Definition of first episode	Study design	Risk of bias*	Characteristics of patients
Amr et al, 2013[45]	Haloperidol (n=33), quetiapine (n=40)	12	Haloperidol: 14·2 (17·8, 26·8, 19·2, 28·4); quetiapine: 705·8 (17·7, 35·3, 21·9, 19·1)	Schizophrenia (DSM-IV-TR)	First-episode schizophrenia	SB-RCT	5	Outpatients; 46 (63%) men, 27 (37%) women; mean age 31·1 years (SD 3·7); mean duration of illness 5·0 months (SD 1·9)
Brewer et al, 2007[46]	Haloperidol (n=4), risperidone (n=4)	8	Haloperidol: 2·0 (2·5, 3·8, 2·7, 4·0); risperidone: 2·0 (4·0, 7·4, 5·3, 6·7)	Schizophrenia (DSM-IV)	Antipsychotic-naive first-episode schizophrenia	DB-RCT	3	Inpatients and outpatients; 8 (100%) men; mean age 21·2 years (SD 3·0); age of onset of symptoms 16–30 years; mean baseline PANSS score: total 50·3 (SD 7·5), positive symptoms 29·7 (2·5), negative symptoms 20·5 (6·9)
Chaudhuri et al, 2000[47]	Haloperidol (n=15), risperidone (n=15)	4	Haloperidol: 15·0 (18·8, 28·3, 20·3, 30·0); risperidone: 4·0 (8·0, 14·8, 10·5, 13·3)	Acute and transient psychotic disorder (ICD-10)	Antipsychotic-naive first-episode schizophrenia	SB-RCT	2	Inpatients; 15 (50%) men, 15 (50%) women; age groups: 16–25 years (n=24), 26–35 years (n=5), 46–55 years (n=1); no history of psychiatric morbidity
Crespo-Facorro et al, 2006[48]	Haloperidol (n=56), olanzapine (n=55), risperidone (n=61)	6	Haloperidol: 5·4 (6·8, 10·2, 7·3, 10·8); olanzapine: 15·3 (15·3, 15·3, 15·3, 15·3); risperidone: 4·0 (8·0, 14·8, 10·5, 13·3)	Schizophreniform disorder, schizophrenia, schizoaffective disorder, brief reactive psychosis, schizotypal personality disorder, or psychosis not otherwise specified (DSM-IV)	First-episode or <6 weeks' antipsychotic treatment	OL-RCT	4	Inpatients and outpatients; 107 (62%) men, 65 (38%) women; mean age 27·3 years (SD 7·8); mean duration of illness 27·9 months (SD 36·7); moderate or worse baseline psychotic symptoms of moderate severity or greater assessed (≥1 of 5 items on SAPS)
Emsley et al, 1999[49]	Haloperidol (n=84), risperidone (n=99)	6	Haloperidol: 5·6 (7·0, 10·6, 7·6, 11·2); risperidone: 6·1 (12·2, 22·6, 16·1, 20·3)	Schizophreniform disorder or schizophrenia (DSM-III-R)	Antipsychotic-naive first-episode schizophrenia	DB-RCT	3	Inpatients and outpatients; 122 (67% men), 61 (33%) women; median age 26 years in risperidone group and 24 years in haloperidol group
Fagerlund et al, 2004[50]	Risperidone (n=15), zuclopenthixol (n=10)	13	Risperidone: 3·6 (7·2, 13·3, 9·5, 12·0); zuclopenthixol: 9·6 (3·2, NC, NC, 3·8)	Schizophrenia (ICD-10)	Antipsychotic-naive first-episode schizophrenia	OL-RCT	3	Inpatients; mean age 27·3 years (SD 5·9); median duration of untreated psychosis 14 months
Gafoor et al, 2010[51]	Quetiapine (n=38), risperidone (n=34)	12	Quetiapine: 375·0 (9·4, 18·8, 11·6, 10·1); risperidone: 2·72 (5·4, 10·1, 7·2, 9·1)	Schizophrenia spectrum disorders (ICD-10)	First-episode with <2 weeks' antipsychotic treatment	SB-RCT	4	Outpatients; 52 (72%) men, 20 (28%) women; mean 24·0 years (SD 4·9); baseline mean scores: PANSS total 70·4 (SD 22·0), CGI 4·94 (SD 0·92)
Gallhofer et al, 2007[52]	Sertindole (n=13), haloperidol (n=13)	12	Sertindole: 11·8 (7·4, 7·4, 10·9, 11·8); haloperidol: 5·8 (7·3, 10·9, 7·8, 11·6)	Schizophreniform disorder, acute schizophrenia, or schizophrenia (DSM-IV)	First-episode schizophrenia	DB-RCT	3	6 (25%) men, 18 (75%) women; mean age 28·1 years (SD 8·2); mean baseline PANSS total score 68·8 (SD 21·6); mean duration of illness 0·07 years (SD 0·22)

(Table continues on next page)

	Study treatments (number of patients)	Trial duration (weeks)	Mean dose (DDD, MED, CMD, IC; mg per day)	Diagnosis	Definition of first episode	Study design	Risk of bias*	Characteristics of patients
(Continued from previous page)								
Fleischhacker et al, 2012,[61] Kahn et al, 2008[62]	Haloperidol (n=103), amisulpride (n=104), olanzapine (n=105), quetiapine (n=104), ziprasidone (n=82)	12 (52†)	Haloperidol: 3·0 (3·8, 5·7, 4·1, 6·0); amisulpride: 450·8 (11·3, NC, 11·8, 13·1); olanzapine: 12·6 (12·6, 12·6, 12·6, 12·6); quetiapine: 498·6 (12·5, 24·9, 15·5, 13·5); ziprasidone: 107·2 (13·4, 20·1, 13·5, 13·4)	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV)	First-episode schizophrenia	OL-RCT	5	Inpatients and outpatients; 298 (60%) men, 200 (40%) women; mean age 26 years (SD 5·6); mean baseline PANSS total score 88·5 (SD 20·6)
Lee et al, 2007[53]	Haloperidol (n=10), risperidone (n=10)	8	Haloperidol: 7·6 (9·5, 14·3, 10·3, 15·2); risperidone: 4·1 (8·2, 15·2, 10·8, 13·7)	Schizophrenia (DSM-IV)	Antipsychotic-naive schizophrenia	DB-RCT	2	Inpatients; 20 (100%) men; mean age 26·6 years (SD 8·8); mean baseline PANSS total 92·3 (SD 12·2)
Lieberman et al, 2003[54]	Olanzapine (n=131), haloperidol (n=132)	12	Olanzapine: 9·1 (9·1, 9·1, 9·1, 9·1); haloperidol: 4·4 (5·5, 8·3, 5·9, 8·8)	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV)	First-episode schizophrenia	DB-RCT	3	Inpatients and outpatients; 215 (82%) men, 48 (18%) women; mean age 23·8 years (SD 4·8); age of onset of psychotic symptoms <35 years; score ≥4 on two or more PANSS psychosis items or ≥5 on one psychosis item and CGI severity score ≥4
McEvoy et al, 2007[55]	Olanzapine (n=133), quetiapine (n=134), risperidone n=133	12 (52†)	Olanzapine: 11·7 (11·7, 11·7, 11·7, 11·7); quetiapine: 506 (12·7, 25·3, 15·7, 13·7); risperidone: 2·4 (4·8, 8·9, 6·3, 8·0)	Schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV)	First-episode schizophrenia, continuously ill for ≥1 month and ≤5 years	DB-RCT	5	Inpatients and outpatients; 292 (73%) men, 108 (27%) women; mean age 24·5 years (SD 5·8); mean duration of illness 12·9 months (SD 17·29); score ≥4 on one or more PANSS psychosis item and CGI severity score ≥4
Möller et al, 2008[56]	Risperidone (n=143), haloperidol (n=146)	8	Risperidone: 3·8 (7·6, 14·1, 10·0, 12·7); haloperidol: 3·7 (4·6, 7·0, 5·0, 7·4)	Schizophrenia (ICD-10)	First-episode schizophrenia	DB-RCT	6	Inpatients; 172 (60%) men, 117 (40%) women; mean age 30·1 years (SD 9·8); mean baseline PANSS total score 79·1 (SD 24·0)
Robinson et al, 2015[57]	Aripiprazole (n=106), risperidone (n=103)	12	Aripiprazole: 14·8 (9·9, 11·1, 10·5, 9·9); risperidone: 3·2 (6·4, 11·9, 8·4, 10·7)	Schizophrenia, schizophreniform, schizoaffective disorder, or psychotic disorder not otherwise specified (DSM-IV)	First-episode schizophrenia	DB-RCT	6	140 (71%) men, 58 (29%) women; mean age 22·1 years (SD 5·6); mean duration of psychotic symptoms 125·5 weeks (SD 208·8)
San et al, 2012[58]	Olanzapine (n=25), quetiapine (n=23), risperidone (n=25), ziprasidone (n=20), haloperidol (n=21)	12 (52†)	Olanzapine: 12·0 (12·0, 12·0, 12·0, 12·0); quetiapine: 572·0 (14·3, 28·6, 17·7, 15·4); risperidone: 3·7 (7·4, 13·7, 9·7, 12·3); ziprasidone: 81·0 (10·1, 15·2, 10·2, 10·1); haloperidol: 4·0 (5·0, 7·5, 5·4, 8·0)	Schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder NOS, brief psychotic disorder (DSM-IV-TR)	Antipsychotic-naive first-episode schizophrenia	OL-RCT	5	Inpatients; 85 (75%) mean, 29 (25%) women; mean age 25·6 years (SD 8·0); mean baseline PANSS total score 91·0 (SD 20·0), mean duration of untreated psychosis 52·5 weeks (SD 170·0)
Sanger et al, 1999[3]	Haloperidol (n=24), olanzapine (n=59)	6	Haloperidol: 10·8 (13·5, 20·4, 14·6, 21·6); olanzapine: 11·6 (11·6, 11·6, 11·6, 11·6)	Schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-III-R)	First-episode schizophrenia, current episode ≤5 years	DB-RCT	3	57 (69%) men, 26 (31%) women; mean age 28·5 years (SD 7·3); mean duration of illness 1·3 years and length of current episode 389·6 days (SD 422·8)
Scottish First Episode, 1987[44]	Flupenthixol (n=23), pimozide (n=23)	5	Flupenthixol: 20·0 (33·3, NC, NC, 40·0); pimozide: 18·8 (47·0, NC, NC, 47·0)	Schizophrenia	Antipsychotic-naive first-episode schizophrenia	DB-RCT	2	Inpatients; mean age 30·6 years (range 16–68); mean length of the first admission 11·8 weeks (SD 10·0)
Sikich et al, 2008[59]	Molindone (n=40), olanzapine (n=35), risperidone (n=41)	8	Molindone: 59·9 (12·0, NC, NC, 12·0); olanzapine: 11·4 (11·4, 11·4, 11·4, 11·4); risperidone: 2·8 (5·6, 10·4, 7·4, 9·3)	Schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-IV [KID-SCID])	First-episode schizophrenia (early onset)	DB-RCT	7	Inpatients and outpatients; 75 (65%) men, 41 (35%) women; age range 8–19 years; at least moderate positive psychotic symptoms at enrolment
Svestka et al, 2003[60]	Olanzapine (n=21), risperidone (n=21)	6	Olanzapine: 18·0 (18·0, 18·0, 18·0, 18·0); risperidone: 4·9 (9·8, 18·1, 12·9, 16·3)	Schizophrenic and schizoform disorders (ICD-10)	First-episode schizophrenia	DB-RCT	2	Inpatients; 42 (100%) women; mean age 28·4 years; mean duration of episode 103·6 days (range 14·0–725·0)

DDD=defined daily doses method (olanzapine equivalent dose). MED=minimum effective dose method (olanzapine equivalent dose). CMD=classic mean dose method (olanzapine equivalent dose). IC=international consensus (olanzapine equivalent dose). TR=text revision. SB=single-blind. RCT=randomised controlled trial. DB=double-blind. PANSS=Positive and Negative Syndrome Scale. OL=open-label. SAPS=Scale for the Assessment of Positive Symptoms. R=revised. NC=not calculable by method. CGI=Clinical Global Impression scale. NOS=not otherwise specified. KID=SCID=Structured Clinical Interview for DMS-IV Childhood Diagnoses. *Number of low-risk judgments. †Long-term data also reported, but only short-term data assessed.

***Table*: Description of included studies**

significant findings. Therefore, the results of these conventional pairwise meta-analyses are always reported together. We used the SUCRA rankings (appendix pp 45–56) to order the results for these analyses.

For the primary outcome, mean score reduction in overall symptoms of schizophrenia, amisulpride, olanzapine, ziprasidone, and risperidone were significantly more efficacious than haloperidol, and amisulpride was significantly more efficacious than quetiapine (figure 3). In terms of all-cause discontinuation, aripiprazole, quetiapine, risperidone, and olanzapine were superior to haloperidol (figure 3). For dropout due to inefficacy, olanzapine and risperidone were superior to haloperidol (appendix p 41).

The network meta-analysis revealed no significant differences between treatments for change in positive symptoms, but for change in negative symptoms, olanzapine was significantly more efficacious than haloperidol and risperidone (figure 4). Categorical response to treatment did not differ between treatments (appendix p 40).

Olanzapine was associated with less frequent use of drugs to treat parkinsonian symptoms than haloperidol, zuclopenthixol, and risperidone, and quetiapine was associated with less use of drugs to treat parkinsonian symptoms than haloperidol and zuclopenthixol (figure 5). Molindone was associated with significantly less weight gain than olanzapine, haloperidol, and risperidone, and haloperidol was superior to olanzapine (figure 5).

Quetiapine was associated with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine, and olanzapine with less than haloperidol, aripiprazole, and risperidone (appendix p 42). Quetiapine was associated with less sedation than risperidone and aripiprazole (appendix p 43). Molindone, aripiprazole, olanzapine, and haloperidol were associated with lower increases in prolactin release than risperidone, as were molindone and olanzapine than haloperidol (appendix p 44). Overall functioning and quality of life outcomes did not differ between drugs in pairwise meta-analyses, but very few data were available. No estimate was produced by network meta-analyses.

When we excluded open-label studies from the sensitivity analysis for the primary outcome, olanzapine was superior to haloperidol and quetiapine in the network meta-analysis. When the 16-week study by Robinson and colleagues[42] was included in the sensitivity analysis of response to treatment and weight gain, the overall results for these outcomes changed little (appendix pp 73–77).

Most outcomes showed low heterogeneity (appendix pp 57–72). None of the methods we used suggested important inconsistency for the primary outcome, but the loop-specific and side-splitting methods revealed some inconsistency for the secondary outcomes (changes in positive symptoms, negative symptoms, and sedation). The design-by-treatment interaction model suggested that the transivity assumption might not be plausible for sedation and increase in prolactin release.

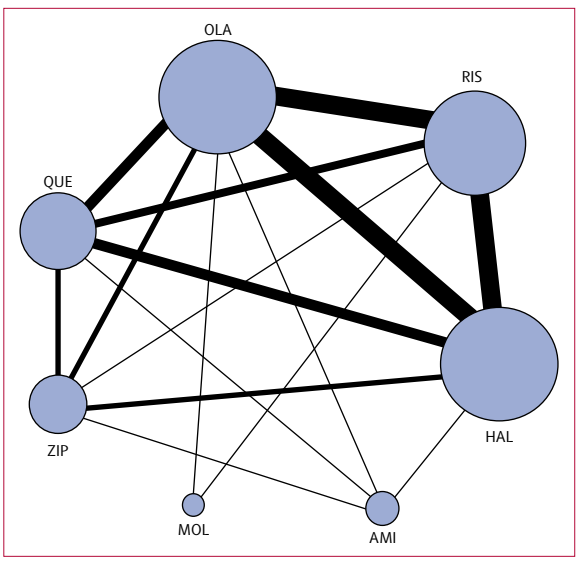

***Figure 2*: Network plot of eligible comparisons for overall change in symptoms**
The circles (nodes) represent the available treatments and the lines (edges) represent the available comparisons. Sizes of nodes and width of edges indicate weighting according to the number of studies involved for each treatment and comparison, respectively. OLA=olanzapine. RIS=risperidone. HAL=haloperidol. AMI=amisulpride. MOL=molindone. ZIP=ziprasidone. QUE=quetiapine.

The network meta-regression analyses for severity of illness at baseline, duration of untreated psychosis, and ratio of the sexes that had been planned a priori were not feasible because too few data were available. The subgroup analyses for antipsychotic-naive patients versus previously treated patients and for haloperidol dose did not show any clear differences (appendix pp 78–82), but interpretation was limited by small group size and differences in the antipsychotics used. The pairwise meta-analyses of overall change in symptoms and at least one use of drugs to treat parkinsonian symptoms by haloperidol and risperidone dose showed that higher haloperidol doses were associated with significantly more use of drugs to treat parkinsonian symptoms than lower doses ($p<0·001$). Risperidone dose had no effect on this outcome. We found no differences for overall change in symptoms with either haloperidol or risperidone dose subgroup (appendix pp 83–87).

The comparison-adjusted funnel plot did not provide clear evidence that antipsychotics introduced to the market later were favoured by small studies compared with those introduced earlier (appendix pp 88–89). Funnel plots for individual comparisons were not meaningful because the maximum number of trials in a comparison was six.

The GRADE approach showed that the quality of the evidence for the outcomes overall change in symptoms and at least one use of drugs to treat parkinsonian symptoms was very low to moderate, depending on the individual comparison. The quality of the ranking was low for these two outcomes (appendix pp 90–95).

ARI	NMA 1·14 (0·45 to 2·87)	NMA 1·17 (0·43 to 3·17)	NMA 1·34 (0·76 to 2·37) PWA 1·34 (0·76 to 2·37)*	NMA 1·38 (0·66 to 2·89)	NMA 3·75 (0·58 to 24·32)	**NMA 2·53 (1·31 to 4·92)**
AMI	QUE	NMA 1·03 (0·36 to 2·97)	NMA 1·18 (0·57 to 2·47)	NMA 1·22 (0·57 to 2·61)	NMA 3·31 (0·51 to 21·33)	**NMA 2·23 (1·16 to 4·28) PWA 2·23 (1·16 to 4·28)***
NMA –0·12 (–0·35 to 0·12) PWA –0·23 (–0·50 to 0·04)*	OLA	MOL	NMA 1·15 (0·51 to 2·60) PWA 0·78 (0·32 to 1·92)*	NMA 1·18 (0·52 to 2·68) PWA 1·78 (0·71 to 4·46)*	NMA 3·20 (0·46 to 22·21)	NMA 2·16 (0·94 to 4·98)
NMA –0·09 (–0·53 to 0·36)	NMA –0·03 (–0·36 to 0·42) PWA 0·02 (–0·43 to 0·48)*	MOL	RIS	NMA 1·03 (0·64 to 1·65) PWA 1·35 (0·34 to 5·30)†	NMA 2·79 (0·47 to 16·55)	**NMA 1·88 (1·34 to 2·65) PWA 1·69 (1·17 to 2·43)‡**
NMA –0·13 (–0·40 to 0·15) PWA –0·10 (–0·39 to 0·19)*	NMA –0·01 (–0·24 to 0·22) PWA –0·03 (–0·46 to 0·40)†	NMA –0·04 (–0·49 to 0·40)	ZIP	OLA	NMA 2·72 (0·45 to 16·32)	**NMA 1·83 (1·23 to 2·74)** PWA 2·17 (0·94 to 5·02)§
NMA –0·23 (–0·48 to 0·02)	NMA –0·11 (–0·26 to 0·03) PWA –0·09 (–0·27 to 0·10)¶	NMA –0·15 (–0·53 to 0·24) PWA –0·15 (–0·58 to 0·29)*	NMA –0·10 (–0·35 to 0·14) PWA 0·05 (–0·54 to 0·64)*	RIS	SER	NMA 0·68 (0·12 to 3·87) PWA 0·68 (0·12 to 3·87)*
NMA –0·25 (–0·50 to –0·01) PWA –0·21 (–0·48 to 0·06)*	NMA –0·13 (–0·30 to 0·03) PWA –0·15 (–0·36 to 0·07)§	NMA –0·17 (–0·58 to 0·25)	NMA –0·13 (–0·37 to 0·12)	NMA –0·02 (–0·20 to 0·16) PWA –0·16 (–0·42 to 0·10)†	QUE	HAL
NMA –0·37 (–0·61 to –0·14) PWA –0·33 (–0·60 to –0·06)*	**NMA –0·25 (–0·39 to –0·12) PWA –0·29 (–0·50 to –0·09)¶**	NMA –0·29 (–0·69 to 0·11)	**NMA –0·25 (–0·48 to –0·01)** PWA –0·25 (–0·52 to 0·01)†	**NMA –0·14 (–0·27 to –0·01)** PWA –0·10 (–0·25 to 0·06)‡	NMA –0·12 (–0·29 to 0·05)	HAL

All-cause discontinuation (OR, 95% CI) | Treatment comparator
Treatment comparator | Overall change in symptoms (SMD, 95% CI)

Figure 3: **Overall change in symptoms and all-cause discontinuation**
Treatments are ranked by the surface under the cumulative ranking probabilities. Bold values are significant. Comparisons between treatments should be read from left to right, with the relevant estimate being in the common cell for the column-defining treatment and the row-defining treatment. For reduction in overall symptoms, SMDs <0 indicate that the treatment specified in the column is more efficacious than that in the row. For all-cause discontinuation, ORs >1 indicate that the treatment specified in the row is more efficacious than that in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. SMD=standardised mean difference. NMA=network meta-analysis. PWA=pairwise analysis. OR=odds ratio. ARI=aripiprazole. AMI=amisulpride. QUE=quetiapine. OLA=olanzapine. MOL=molindone. RIS=risperidone. ZIP=ziprasidone. SER=sertindole. HAL=haloperidol. *Includes one direct comparison study. †Includes two direct comparison studies. ‡Includes six direct comparison studies. §Includes three direct comparison studies. ¶Includes five direct comparison studies.

Discussion

We used pairwise and network meta-analyses to summarise the evidence from randomised trials for efficacy and tolerability of antipsychotic drugs in the short-term treatment of first-episode schizophrenia. We found some significant differences between drugs in terms of efficacy and premature all-cause discontinuation, dropout for inefficacy, or both, mainly showing a disadvantage for haloperidol, but tolerability results were generally similar to those seen in patients with chronic schizophrenia.[13]

The network meta-analysis suggested significant superiority for amisulpride, olanzapine, ziprasidone, and risperidone over haloperidol in the reduction of overall symptoms, and of olanzapine over haloperidol in reduction of negative symptoms. This superiority of several second-generation antipsychotics over haloperidol is similar to the pattern seen in a conventional meta-analysis by Zhang and colleagues.[16] By contrast, little difference was seen between second-generation antipsychotics, with the only significant differences being amisulpride superior to quetiapine for overall reduction of symptoms and olanzapine superior to risperidone for reduction of negative symptoms. The superiority of amisulpride over quetiapine was based on one open-label trial, and this result did not remain significant when open-label studies were excluded from the sensitivity analysis of the primary outcome. The only significant finding after this analysis was superiority of olanzapine over haloperidol and quetiapine. We conclude, therefore, that there is little evidence that treatment recommendations for second-generation antipsychotics, which are the most frequently used drugs in developed countries, can be based on differences in efficacy.

A possible explanation for the little difference between second-generation antipsychotics could be that patients having a first episode generally respond better to treatment than patients who have been taking antipsychotics long term, which might lead to ceiling effects. For example, in a meta-analysis of 167 randomised controlled trials involving 28 102 patients mainly with chronic disease, only 51% of drug-treated patients had minimal responses (defined as reductions of ≥20% in PANSS in BPRS or at least minimum improvement in Clinical Global Impression rating from baseline) and 23% had good responses (defined as reductions of ≥50% in PANSS or BPRS or a Clinical Global Impression rating of at least much improved from baseline).[14] By contrast, among first-episode patients, Robinson and colleagues[63] and Lieberman and colleagues[64] reported that 87% and 90% achieved remission by 1 year and 2 years, respectively. Such high remission rates might leave little leeway for differences between drugs.

In terms of all-cause discontinuation, most of the second-generation antipsychotics analysed—aripiprazole, quetiapine, risperidone, and olanzapine—were superior to haloperidol, and the ORs were high. Because all-cause discontinuation includes patients who drop out of studies due to inefficacy and side-effects, it is widely viewed as a measure of overall acceptability.[65] Our findings, therefore, suggest that second-generation antipsychotics are more acceptable than haloperidol for treatment of a first episode.

We feel that the results on side-effects in our network meta-analyses are compatible to some degree with those in patients with chronic disease,[13] although the doses used to treat first episodes were lower. In terms of use of drugs to treat parkinsonian symptoms as a broad measure of movement disorders, several second-generation antipsychotics were superior to the first-generation antipsychotics haloperidol and zuclopenthixol. Olanzapine was superior to risperidone, although this result was not unexpected because the latter drug is not free from extrapyramidal symptoms.[13] In terms of akathisia, quetiapine and olanzapine were superior not only to haloperidol but also to risperidone and aripiprazole, which indicates the associated low risk of movement disorders, especially with quetiapine, which was further superior to olanzapine. By contrast, risperidone and aripiprazole were clearly associated with akathisia in first-episode patients, although akathisia-like symptoms have been proposed to be an expression of the serotonergic effects of aripiprazole.[66]

Olanzapine was associated with more weight gain than all other second-generation antipsychotics in the network meta-analysis. Because of this feature, some guidelines do not recommend this drug for first-line use in people with a first episode of schizophrenia.[67,68] Risperidone, despite statistical inconsistency, was associated with most increase in prolactin release in our network meta-analysis, even more than haloperidol. No data were available for amisulpride and paliperidone, which have previously been associated with prolactin release.[13] This side-effect is important because it can be associated with amenorrhoea, galactorrhoea, hirsutism, gynaecomastia, erectile dysfunction, and osteoporosis. By contrast, the finding that quetiapine was less associated with sedation than aripiprazole and risperidone could be artifactual because a large network meta-analysis in patients with chronic schizophrenia has shown that quetiapine is the most sedating of these three drugs.[13] We found that the data for this outcome were significantly inconsistent, which suggests that the result is unreliable. Sedation is only assessed by open interviews in antipsychotic drug trials, and improved operationalisation might make the results more reliable.

Dose effects are extremely important.[69–71] We addressed this issue in several analyses that used doses as moderators of the outcomes overall change in symptoms and use of drugs to treat parkinsonian symptoms, for which dose effects might be the most relevant. We found no dose effects on the primary outcome, which is in line with some[13,72] but not other[69] previous meta-analyses in patients with chronic schizophrenia. For use of drugs to treat parkinsonian symptoms, however, we did find an association with haloperidol doses of 4 mg or more per

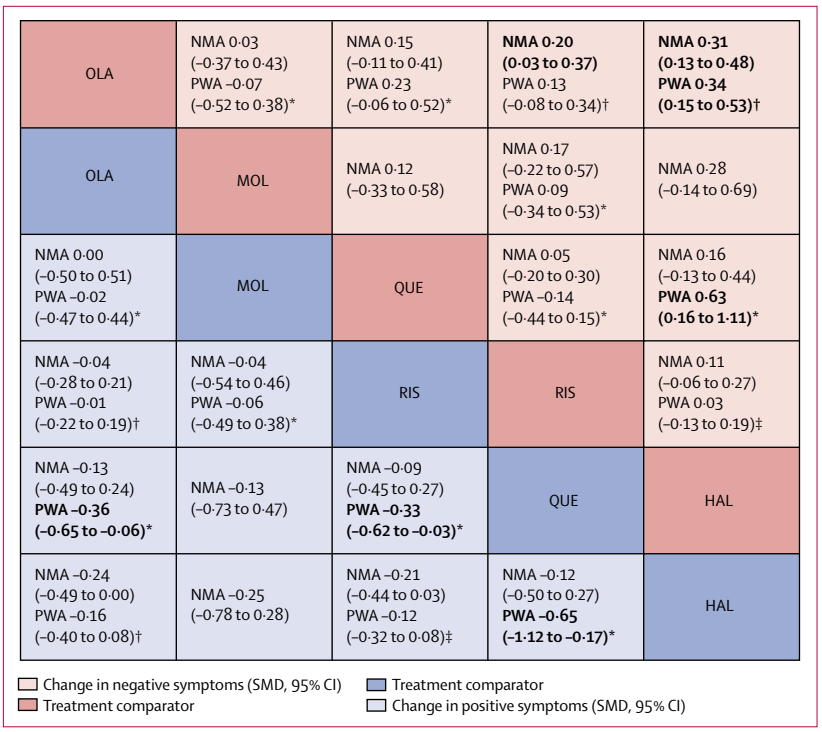

***Figure 4*: Change in positive symptoms and negative symptoms**
Treatments are ranked by the surface under the cumulative ranking probabilities. Bold values are significant. Comparisons between treatments should be read from left to right, with the relevant estimate being in the common cell for the column-defining treatment and the row-defining treatment. For negative symptoms, SMDs >0 indicate that the treatment specified in the row is more efficacious than that in the column. For positive symptoms, SMDs <0 indicate that the treatment specified in the column is more efficacious than that in the row. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. SMD=standardised mean difference. NMA=network meta-analysis. PWA=pairwise analysis. OLA=olanzapine. MOL=molindone. QUE=quetiapine. RIS=risperidone. HAL=haloperidol. *Includes one direct comparison study. †Includes three direct comparison studies. ‡Includes four direct comparison studies.

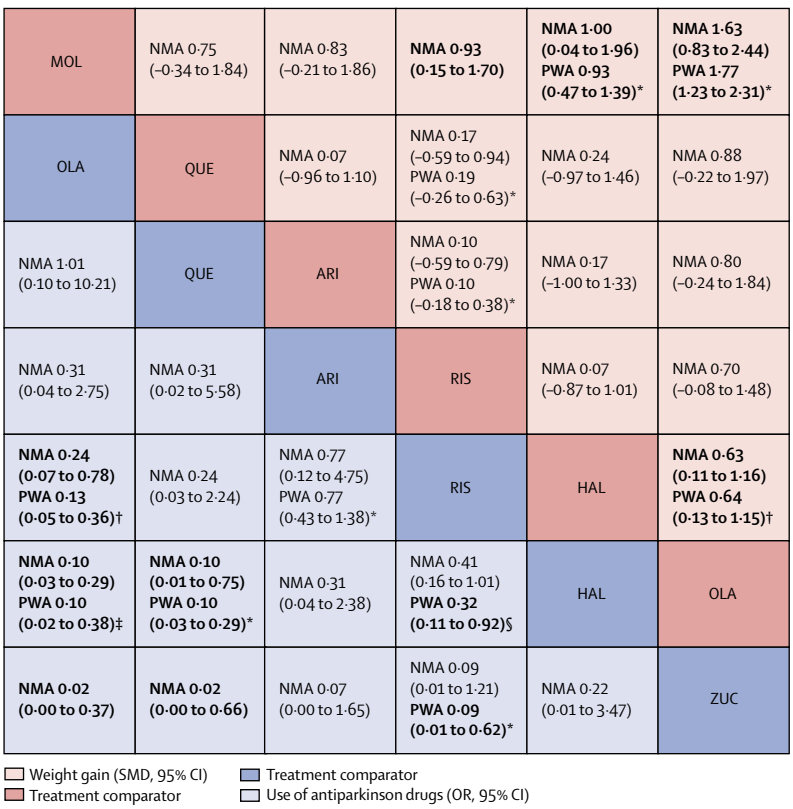

Figure 5: **Weight gain and use of drugs to treat parkinsonian symptoms**
Treatments are ranked by the surface under the cumulative ranking probabilities. Bold values are significant. Comparisons between treatments should be read from left to right, with the relevant estimate being in the common cell for the column-defining treatment and the row-defining treatment. For use of drugs to treat parkinsonian symptoms, ORs <1 indicate that the treatment specified in the column is more efficacious than that in the row. For weight gain, SMDs >0 indicate that the treatment specified in the row is more efficacious than that in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. SMD=standardised mean difference. NMA=network meta-analysis. PWA=pairwise analysis. OR=odds ratio. MOL=molindone. OLA=olanzapine. QUE=quetiapine. ARI=aripiprazole. RIS=risperidone. HAL=haloperidol. ZUC=zuclopenthixol. *Includes one direct comparison study. †Includes two direct comparison studies. ‡Includes three direct comparison studies. §Includes four direct comparison studies.

day, but not with lower doses. As haloperidol carries a particularly high risk of movement disorders, however, the results in our network meta-analysis are not generalisable to other first-generation antipsychotics. Moreover, even in patients with chronic disease, the dose–response curve of haloperidol seems to start to flatten at about 4 mg per day[71] and in patients having a first episode, doses as low as 2 mg per day might be sufficient.[70] All the included studies assessed doses higher than 2 mg per day, which must be taken into account when interpreting the results. Dose-finding studies in first-episode patients might be useful to identify optimum antipsychotic doses.

This network meta-analysis had some strengths and limitations. Strengths were that the methods were stringent and followed the PRISMA guidelines, including publishing a protocol and the comprehensiveness of the outcome measures. Network meta-analysis has an advantage over conventional pairwise meta-analysis because it can synthesise direct and indirect evidence, which increases the precision of the estimates. However, although we included 19 trials with 2669 participants, multiple trials were available only for haloperidol, risperidone, olanzapine, and quetiapine. These drugs also had the most significant differences, whereas the results for all other drugs were based on data from single trials, meaning that many results were derived from indirect evidence. Moreover, the only first-generation antipsychotic for which several trials were available was haloperidol, whereas for molindone and pimozide only one randomised controlled trial was available for each. For the second-generation antipsychotics brexpiprazole, cariprazine, iloperidone, lurasidone, and paliperidone, which were the latest to enter the market, none had been assessed in a randomised controlled trial. In the network meta-analyses with few studies, the transitivity assumption is difficult to assess. We found no statistical inconsistency for the primary outcome, but we did see inconsistency in some secondary outcomes. Owing to the statistical power of the subgroup analyses in terms of duration of untreated psychosis,[8] antipsychotic dose, and antipsychotic-naive patients, the usefulness of the results was limited, but the effect of haloperidol dose on the use of drugs to treat parkinsonian symptoms was significant. Another limitation is that we only included short-term results of up to 13 weeks. A few long-term studies are available, but combining short-term and long-term studies in network meta-analysis would be difficult due to heterogeneity. Quality of life and functioning are becoming increasingly important in assessments of antipsychotic drugs, but very few data were available. These outcomes should be included in future studies. Finally, the GRADE approach used in the network meta-analysis[19] suggested only very low to moderate quality of evidence for overall symptoms and use of drugs to treat parkinsonian symptoms, which restricts the confidence that can be placed in the findings.

We found that most second-generation antipsychotics are superior to haloperidol in the domains of efficacy and acceptability, and in certain aspects of tolerability. Importantly, though, there were few significant differences between second-generation antipsychotics, which are the mainstay of treatment in many developed countries. Until findings are available from better-quality studies to elucidate differences in efficacy, treatment decisions for first-episode schizophrenia should be guided mainly by side-effects, for which the general patterns were similar to those found in chronic patients.

Contributors
YZ and SL designed the study. YZ, MK, and MH assessed the studies. YZ, SL, and PR extracted the data. YZ, MK, JS-T, and AC analysed the data. YZ and MK drew the tables and figures. YZ, CL, JMD, and SL interpreted data. YZ and SL wrote the first draft of the manuscript and all authors contributed to and have approved the final version.

Declaration of interests
SL has received honoraria for consulting from LB Pharma, Lundbeck, Otsuka, Roche, and TEVA, for lectures from AOP Orphan, ICON, Janssen, Lilly, Lundbeck, Otsuka, Pfizer, Roche, and Servier, and for a publication from Roche. MH has received speaker's honoraria from Janssen and Lundbeck. The other authors declare no competing interests.

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Supplementary Appendix

eAppendix 1. Study protocol

eAppendix 2. Description of Search Strategy

eAppendix 3. Risk of Bias Assessment

eAppendix 4. Network Plot for Secondary Outcomes

eAppendix 5. Results of Network and Pairwise Meta-analyses of Secondary Outcomes

eAppendix 6. Cumulative Ranking Curves for All Outcomes

eAppendix 7. Evaluation of Heterogeneity and Inconsistency

eAppendix 8. Sensitivity Analyses

eAppendix 9. . Subgroup analyses

eAppendix 10. Investigation of Small Study Effects

eAppendix 11. Evaluation of the quality of evidence

eAppendix 1

Study Protocol

Comparative efficacy and tolerability of antipsychotic drugs in first-episode schizophrenia: a network meta-analysis

Stefan Leucht, Yikang Zhu, Maximilian Huhn, Philipp Rothe, John Davis

Citation

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Review question(s)

To examine the comparative efficacy, acceptability, and tolerability of antipsychotic drugs in first-episode schizophrenia by applying a network meta-analysis approach.

Searches

We will search the register of controlled therapy studies of the Cochrane Schizophrenia Group (CSG), for which a number of electronic databases are regularly searched: Biological Abstracts, CINAHL, Cochrane Library, EMBASE, LILACS, MEDLINE, PSYNDEX, PsycINFO, System for the Information on Grey Literature in Europe, Sociofile etc. The CSG also regularly hand searches abstract books of major conferences, and various trial registers such as clinicaltrials.gov. First authors of included studies will be contacted for missing data, and we will also contact pharmaceutical companies manufacturing antipsychotics.

The search strategy has not yet been fully developed, but the terms will be broad and specified with the librarians.

There will be no restrictions in language other than articles from mainland China, and no restriction in publication period.

Types of study to be included

We will only include studies that randomly assigned participants with schizophrenia or related disorders to antipsychotic drugs. Quasi-randomized studies (e.g. allocation by day of the week) will be excluded. Due to the limited number of RCTs in first-episode schizophrenia, we will also include open-label RCTs. In cross-over trials only data up to the point of the first cross-over will be used. Cluster-randomized trials will be generally excluded. We will exclude open-label RCTs in a sensitivity analysis.

Condition or domain being studied

Schizophrenia.

Participants/ population

We will include people (no age limit, no restriction in setting, gender, ethnicity) with first-episode schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders) . We allow all definitions of “first episode” by the original authors. We will exclude studies in treatment resistant patients, in patients with

predominant negative symptoms, in patients with concomitant medical illness, and studies in stable patients (mainly relapse prevention studies), because these are different patient populations and it is an important requirement of network meta-analysis to have reasonably homogeneous samples. Studies in which less than 20% of the participants were suffering from other psychiatric disorders than schizophrenia (e.g. depression or mental retardation) or less than 20% were non-first-episode patients will be acceptable. We will include the trials irrespective of the diagnostic criteria used. we will exclude studies that did not use operationalised criteria such as ICD-10 or DSM-IV in a sensitivity analysis.

Intervention(s), exposure(s)

The intervention will be antipsychotics (SGAs and FGAs) that are marketed in at least one country, administered by any mode (oral tablets, oral liquid). In fixed-dose studies we will include target to maximum doses, but also allow lower doses. According to the International Consensus Study on Antipsychotic dose, the first-episode of psychotic illness led to 25%-30% lower recommended dose than repeatedly acutely psychotic patients (Gardner 2010). Therefore, we will also accept lower doses than those recommended for multiple episode patients in the International Consensus Study. We will include all flexible-dose studies, because these allow the investigators to titrate to the adequate dose for the individual patient. We will exclude depot formulations which are mainly used for long-term relapse prevention which is not the focus of this review.

Comparator(s)/ control

The comparator will be placebo (active or inactive) or one of the antipsychotic drugs (SGAs and FGAs) available in the Europe or the US..

Context

We will include studies irrespective of setting (in- or outpatients) and participant age, gender or illness history (a broad inclusion criteria for first-episode schizophrenia), but not from mainland China.

Outcome(s)

Primary outcomes

Overall symptoms of schizophrenia

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. 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.

Secondary outcomes

1. Response to treatment (dichotomous)

2. Change in positive symptoms of schizophrenia

3. Change in negative symptoms of schizophrenia

4. Dropout due to any reason (all-cause discontinuation)

5. Dropout due to inefficacy of treatment

6. Adverse events

a) Extrapyramidal side-effects

b) Akathisia

c) Weight gain (mean change and number of participants with significant weight gain)

d) Prolactin levels (mean change and number of participants with a significant increase)

e) Sexual side-effects

f) Sedation/somnolence

g) Cardiac side-effects

h) Cholinesterase side-effects: constipation, blurred vision and urinary retention.

i) Hypotension/orthostasis problems

j) Seizures: a rare, but dangerous side-effect of some antipsychotics

k) Neutropenia including agranulocytosis.

l) Deep vein thrombosis

m) Death

7. Patient subjective well-being, quality of life

8. Overall functioning

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.Response to treatment (dichotomous): Dichotomous responder data will only be secondary outcomes, because it must be expected that different criteria to define response were applied. We will have to use the definitions used by the original authors.

2.Change in positive symptoms of schizophrenia We will examine the positive symptoms of schizophrenia according to the positive subscale of the PANSS or the “Scale for Assessment of Positive Symptoms” (SAPS) or other validated positive symptom scales.

3.Change in negative symptoms of schizophrenia We will investigate the negative symptoms of schizophrenia according to the negative subscale of the PANSS or the “Scale for the Assessment of Negative Symptoms” (SANS) or other validated negative symptom scales.

4.Dropout due to any reason (all-cause discontinuation) All-cause discontinuation ('dropping out') due to any reason combines efficacy, tolerability, and other factors and has therefore been considered as a measure of 'acceptability of treatment'. It is applied more and more frequently in psychiatric trials.

5.Dropout due to inefficacy of treatment: Dropout due to inefficacy of treatment is an additional outcome of the efficacy of treatment that has been frequently used in other systematic reviews. We will not analyse dropout due to adverse events. Although this at first glance seems to be a measure of overall tolerability, it is frequently confounded by efficacy related adverse events such as "exacerbation of psychosis".

6.Adverse events Antipsychotics are associated with a wide variety of side-effects. We feel that the following selection covers the most important domains which are usually also mentioned in side-effect tables of guidelines, but we would add other ones if reviewers felt strongly: a) Extrapyramidal side-effects Use of antiparkinson medication has been successfully used as an objective, global measure for extrapyramidal side-effects (EPS) such as parkinsonism, akinesia or dystonia b) Akathisia: This movement disorder probably has a different mechanism of action than other EPS and therefore seems to be quite frequent with SGAs such as aripipraole or amisulpride which are otherwise relatively benign in terms of EPS. The treatment of akathisia is also in part different from that of other EPS (e.g. beta-blockers are recommended) so that it cannot be fully covered by use of antiparkinson medication. c) Weight gain (mean change and number of participants with significant weight gain). This is the most important side-effect of many SGAs which is to an important degree correlated with increases in glucose, cholesterol and triglycerides. We decided against the additional analysis of the latter metabolic effects, because it is unlikely that they have been frequently analysed in old RCTs, but if reviewers felt strongly we would add them. d) Prolactin levels (mean change and number of participants with a significant increase), an objective measure which can be a cause of sexual side-effects and osteoporosis. e) Sexual side-effects: we will examine "organic" sexual side-effects (e.g. dysmenorrhea, amenorrhea) and more "psychological" ones such as lack of libido, separately for men and women. f) Sedation/somnolence g) Cardiac side-effects - Potentially dangerous QTc prolongation (mean change and the number of participants with significant QTc prolongation, as defined by the original studies. - The number of participants with ECG abnormalities h) Anticholinergic side-effects: constipation, blurred vision and urinary retention. i) Hypotension/orthostasis problems j) Seizures: a rare, but dangerous side-effect of some antipsychotics k) Neutropenia including agranulocytosis. l) Deep vein thrombosis m) Death: to address the debate whether antipsychotics increase mortality by their side-effects or whether they reduce it by the prevention of suicides. Again, if reviewers felt strongly we would add other side-effects, but some selection must be made.

7. Patient subjective well-being, quality of life For many patients overall quality of life may be more important than the mere reduction of schizophrenic symptoms. This outcome will be measured by the mean values of rating scales on these concepts (e.g. "Subjective well-being under neuroleptics scale" (SWUN)).

8. Overall functioning Outcomes of social participation have increasingly been asked for. Functioning will be measured by rating scales such as the Global Assessment of Functioning or the Psychosocial Performance Scale.

Data extraction, (selection and coding)

Selection of trials: Two reviewers will independently inspect all abstracts identified in the searches. Disagreement will be resolved by discussion, and where doubt still remains, we will acquire the full article for further inspection.

Once the full articles are obtained, at least two reviewers will independently decide whether the studies meet the review criteria. If disagreement cannot be resolved by discussion, we will resolve it with a third reviewer or seek further information from the study authors.

Data extraction: Two reviewers will independently extract data from all selected trials on electronic 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.

Risk of bias (quality) assessment

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.

Strategy for data synthesis

In general we will conduct network meta-analysis in a frequentist framework to estimate the summary effect size assuming a random effects model, but a fixed effects model will be used in a sensitivity analysis. We will assume that heterogeneity is the same for all treatment comparisons. Network meta-analysis synthesizes both direct and indirect evidence, allows comparison of the relative effectiveness between a pair of antipsychotics that has not been compared in any of the included trials and provides a hierarchy of treatments according to any outcome considered. The main assumption of network meta-analysis is that of transitivity stating that the distribution of effect modifiers is the same across treatment comparisons. This assumption can be tested statistically in a closed loop of evidence by exploring if direct and indirect evidence is in agreement. This is called the consistency assumption. For example, if a closed loop of evidence is formed by placebo, haloperidol and olanzapine, the direct evidence derived from studies comparing haloperidol and olanzapine should be similar to the indirect evidence about the relative effectiveness of these two antipsychotics that is derived by comparing each of them to placebo. We test consistency in every closed loop of evidence and we will depict differences between direct and indirect evidence and their uncertainty graphically.

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). 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 could have some 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. Hierarchy of the treatments: We will use the surface under the cumulative ranking curve (SUCRA) and the mean rank to provide a hierarchy of the competing treatments.

4. Publication bias: We will examine potential publication bias (presence of small study effects) by 'comparison-adjusted funnel-plots'. In principle, a funnel plot is a scatterplot of the study effect size versus some measure of its precision, often its inverted standard error. Extending the use of funnel plots into network meta-analysis, we have to take into account that studies estimate effects for different comparisons and there is not a single reference line against which symmetry can be judged. Therefore, before using this plot, we will order the treatments in a meaningful way and make assumptions about how small studies differ from large ones. Each comparison in the plot will be represented by a different colored bulletin.

Analysis of subgroups or subsets

The planned subgroups analysis: 1. Antipsychotic drug naive: The antipsychotic-naive patients are thought to respond better than patients with those who used antipsychotics before.

The planned meta-regression analyses:

1. Severity of illness at baseline: there may be floor effects that limit drug-placebo or drug-drug differences in less severely ill patients.

2. Duration of untreated psychosis (DUP): It has been reported that the patients with longer DUP would have worse outcome or prognosis. It is unclear whether the patients with longer DUP would have worse response to treatment, and whether their side effects would be more severe.

3. Percentage women: women might have a better outcome than men.

The planned sensitivity analyses:

1. Open-label RCTs will be excluded.

2. The studies that did not use operationalised criteria such as ICD-10 or DSM-IV will be excluded.

3. A fixed effects model for network meta-analysis in a frequentist framework will be used.

4. Placebo controlled trials will be excluded.

Dissemination plans

The results will be published in major psychiatric journals and presented at major international 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.

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Anticipated or actual start date

27 August 2015

Anticipated completion date

26 August 2016

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Visiting-scholar program of Shanghai Municipal Education Commission for Yikang Zhu

Conflicts of interest

In the last three years Stefan Leucht has received honoraria for lectures from Abbvie, Astra Zeneca, BristolMyersSquibb, ICON, EliLilly, Janssen, Johnson & Johnson, Roche, SanofiAventis, Lundbeck and Pfizer; for consulting/advisory boards from Roche, EliLilly, Medavante, BristolMyersSquibb, Alkermes, Janssen, Johnson & Johnson and Lundbeck. EliLilly has provided medication for a study with SL as primary investigator.

Language

English

Country

Germany

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Antipsychotic Agents; Humans; Schizophrenia

Stage of review

Ongoing

Date of registration in PROSPERO

28 August 2015

Date of publication of this revision

28 August 2015

DOI

10.15124/CRD42015025111

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	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

PROSPERO

This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.

eAppendix 2

Description of Search Strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> 17-11-16

1 Benperidol/ or Chlorpromazine/ or Clopenthixol/ or Clozapine/ or Flupenthixol/ or Fluphenazine/ or Fluspirilene/ or Haloperidol/ or Methotrimeprazine/ or Loxapine/ or Molindone/ or Penfluridol/ or Perazine/ or Perphenazine/ or Pimozide/ or Risperidone/ or Sulpiride/ or Thioridazine/ or Thiothixene/ or Trifluoperazine/ or Clopenthixol/ (57251)
2 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol).tw. (63172)
3 or/1-2 (81692)
4 exp schizophrenia/ (105265)
5 exp Paranoid Disorders/ (4124)
6 schizo$.mp. (165151)
7 hebephreni$.mp. (284)
8 oligophreni$.mp. (1133)
9 psychotic$.mp. (64365)
10 psychosis.mp. (33016)
11 psychoses.mp. (21069)
12 or/4-11 (219822)
13 exp clinical trial/ (816569)
14 exp randomized controlled trials/ (121318)
15 exp cross-over studies/ (42567)
16 randomized controlled trial.pt. (469524)
17 clinical trial.pt. (527674)
18 controlled clinical trial.pt. (95062)
19 (clinic$ adj2 trial).mp. (679427)
20 (random$ adj5 control$ adj5 trial$).mp. (641350)
21 (crossover or cross-over).mp. (84560)
22 ((singl$ or double$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (213755)
23 randomi$.mp. (763720)
24 (random$ adj5 (assign$ or allocat$ or assort$ or reciev$)).mp. (213531)
25 or/13-24 (1266765)
26 3 and 12 and 25 (6781)

Embase <1974 to 2016 Week 46> 17-11-16

1 Amisulpride/ or Aripiprazole/ or Asenapine/ or Benperidol/ or Brexpiprazole/ or Cariprazine/ or Chlorpromazine/ or Clopenthixol/ or Clozapine/ or Flupenthixol/ or Fluphenazine/ or Fluspirilene/ or Haloperidol/ or Iloperidone/ or Levomepromazine/ or Loxapine/ or Lurasidone/ or Molindone/ or Olanzapine/ or Paliperidone/ or Quetiapine/ or Penfluridol/ or

Perazine/ or Perphenazine/ or Pimozide/ or Risperidone/ or Sertindole/ or Sulpiride/ or Thioridazine/ or Tiotixene/ or Trifluoperazine/ or Ziprasidone/ or Zotepine/ or Zuclopenthixol/ (159934)

2 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol).tw. (77040)

3 or/1-2 (164856)

4 exp schizophrenia/ (169636)

5 exp psychosis/ (256535)

6 schizo$.mp. (201677)

7 hebephreni$.mp. (919)

8 oligophreni$.mp. (1692)

9 psychotic$.mp. (45582)

10 psychosis.mp. (114859)

11 psychoses.mp. (11520)

12 or/4-11 (304013)

13 (clin$ adj2 trial).mp. (1276210)

14 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (250429)

15 (random$ adj5 (assign$ or allocat$)).mp. (147029)

16 randomi$.mp. (920055)

17 crossover.mp. (80687)

18 exp randomized-controlled-trial/ (461003)

19 exp crossover-procedure/ (53742)

20 exp randomization/ (83533)

21 or/13-20 (1824314)

22 3 and 12 and 21 (13576)

PsycINFO <1806 to November Week 1 2016> 17-11-16

1 Aripiprazole/ or Chlorpromazine/ or Clozapine/ or Fluphenazine/ or Haloperidol/ or Loxapine/ or Molindone/ or Olanzapine/ or Quetiapine/ or Perphenazine/ or Pimozide/ or Risperidone/ or Sulpiride/ or Thioridazine/ or Thiothixene/ or Trifluoperazine/ (18355)

2 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol).tw. (29586)

3 or/1-2 (29715)

4 exp schizophrenia/ (80506)

5 exp Schizoaffective Disorder/ (2803)

6 exp schizophreniform disorder/ (336)

7 schizo$.mp. (122037)
8 exp psychosis/ (102688)
9 hebephreni$.mp. (535)
10 oligophreni$.mp. (520)
11 psychotic$.mp. (41816)
12 psychosis.mp. (47508)
13 psychoses.mp. (14914)
14 or/4-13 (168469)
15 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp. (22653)
16 (random$ adj5 (assign$ or allocat$)).mp. (36234)
17 randomi$.mp. (64298)
18 crossover.mp. (6226)
19 or/15-18 (104391)
20 3 and 14 and 19 (2754)

Cochrane Library 17-11-16

#1 MeSH descriptor: [Benperidol] this term only
#2 MeSH descriptor: [Chlorpromazine] this term only
#3 MeSH descriptor: [Clopenthixol] this term only
#4 MeSH descriptor: [Clozapine] this term only
#5 MeSH descriptor: [Flupenthixol] this term only
#6 MeSH descriptor: [Fluphenazine] this term only
#7 MeSH descriptor: [Fluspirilene] this term only
#8 MeSH descriptor: [Haloperidol] this term only
#9 MeSH descriptor: [Methotrimeprazine] this term only
#10 MeSH descriptor: [Loxapine] this term only
#11 MeSH descriptor: [Molindone] this term only
#12 MeSH descriptor: [Penfluridol] this term only
#13 MeSH descriptor: [Perazine] this term only
#14 MeSH descriptor: [Perphenazine] this term only
#15 MeSH descriptor: [Pimozide] this term only
#16 MeSH descriptor: [Risperidone] this term only
#17 MeSH descriptor: [Sulpiride] this term only
#18 MeSH descriptor: [Thioridazine] this term only
#19 MeSH descriptor: [Thiothixene] this term only
#20 MeSH descriptor: [Trifluoperazine] this term only
#21 (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol):ti,ab,kw (Word variations have been searched)
#22 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15

or #16 or #17 or #18 or #19 or #20 or #21
#23 MeSH descriptor: [Schizophrenia] explode all trees
#24 MeSH descriptor: [Paranoid Disorders] explode all trees
#25 (schizo* or hebephrenic* or oligophreni* or psychotic* or psychosis or psychoses):ti,ab,kw (Word variations have been searched)
#26 #23 or #24 or #25
#27 #22 and #26 in Trials = 5722

Pubmed 17-11-16

#8 Search (#3 and #6 and #7) 5206

#7 Search ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR clinical trials as topic[mesh:noexp] OR randomly[tiab] OR trial[ti] NOT (animals[mh] NOT humans [mh]))) 977609

#6 Search (#4 or #5) 191498

#5 Search (("Schizophrenia"[Mesh]) OR "Psychotic Disorders"[Mesh]) 127832

#4 Search ((schizo*[Title/Abstract] OR hebephrenic*[Title/Abstract] OR oligophreni*[Title/Abstract] OR psychotic*[Title/Abstract] OR psychosis[Title/Abstract] OR psychoses[Title/Abstract])) 162906

#3 Search (#1 or #2) 79041

#2 Search ((Amisulpride[Title/Abstract] OR Aripiprazole[Title/Abstract] OR Asenapine[Title/Abstract] OR Benperidol[Title/Abstract] OR Brexpiprazole[Title/Abstract] OR Cariprazine[Title/Abstract] OR Chlorpromazine[Title/Abstract] OR Clopenthixol[Title/Abstract] OR Clozapine[Title/Abstract] OR Flupenthixol[Title/Abstract] OR Fluphenazine[Title/Abstract] OR Fluspirilene[Title/Abstract] OR Haloperidol[Title/Abstract] OR Iloperidone[Title/Abstract] OR Levomepromazine[Title/Abstract] OR Loxapine[Title/Abstract] OR Lurasidone[Title/Abstract] OR Molindone[Title/Abstract] OR Olanzapine[Title/Abstract] OR Paliperidone[Title/Abstract] OR Quetiapine[Title/Abstract] OR Penfluridol[Title/Abstract] OR Perazine[Title/Abstract] OR Perphenazine[Title/Abstract] OR Pimozide[Title/Abstract] OR Risperidone[Title/Abstract] OR Sertindole[Title/Abstract] OR Sulpiride[Title/Abstract] OR Thioridazine[Title/Abstract] OR Thiothixene[Title/Abstract] OR Trifluoperazine[Title/Abstract] OR Ziprasidone[Title/Abstract] OR Zotepine[Title/Abstract] OR Zuclopenthixol[Title/Abstract])) 63302

#1 Search ("Brexpiprazole" [Supplementary Concept] or "sultopride" [Supplementary Concept] or "aripiprazole" [Supplementary Concept] or "Asenapine" [Supplementary Concept] or "Benperidol"[Mesh] or "cariprazine" [Supplementary Concept] or "Chlorpromazine"[Mesh] or

"Clopenthixol"[Mesh] or "Clozapine"[Mesh] or "Flupenthixol"[Mesh] or "Fluphenazine"[Mesh] or "Fluspirilene"[Mesh] or "Haloperidol"[Mesh] or "iloperidone" [Supplementary Concept] or "Methotrimeprazine"[Mesh] or "Loxapine"[Mesh] or "lurasidone" [Supplementary Concept] or "Molindone"[Mesh] or "olanzapine" [Supplementary Concept] or "paliperidone" [Supplementary Concept] or "quetiapine" [Supplementary Concept] or "Penfluridol"[Mesh] or "Perazine"[Mesh] or "Perphenazine"[Mesh] or "Pimozide"[Mesh] or "Risperidone"[Mesh] or "sertindole" [Supplementary Concept] or "Sulpiride"[Mesh] or "Thioridazine"[Mesh] or "Thiothixene"[Mesh] or "Trifluoperazine"[Mesh] or "ziprasidone" [Supplementary Concept] or "zotepine" [Supplementary Concept] or "Clopenthixol"[Mesh])

Biosis 17-11-16

12 **2,154** #11 AND #10 AND #9

Indexes=BCI Timespan=All years

11 **68,089** **TOPIC:** (Amisulpride or Aripiprazole or Asenapine or Benperidol or Brexpiprazole or Cariprazine or Chlorpromazine or Clopenthixol or Clozapine or Flupenthixol or Fluphenazine or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Loxapine or Lurasidone or Molindone or Olanzapine or Paliperidone or Quetiapine or Penfluridol or Perazine or Perphenazine or Pimozide or Risperidone or Sertindole or Sulpiride or Thioridazine or Thiothixene or Trifluoperazine or Ziprasidone or Zotepine or Zuclopenthixol)

Indexes=BCI Timespan=All years

10 **146,041** **TOPIC:** (schizo* or hebephrenic* OR oligophreni* OR psychotic* OR psychosis OR psychoses)

Indexes=BCI Timespan=All years

9 **357,316** #8 OR #7 OR #6 OR #5 OR #2 OR #1

Indexes=BCI Timespan=All years

8 **37,619** TS=crossover* OR TI=crossover*

Indexes=BCI Timespan=All years

7 **425** TS=(randomi* Near/1 assign*) or TI=(randomi* Near/1 assign*)

Indexes=BCI Timespan=All years

6 **70** TS=(randomi* Near/1 allocate*) or TI=(randomi* Near/1 allocate*)

Indexes=BCI Timespan=All years

5 **116,868** #4 AND #3

Indexes=BCI Timespan=All years

4 **213,862** TS=(mask* OR blind*) OR TI=(mask* OR blind*)

Indexes=BCI Timespan=All years

3 **2,138,069** TS=(singl* OR Doubl* OR Tripl* OR Trebl*) OR TI=(singl* OR Doubl* OR Tripl* OR Trebl*)

Indexes=BCI Timespan=All years

2 **292,770** TI=(randomi*) OR TS=(randomi*)

Indexes=BCI Timespan=All years

1 **151,595** TS=(Randomized clinical trial*) OR TI=(Randomized clinical trial*)

Indexes=BCI Timespan=All years

Clinicaltrials.gov 18-11-16

Amisulpride and schizophrenia and randomised = 0
Aripiprazole and schizophrenia and randomised = 0
Asenapine and schizophrenia and randomised = 0
Benperidol and schizophrenia and randomised = 0
Brexpiprazole and schizophrenia and randomised = 1
Cariprazine and schizophrenia and randomised = 0
Chlorpromazine and schizophrenia and randomised = 0
Clopenthixol and schizophrenia and randomised = 0
Clozapine and schizophrenia and randomised = 1
Flupenthixol and schizophrenia and randomised = 0
Fluphenazine and schizophrenia and randomised = 0
Fluspirilene and schizophrenia and randomised = 0
Haloperidol and schizophrenia and randomised = 0
Iloperidone and schizophrenia and randomised = 0
Levomepromazine and schizophrenia and randomised = 0
Loxapine and schizophrenia and randomised = 0
Lurasidone and schizophrenia and randomised = 0
Molindone and schizophrenia and randomised = 0
Olanzapine and schizophrenia and randomised = 1
Paliperidone and schizophrenia and randomised = 0
Quetiapine and schizophrenia and randomised = 1

Penfluridol and schizophrenia and randomised = 0
Perazine and schizophrenia and randomised = 0
Perphenazine and schizophrenia and randomised = 0
Pimozide and schizophrenia and randomised = 0
Risperidone and schizophrenia and randomised = 2
Sertindole and schizophrenia and randomised = 0
Sulpiride and schizophrenia and randomised = 0
Thioridazine and schizophrenia and randomised = 0
Thiothixene and schizophrenia and randomised = 0
Trifluoperazine and schizophrenia and randomised = 0
Ziprasidone and schizophrenia and randomised = 0
Zotepine and schizophrenia and randomised = 0
Zuclopenthixol and schizophrenia and randomised = 0
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Asenapine and schizophreniform and randomised = 0
Benperidol and schizophreniform and randomised = 0
Brexpiprazole and schizophreniform and randomised = 0
Cariprazine and schizophreniform and randomised = 0
Chlorpromazine and schizophreniform and randomised = 0
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Clozapine and schizophreniform and randomised = 0
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Fluphenazine and schizophreniform and randomised = 0
Fluspirilene and schizophreniform and randomised = 0
Haloperidol and schizophreniform and randomised = 0
Iloperidone and schizophreniform and randomised = 0
Levomepromazine and schizophreniform and randomised = 0
Loxapine and schizophreniform and randomised = 0
Lurasidone and schizophreniform and randomised = 0
Molindone and schizophreniform and randomised = 0
Olanzapine and schizophreniform and randomised = 0
Paliperidone and schizophreniform and randomised = 0
Quetiapine and schizophreniform and randomised = 0
Penfluridol and schizophreniform and randomised = 0
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Sertindole and schizophreniform and randomised = 0
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Ziprasidone and schizophreniform and randomised = 0
Zotepine and schizophreniform and randomised = 0
Zuclopenthixol and schizophreniform and randomised = 0
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Asenapine and schizoaffective and randomised = 0
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Chlorpromazine and schizoaffective and randomised = 0
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Iloperidone and schizoaffective and randomised = 0
Levomepromazine and schizoaffective and randomised = 0
Loxapine and schizoaffective and randomised = 0
Lurasidone and schizoaffective and randomised = 0
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Olanzapine and schizoaffective and randomised = 0
Paliperidone and schizoaffective and randomised = 0
Quetiapine and schizoaffective and randomised = 1
Penfluridol and schizoaffective and randomised = 0
Perazine and schizoaffective and randomised = 0
Perphenazine and schizoaffective and randomised = 0
Pimozide and schizoaffective and randomised = 0
Risperidone and schizoaffective and randomised = 0
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Thiothixene and schizoaffective and randomised = 0
Trifluoperazine and schizoaffective and randomised = 0
Ziprasidone and schizoaffective and randomised = 0
Zotepine and schizoaffective and randomised = 0
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Asenapine and Psychosis and randomised = 0
Benperidol and Psychosis and randomised = 0
Brexpiprazole and Psychosis and randomised = 1
Cariprazine and Psychosis and randomised = 0
Chlorpromazine and Psychosis and randomised = 0

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Fluphenazine and Psychosis and randomised = 0
Fluspirilene and Psychosis and randomised = 0
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Iloperidone and Psychosis and randomised = 0
Levomepromazine and Psychosis and randomised = 0
Loxapine and Psychosis and randomised = 0
Lurasidone and Psychosis and randomised = 1
Molindone and Psychosis and randomised = 0
Olanzapine and Psychosis and randomised = 1
Paliperidone and Psychosis and randomised = 0
Quetiapine and Psychosis and randomised = 1
Penfluridol and Psychosis and randomised = 0
Perazine and Psychosis and randomised = 0
Perphenazine and Psychosis and randomised = 0
Pimozide and Psychosis and randomised = 0
Risperidone and Psychosis and randomised = 2
Sertindole and Psychosis and randomised = 0
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Thioridazine and Psychosis and randomised = 0
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Zuclopenthixol and Psychosis and randomised = 0
Total = 12

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Amisulpride and schizo* and random* = 3
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Levomepromazine and schizo* and random* = 0
Loxapine and schizo* and random* = 0
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Perazine and schizo* and random* = 0
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Pimozide and schizo* and random* = 0
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Cariprazine and psycho* and random* = 0
Chlorpromazine and psycho* and random* = 0
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Clozapine and psycho* and random* = 1
Flupenthixol and psycho* and random* = 0
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Fluspirilene and psycho* and random* = 0
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Iloperidone and psycho* and random* = 0
Levomepromazine and psycho* and random* = 0
Loxapine and psycho* and random* = 0
Lurasidone and psycho* and random* = 2
Molindone and psycho* and random* = 0
Olanzapine and psycho* and random* = 2
Paliperidone and psycho* and random* = 0
Quetiapine and psycho* and random* = 3
Penfluridol and psycho* and random* = 0
Perazine and psycho* and random* = 0

Perphenazine and psycho* and random* = 1
Pimozide and psycho* and random* = 0
Risperidone and psycho* and random* = 1
Sertindole and psycho* and random* = 0
Sulpiride and psycho* and random* = 0
Thioridazine and psycho* and random* = 0
Thiothixene and psycho* and random* = 0
Trifluoperazine and psycho* and random* = 0
Ziprasidone and psycho* and random* = 1
Zotepine and psycho* and random* = 0
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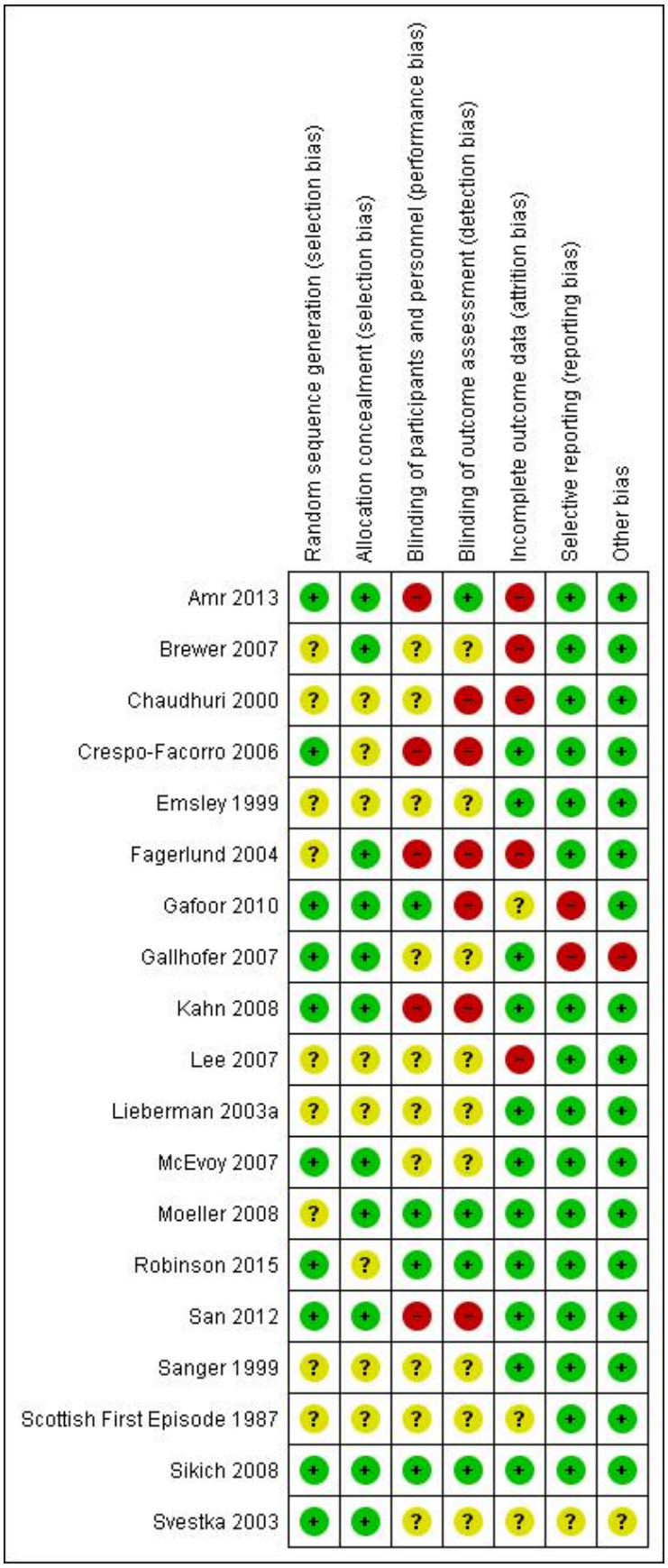
Total = 61

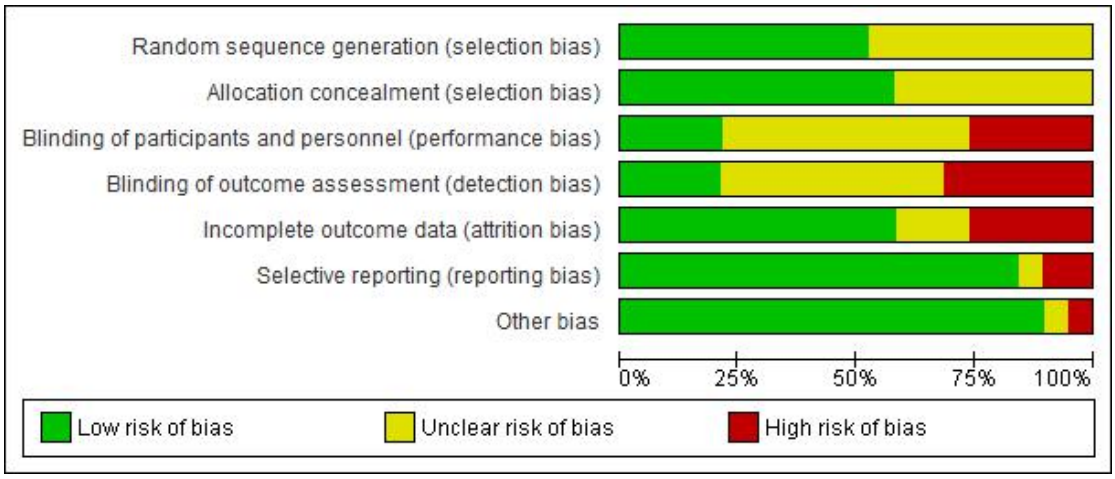
eAppendix 3

Risk of Bias Assessment

eFigure 1: Risk of bias summary: judgements about each bias item for each study



eFigure 2: Risk of bias graph: review authors' judgements (Low, Unclear and High) about each risk of bias item presented as percentages across all included studies.



eAppendix 4.

Network Plot for Secondary Outcomes

The network plots show the eligible comparisons for each outcome. Nodes represent the available treatments and edges represent the available comparisons. Both nodes and edges are weighted according to the number of studies involved in each treatment or comparison respectively .

Abbreviations:

HAL = haloperidol

RIS = risperidone

OLA = olanzapine

ZUC = zuclopenthixol

QUE = quetiapine

ZIP = ziprasidone

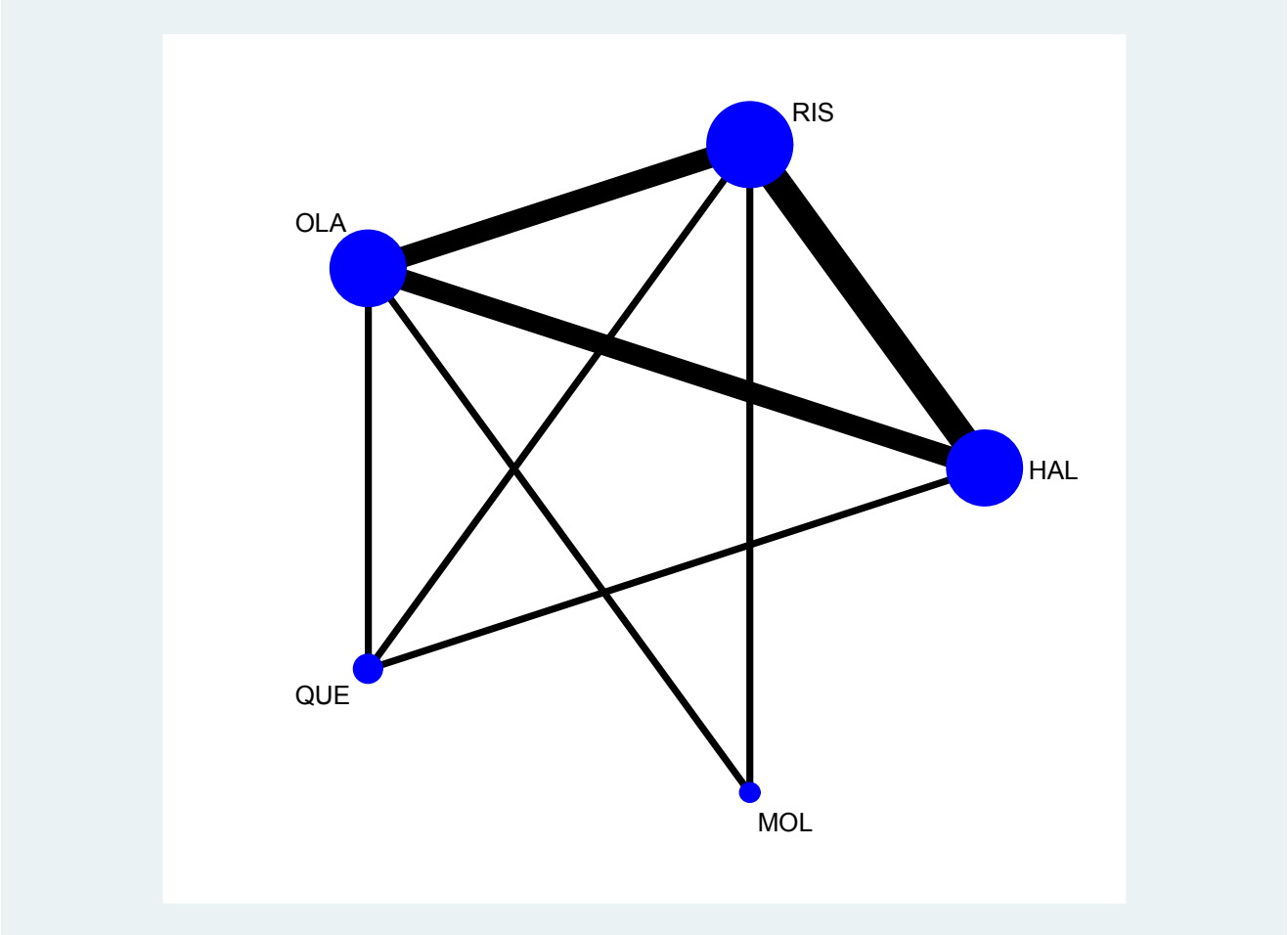
MOL = molindone

AMI = amisulpride

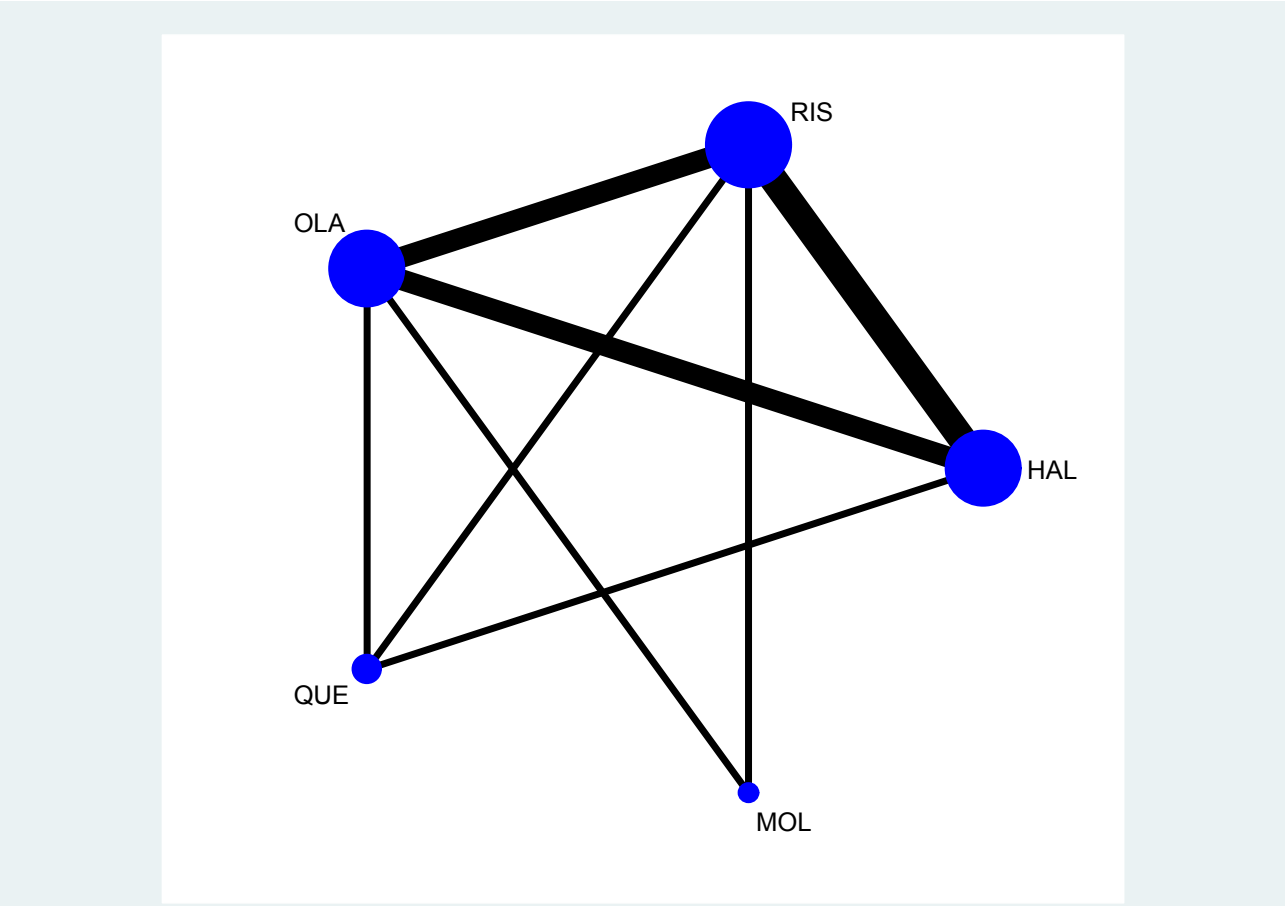
ARI = aripiprazole

SER = sertindole

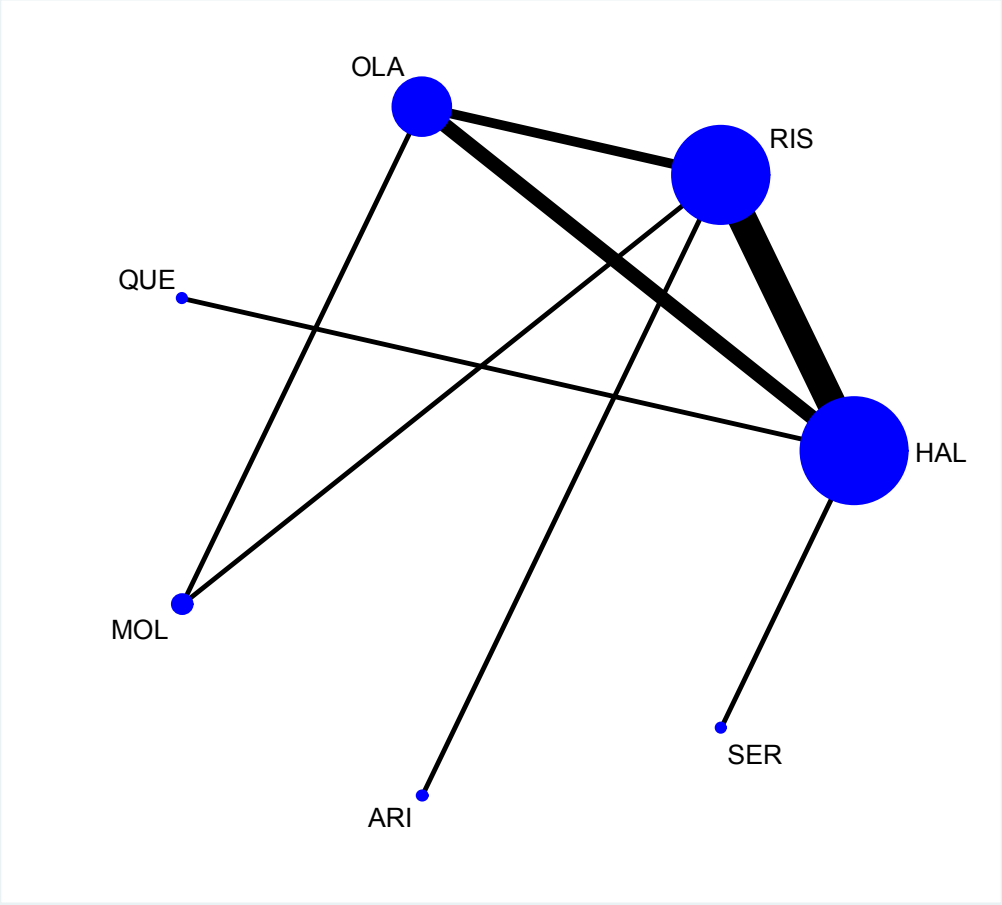
eFigure 3: Network plot for the secondary outcome ‘Positive symptoms’



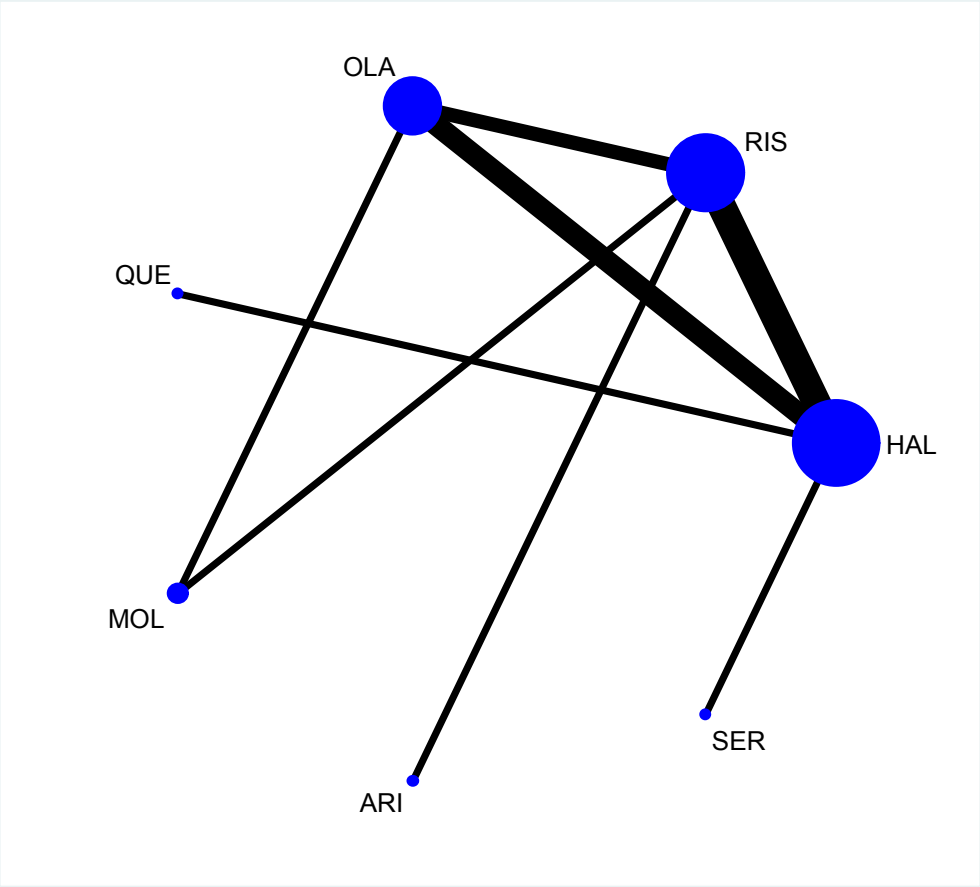
eFigure 4: Network plot for the secondary outcome 'Negative symptoms'



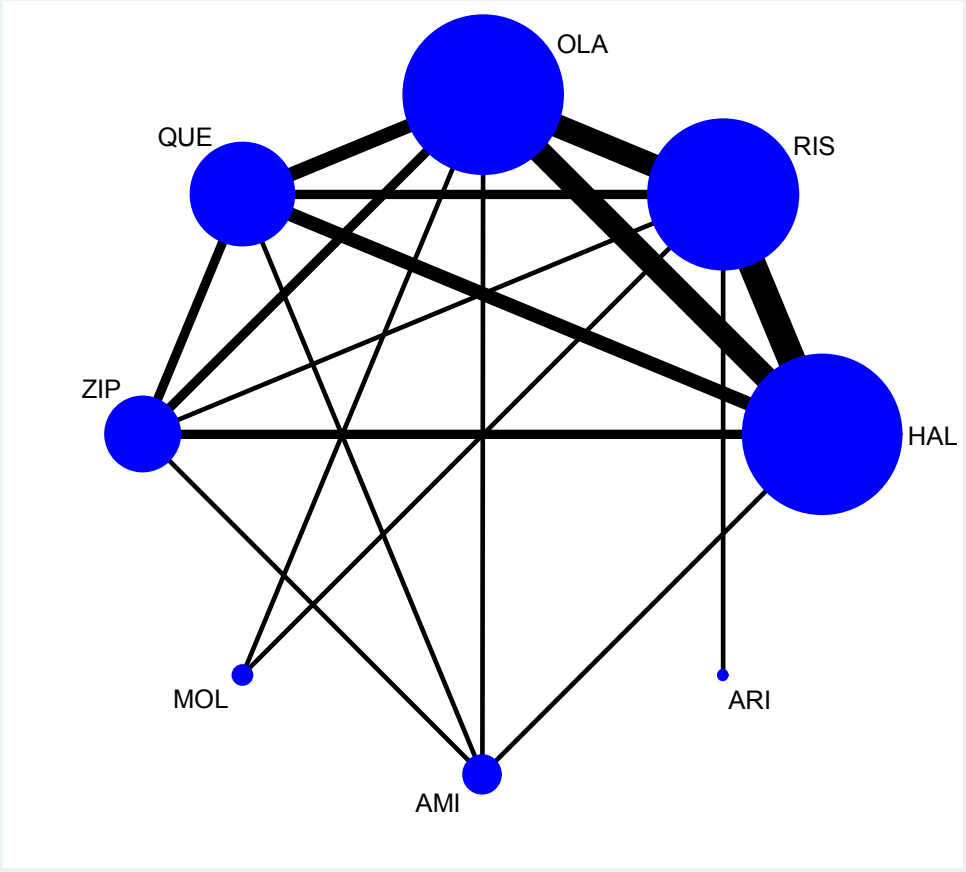
eFigure 5: Network plot for the secondary outcome ‘Discontinuation due to any reason’



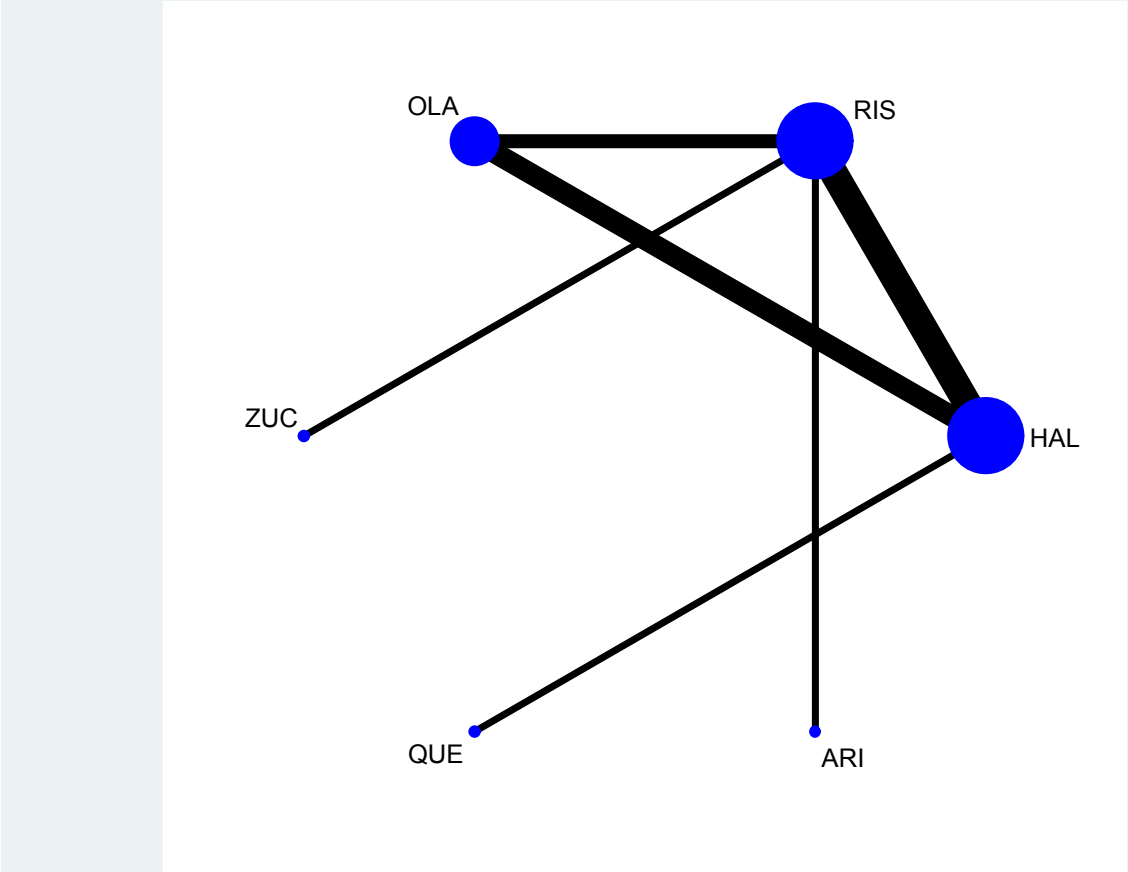
eFigure 6: Network plot for the secondary outcome ‘Discontinuation due to inefficacy’



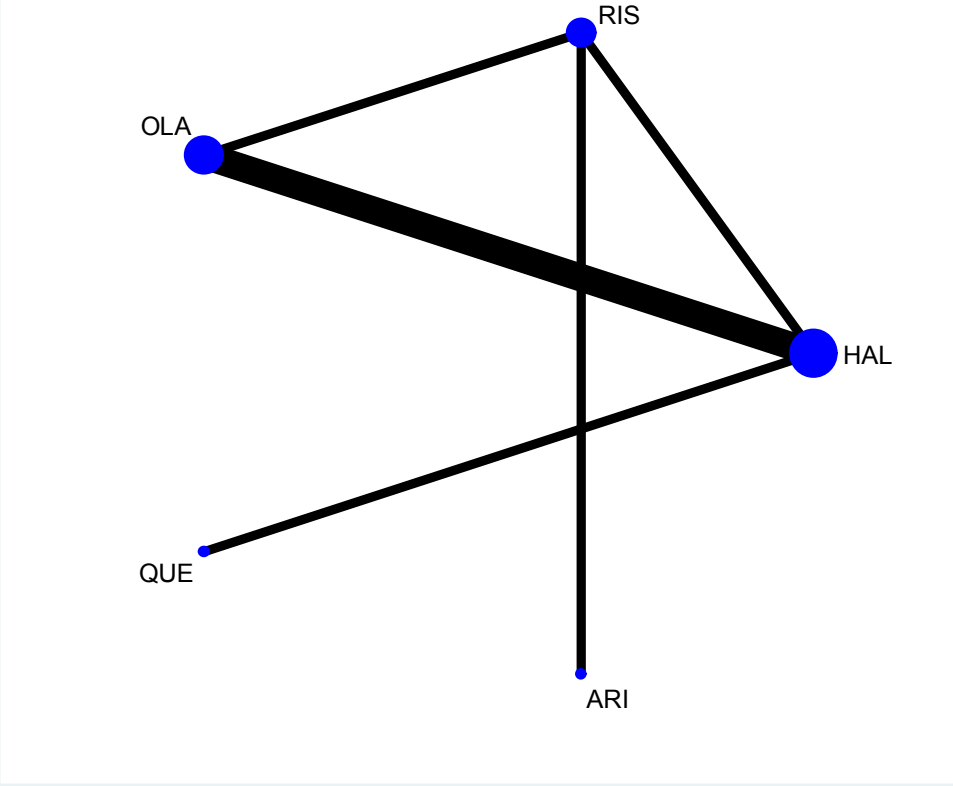
eFigure 7: Network plot for the secondary outcome ‘Response rate’



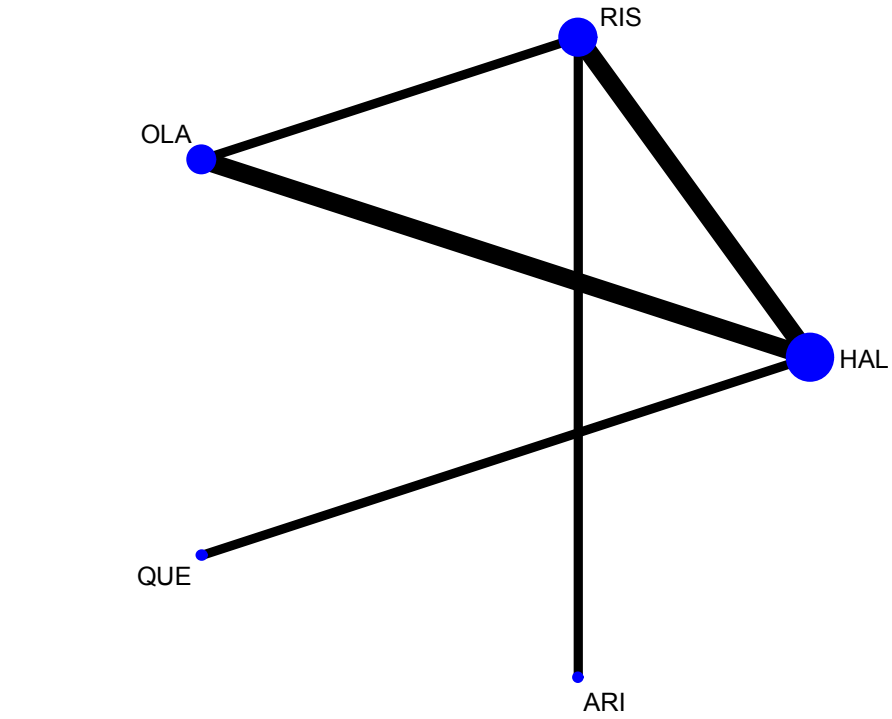
eFigure 8: Network plot for the secondary outcome ‘Antiparkinson medication’



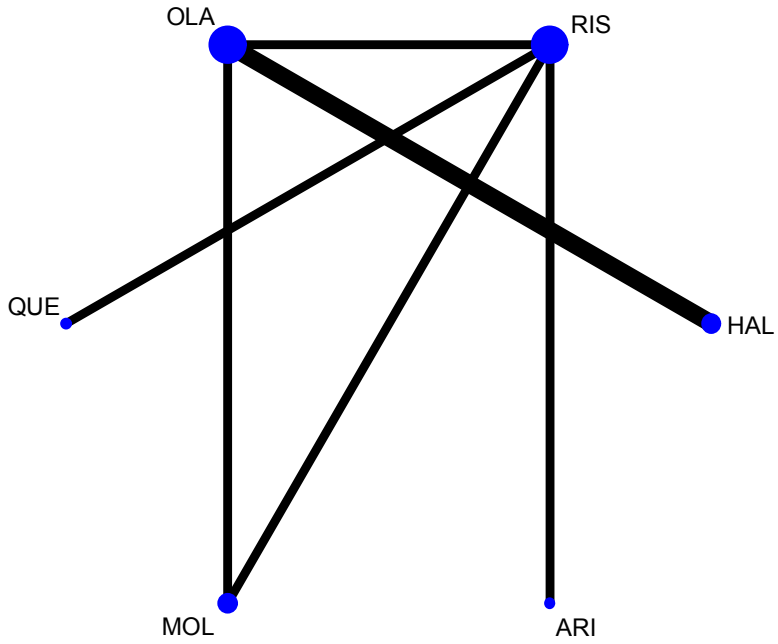
eFigure 9: Network plot for the secondary outcome ‘Akathisia’



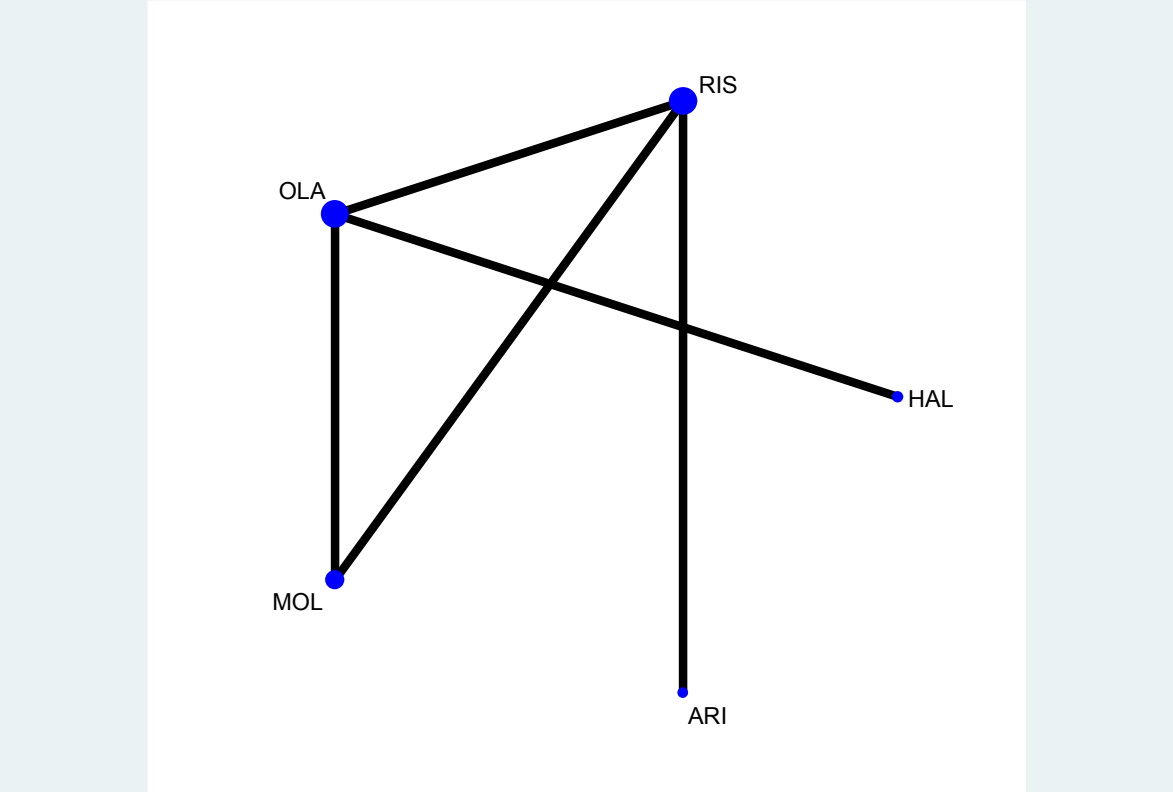
eFigure 10: Network plot for the secondary outcome ‘Sedation’



eFigure 11: Network plot for the secondary outcome ‘Weight gain’



eFigure 12: Network plot for the secondary outcome ‘Prolactin increase’



eAppendix 5

Results of Network and Pairwise Meta-analyses of Secondary Outcomes

Pairwise (upper triangle) and network meta-analysis (lower triangle) results for the secondary outcomes. For pairwise results, standardized mean differences (SMDs)/odds ratios (ORs) lower than 0/1 indicate that the treatment specified in the row is more efficacious. For NMA results, SMDs/ORs lower than 0/1 indicate that the treatment specified in the column is more efficacious. Bold underlined results indicate statistical significance.

Abbreviations:

HAL = haloperidol

RIS = risperidone

OLA = olanzapine

ZUC = zuclopenthixol

QUE = quetiapine

ZIP = ziprasidone

MOL = molindone

AMI = amisulpride

ARI = aripiprazole

SER = sertindole

eTable 1: Response rate

MOL				1.92 (0.75, 4.87) (1 study, 75 patients)		1.16 (0.48, 2.77) (1 study, 81 patients)	
1.18 (0.50,2.80)	QUE		1.04 (0.59, 1.84) (1 study, 208 patients)	1.03 (0.67, 1.59) (3 studies, 524 patients)	1.18 (0.69, 2.02) (2 studies, 229 patients)	0.87 (0.47, 1.60) (2 studies, 315 patients)	2.00 (1.22, 3.27) (3 studies, 407 patients)
1.16 (0.44,3.10)	0.99 (0.49,1.97)	ARI				1.33 (0.77, 2.30) (1 study, 209 patients)	
1.22 (0.48,3.12)	1.04 (0.61,1.75)	1.05 (0.48,2.32)	AMI	1.30 (0.75, 2.27) (1 study, 209 patients)	1.11 (0.61, 2.02) (1 study, 186 patients)		1.40 (0.80, 2.45) (1 study, 207 patients)
1.32 (0.59,2.95)	1.12 (0.77,1.63)	1.14 (0.59,2.18)	1.08 (0.65,1.80)	OLA	1.13 (0.50, 2.56) (2 studies, 232 patients)	1.13(0.76, 1.68) (5 studies, 550 patients)	1.69(1.06, 2.69) (5 studies, 711 patients)
1.42 (0.56,3.60)	1.21 (0.72,2.01)	1.22 (0.56,2.66)	1.16 (0.65,2.09)	1.08 (0.65,1.78)	ZIP	0.81(0.25, 2.68) (1 study, 45 patients)	1.32(0.78, 2.25) (2 studies, 226 patients)
1.55 (0.70,3.43)	1.31 (0.88,1.95)	1.33 (0.75,2.35)	1.26 (0.73,2.18)	1.17 (0.85,1.60)	1.09 (0.64,1.84)	RIS	1.13(0.83, 1.54) (6 studies, 697 patients)
1.99 (0.87,4.55)	1.69 (1.18,2.41)	1.71 (0.90,3.25)	1.63 (0.98,2.69)	1.50 (1.11,2.04)	1.40 (0.86,2.27)	1.29 (0.96,1.73)	HAL

eTable 2: Discontinuation due to inefficacy

OLA	0.73 (0.18, 3.01) (2 studies, 192 patients)	0.66 (0.15, 2.97) (1 study, 75 patients)				**0.40 (0.20, 0.81)** **(3 studies, 457 patients)**
0.82 (0.38,1.80)	RIS	0.76 (0.19, 3.05) (1 study, 81 patients)		0.67 (0.18, 2.46) (1 study, 209 patients)		**0.48 (0.25, 0.90)** **(4 studies, 616 patients)**
0.64 (0.17,2.33)	0.77 (0.22,2.74)	MOL				
0.59 (0.22,1.61)	0.72 (0.27,1.89)	0.93 (0.20,4.22)	QUE			0.68 (0.31, 1.48) (1 study, 156 patients)
0.55 (0.12,2.51)	0.67 (0.18,2.46)	0.87 (0.14,5.31)	0.94 (0.19,4.73)	ARI		
0.40 (0.01,22.80)	0.49 (0.01,27.53)	0.63 (0.01,41.93)	0.68 (0.01,39.64)	0.72 (0.01,50.08)	SER	
0.40 (0.21,0.75)	**0.49 (0.27,0.87)**	0.63 (0.17,2.32)	0.68 (0.31,1.48)	0.72 (0.18,2.99)	1.00 (0.02,54.16)	HAL

eTable 3: Akathisia

QUE				**0.00 (0.00, 0.05) (1 study, 156 patients)**
0.02 (0.00,0.37)	OLA	0.33 (0.09, 1.30) (1 study, 116 patients)		**0.14 (0.08, 0.24) (3 studies, 457 patients)**
0.01 (0.00,0.11)	**0.27 (0.10,0.72)**	RIS	0.56 (0.29, 1.09) (1 study, 209 patients)	0.57 (0.22, 1.47) (1 study, 117 patients)
0.00 (0.00,0.07)	**0.15 (0.05,0.49)**	0.56 (0.29,1.09)	ARI	
0.00 (0.00,0.05)	**0.14 (0.08,0.25)**	0.54 (0.22,1.33)	0.96 (0.31,2.93)	HAL

eTable 4: Sedation

QUE		**0.36 (0.17, 0.79)** **(1 study, 156 patients)**		
0.38 (0.13,1.11)	OLA	2.33 (0.20, 27.31) (2 studies, 194 patients)		2.80 (1.26, 6.22) (1 study, 116 patients)
12.08 (0.62,235.12)	2.70 (0.71,10.31)	HAL		1.12 (0.15, 8.44) (2 studies, 300 patients)
0.15 (0.03,0.79)	0.40 (0.08,2.07)	1.04 (0.49,2.19)	ARI	0.88 (0.51, 1.53) (1 study, 209 patients)
0.13 (0.03,0.63)	0.36 (0.08,1.65)	7.85 (1.65,37.32)	0.88 (0.51,1.53)	RIS

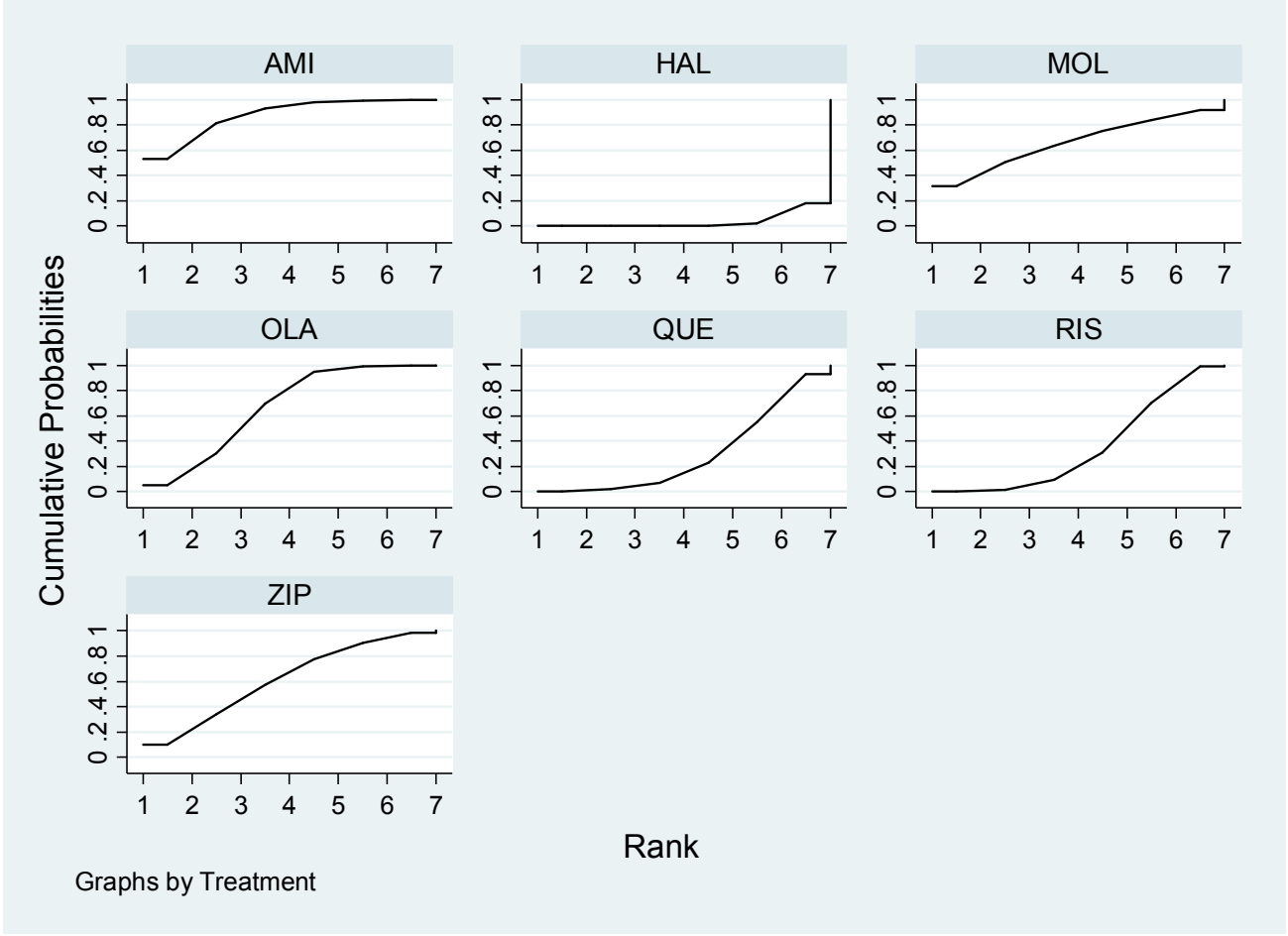
eTable 5: Prolactin increase

MOL		-0.32 (-0.77, 0.14) (1 study, 75 patients)		**-1.21 (-1.68, -0.73)** **(1 study, 81 patients)**
-0.25 (-0.81,0.30)	ARI			**-1.01 (-1.30, -0.71)** **(1 study, 198 patients)**
-0.32 (-0.78,0.13)	-0.07 (-0.63,0.48)	OLA	**-0.35 (-0.61, -0.09)** **(1 study, 229 patients)**	**-0.99 (-1.47, -0.51)** **(1 study, 76 patients)**
-0.67 (-1.20,-0.14)	-0.42 (-1.04,0.20)	-0.35 (-0.61,-0.08)	HAL	
-1.26 (-1.72,-0.79)	**-1.01 (-1.30,-0.71)**	**-0.93 (-1.40,-0.46)**	**-0.58 (-1.12,-0.04)**	RIS

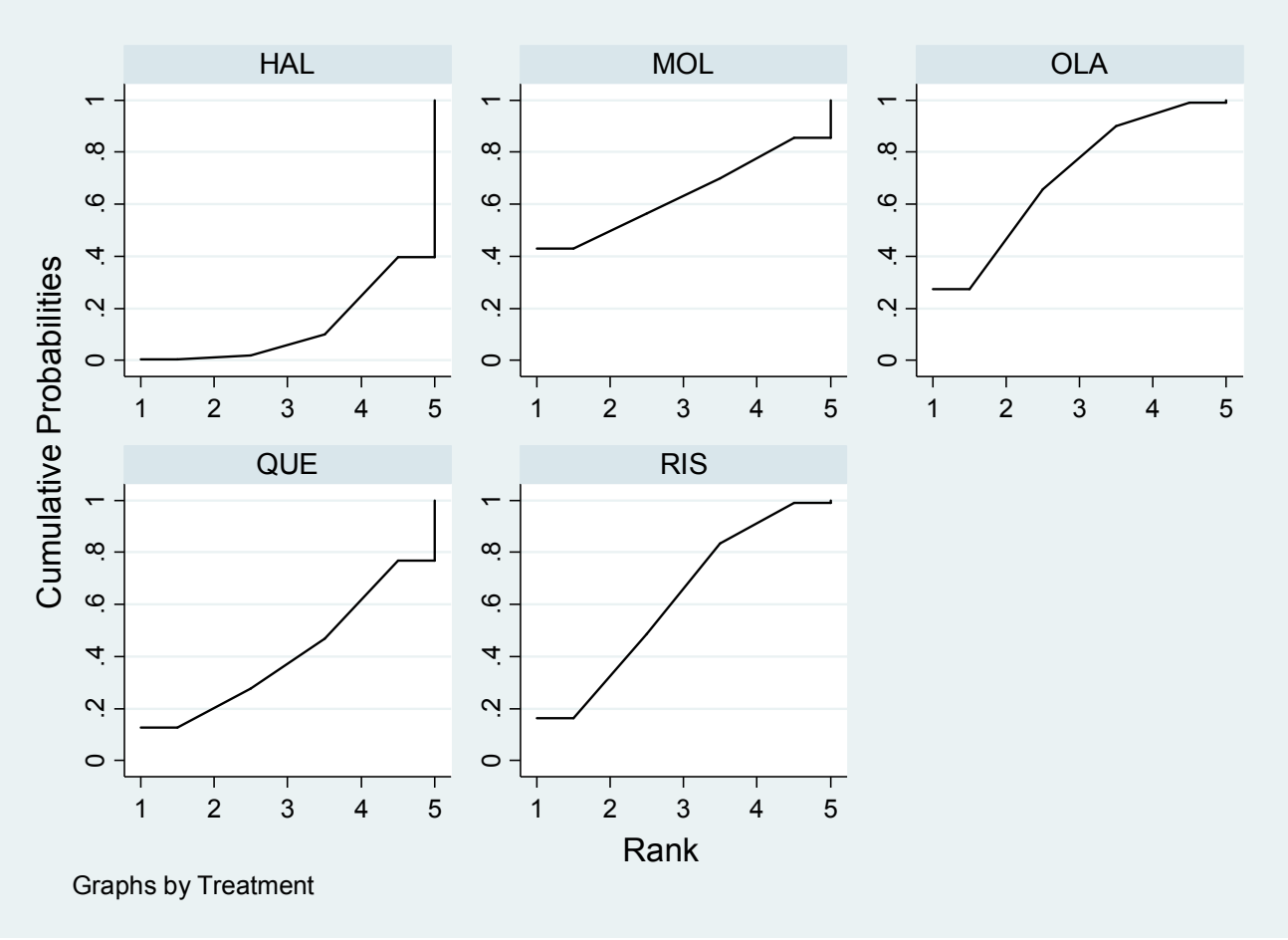
eAppendix 6

Cumulative Ranking Curves for All Outcomes

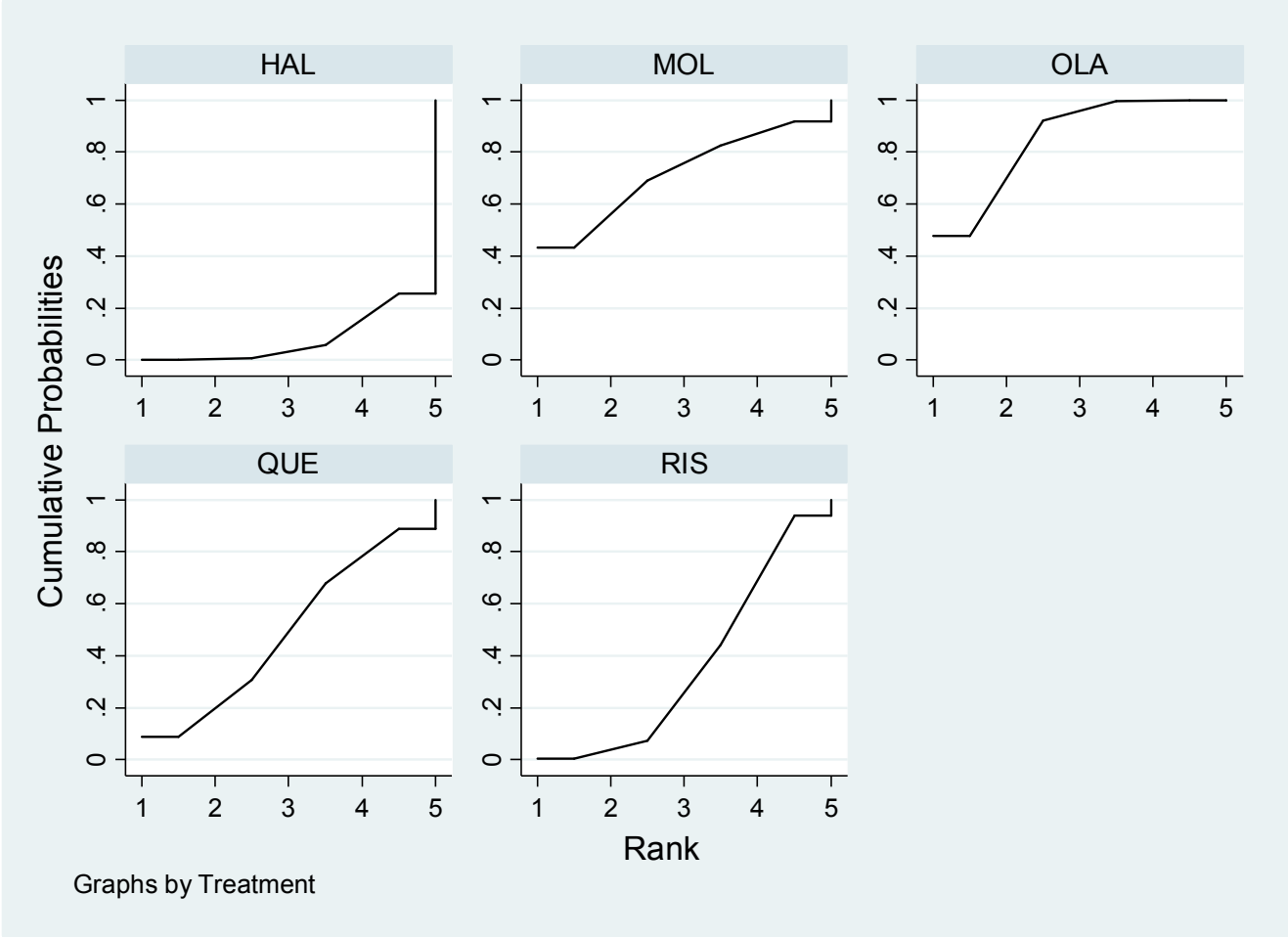
eFigure 13: SUCRA plots for the primary outcome 'Overall symptoms change'



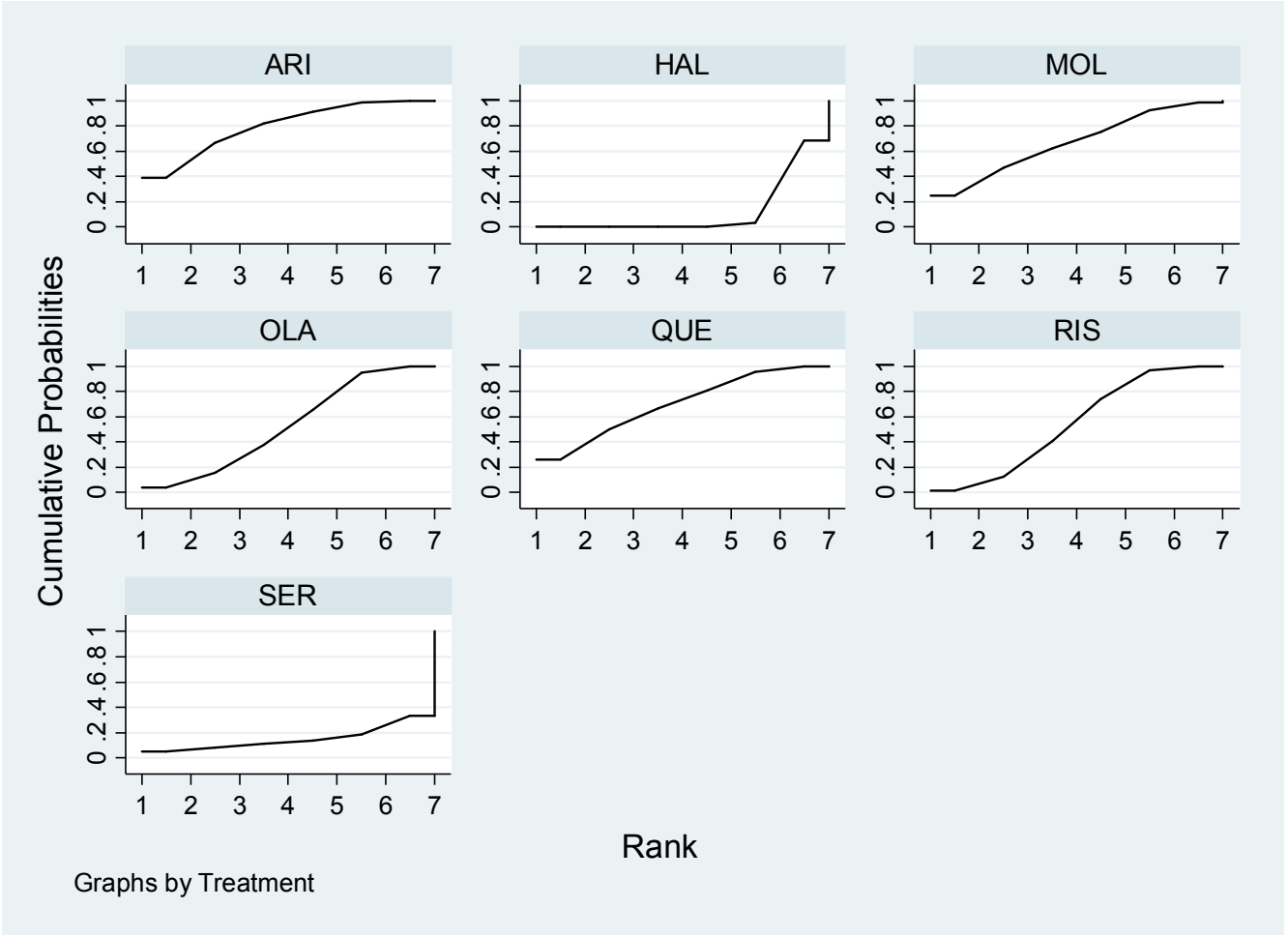
eFigure 14: SUCRA plots for the secondary outcome 'Positive symptoms'



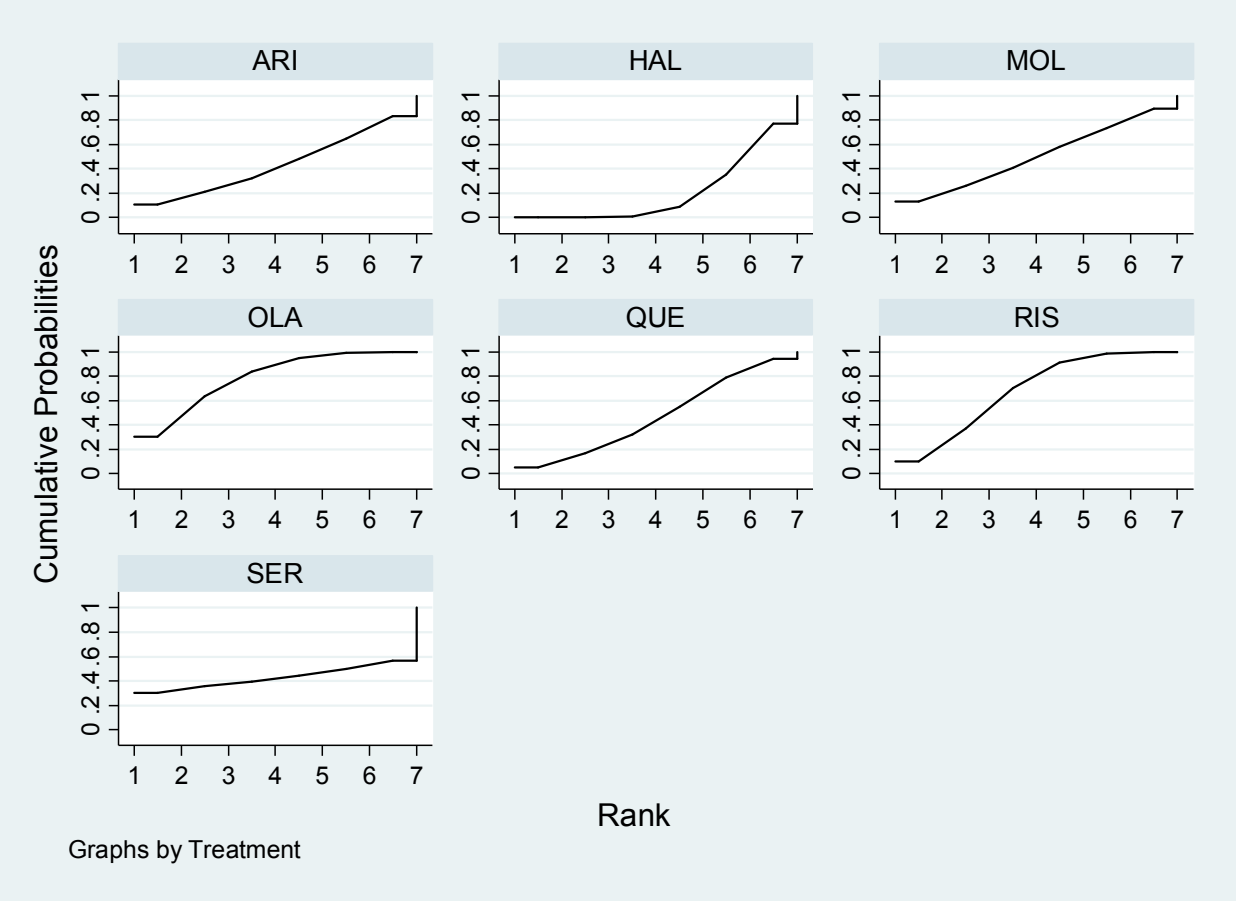
eFigure 15: SUCRA plots for the secondary outcome 'Negative symptoms'



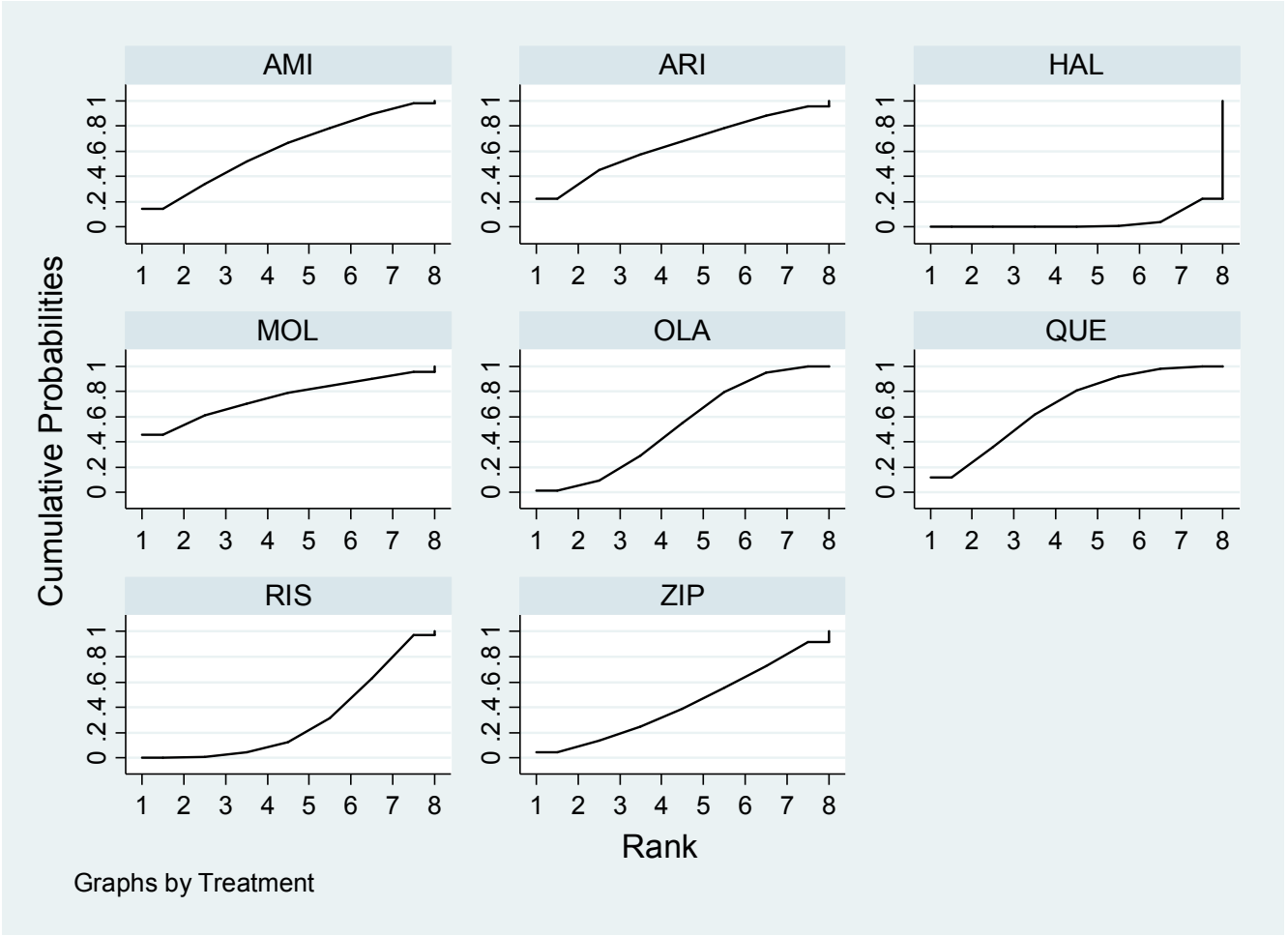
eFigure 16: SUCRA plots for the secondary outcome 'Discontinuation due to any reason'



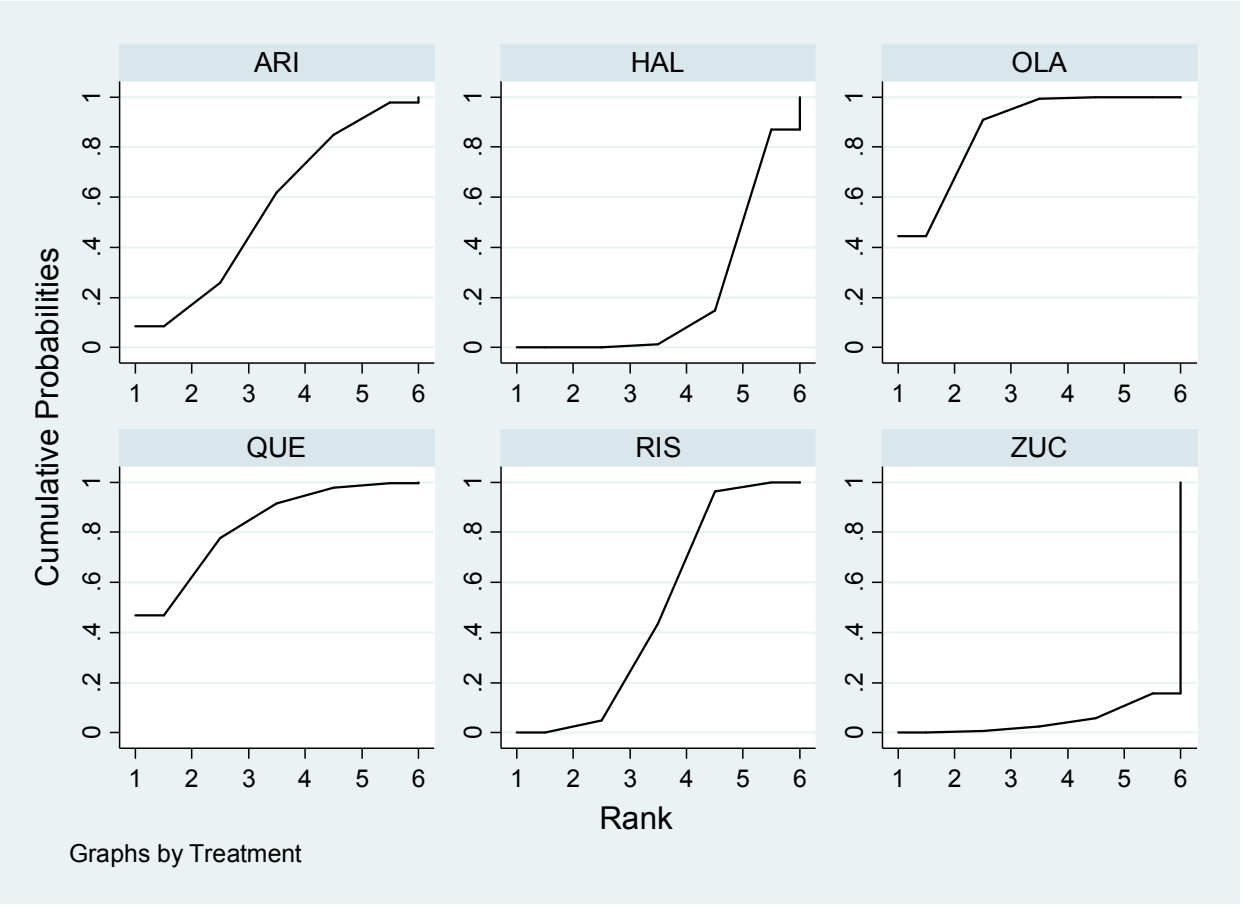
eFigure 17: SUCRA plots for the secondary outcome 'Discontinuation due to inefficacy'



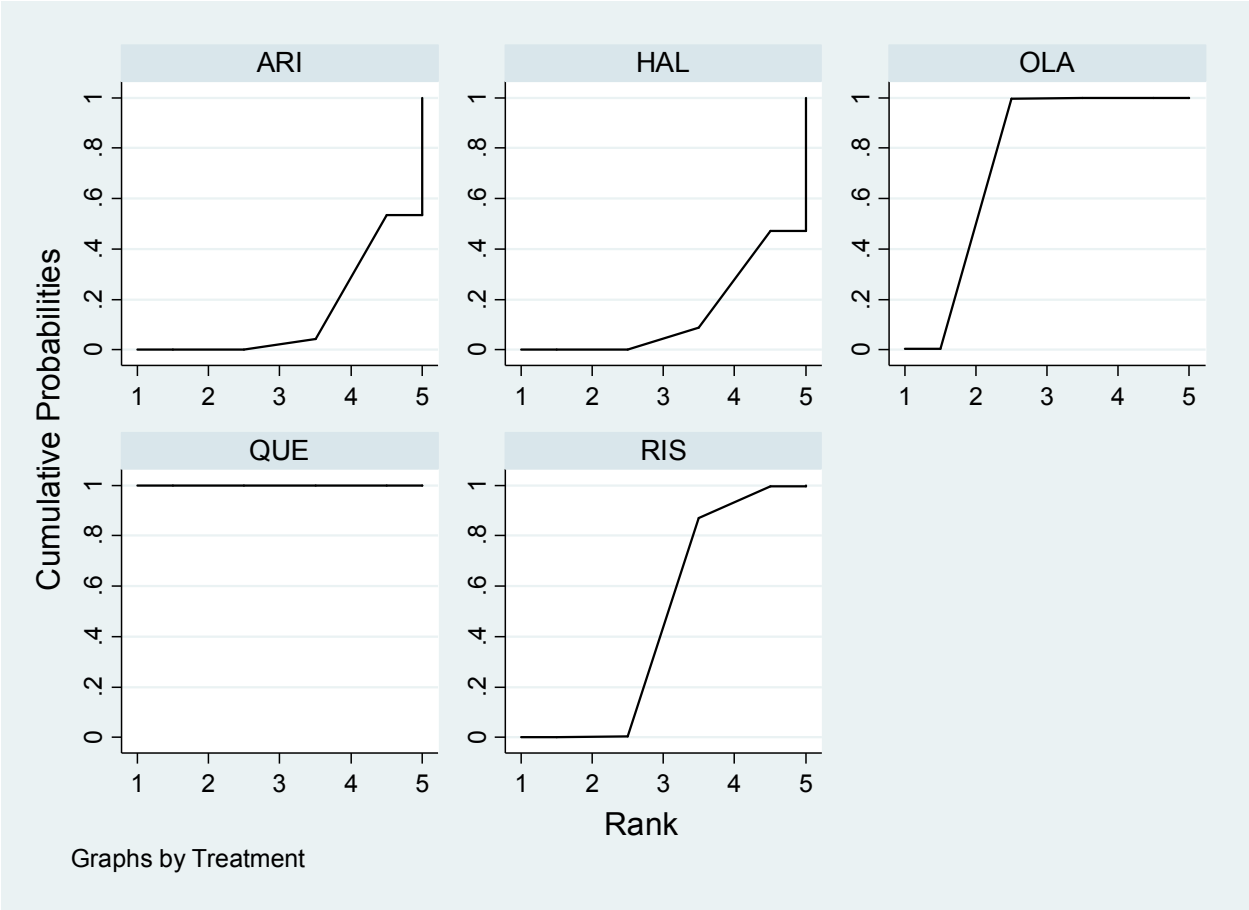
eFigure 18: SUCRA plots for the secondary outcome 'Response rate'



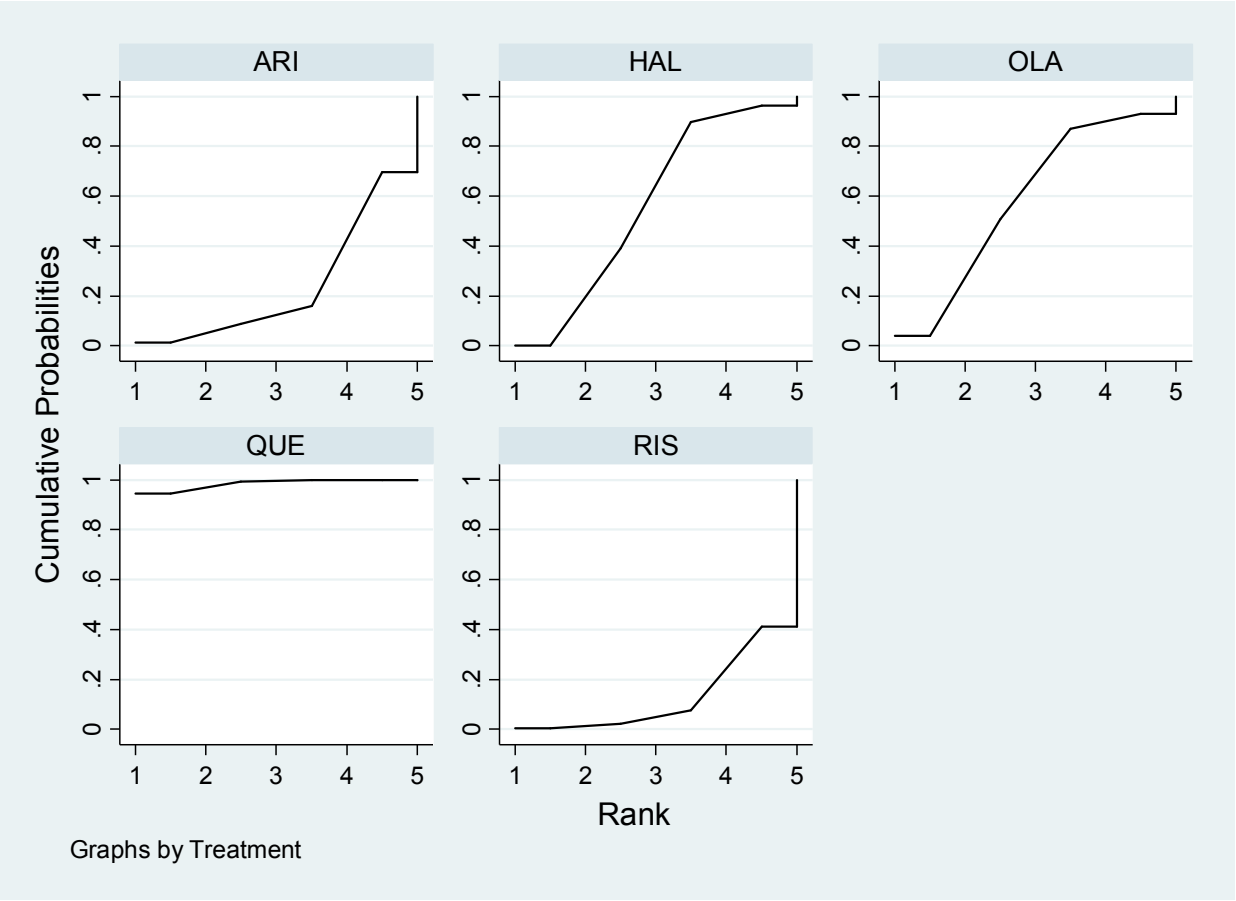
eFigure 19: SUCRA plots for the secondary outcome ‘Antiparkinson medication’



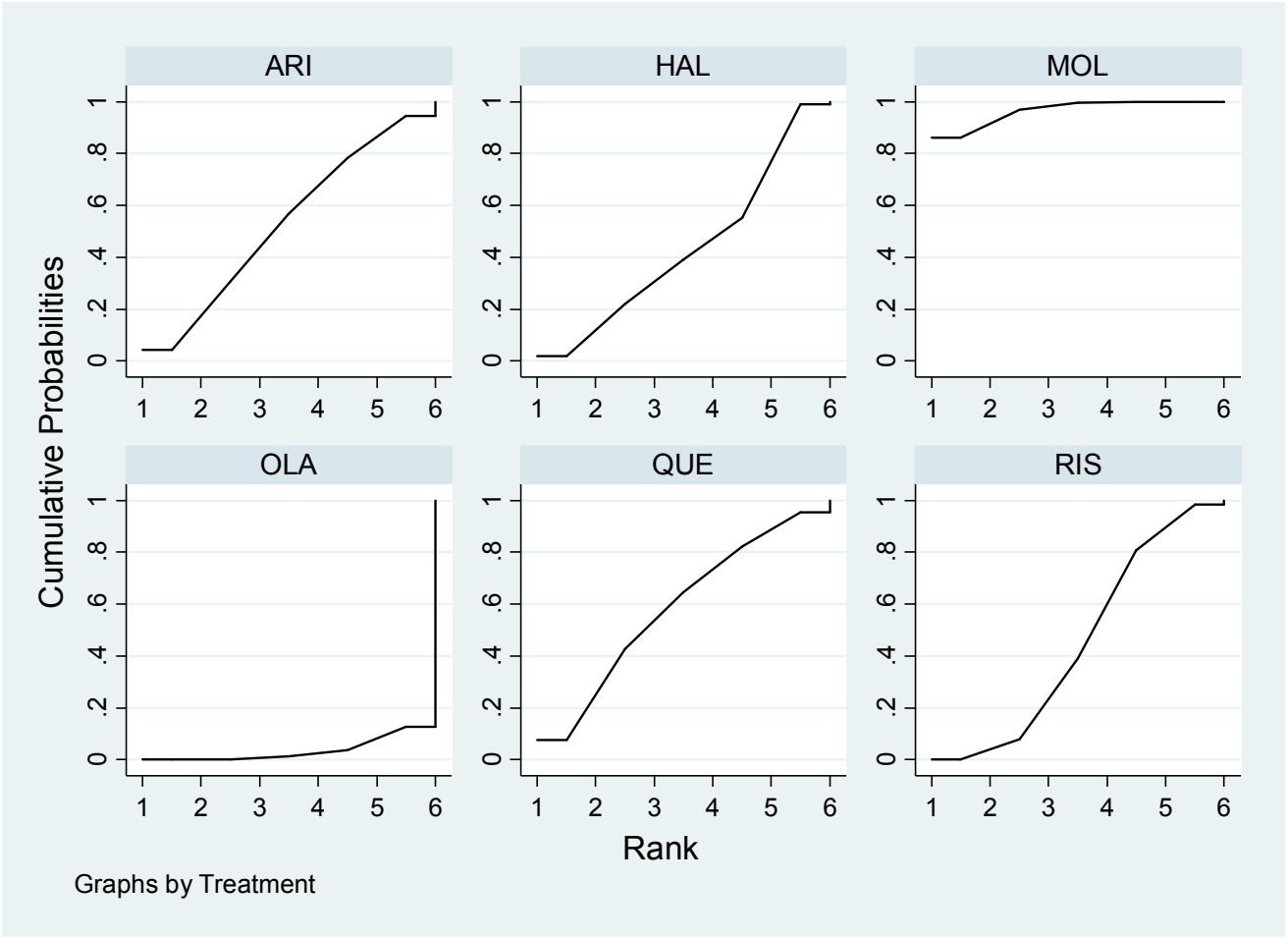
eFigure 20: SUCRA plots for the secondary outcome 'Akathisia'



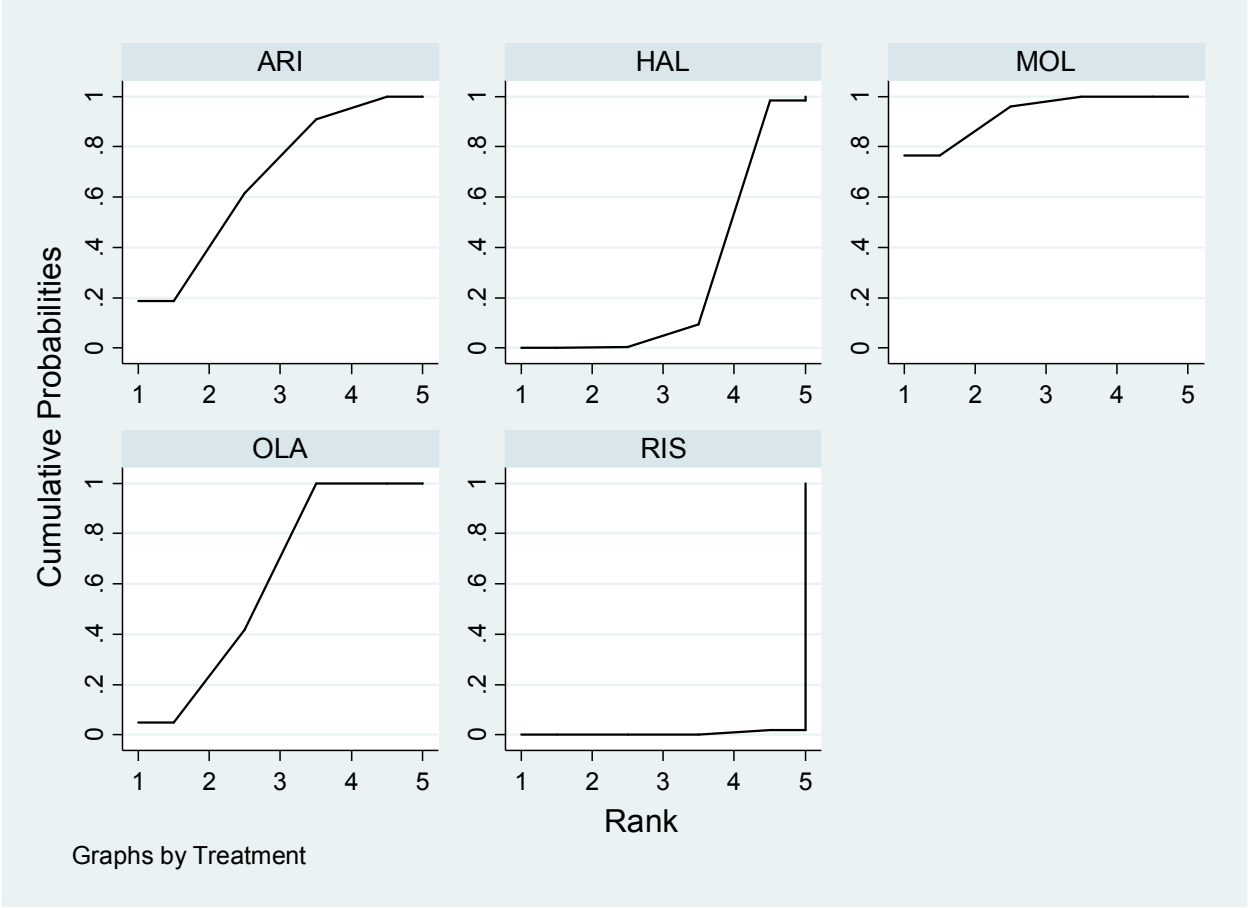
eFigure 21: SUCRA plots for the secondary outcome ‘Sedation’



eFigure 22: SUCRA plots for the secondary outcome 'Weight gain'



eFigure 23: SUCRA plots for the secondary outcome ‘Prolactin increase’



eAppendix 7

Evaluation of Heterogeneity and Inconsistency

Heterogeneity assessment

We inferred on the magnitude of heterogeneity by comparing the estimated tau^2 to empirical distributions of heterogeneity typically found in meta-analyses (Turner 2012, Rhodes 2015). Low heterogeneity could be considered when the estimated tau^2 is less than the 25% quantile of the empirical distribution, moderate heterogeneity for tau^2 between 25% and 50% quantile and high heterogeneity for tau^2 larger than the 50% quantile.

Outcome	Between study variance (tau^2)	Heterogeneity assessment
Overall symptoms change	0	0
Positive symptoms	0.03	low to moderate
Negative symptoms	0.001	low
All-cause discontinuation	0	0
Dropout due to inefficacy	0	0
Response	0.006	low
Antiparkinson medication use	0.78	moderate to high
Akathisia	0	0
Sedation	1.59	high
Prolactin increase	0	0
Weight gain	0.10	moderate to high

Summary: Most outcomes presented low heterogeneity except use of antiparkinson medication, sedation and weight gain.

We evaluated the consistency assumption using the loop-specific approach in Stata. The following eFigures present the inconsistency plots for each outcome using a common heterogeneity within each loop (but different across loops). For the continuous and dichotomous outcomes inconsistency factors (IF) are the differences of standardized mean differences (SMDs) and ratios of odds ratios (ORs) respectively. Most loops were consistent (p value >0.10) indicating lack of evidence of inconsistency in the network.

Abbreviations:

HAL = haloperidol

RIS = risperidone

OLA = olanzapine

ZUC = zuclopenthixol

QUE = quetiapine

ZIP = ziprasidone

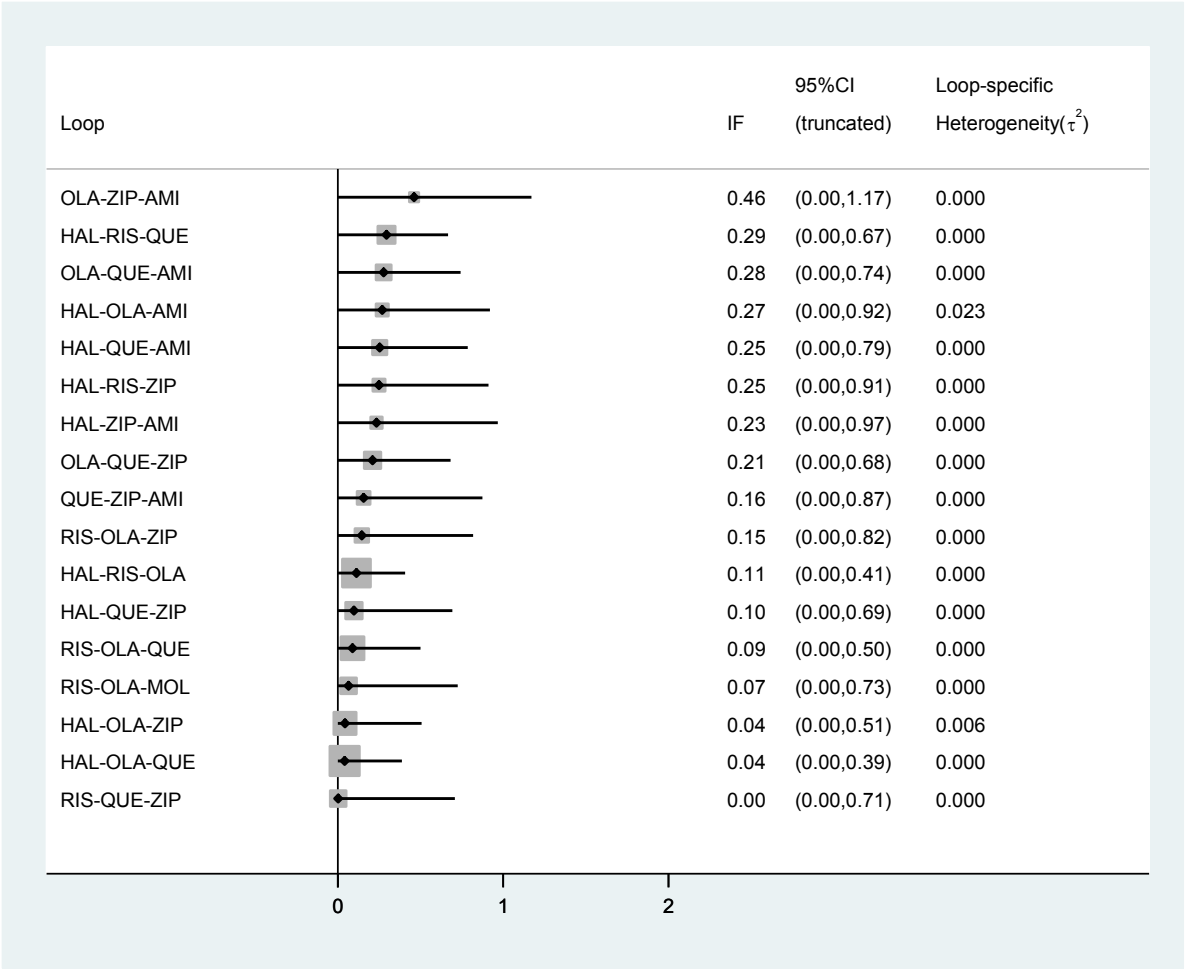
MOL = molindone

AMI = amisulpride

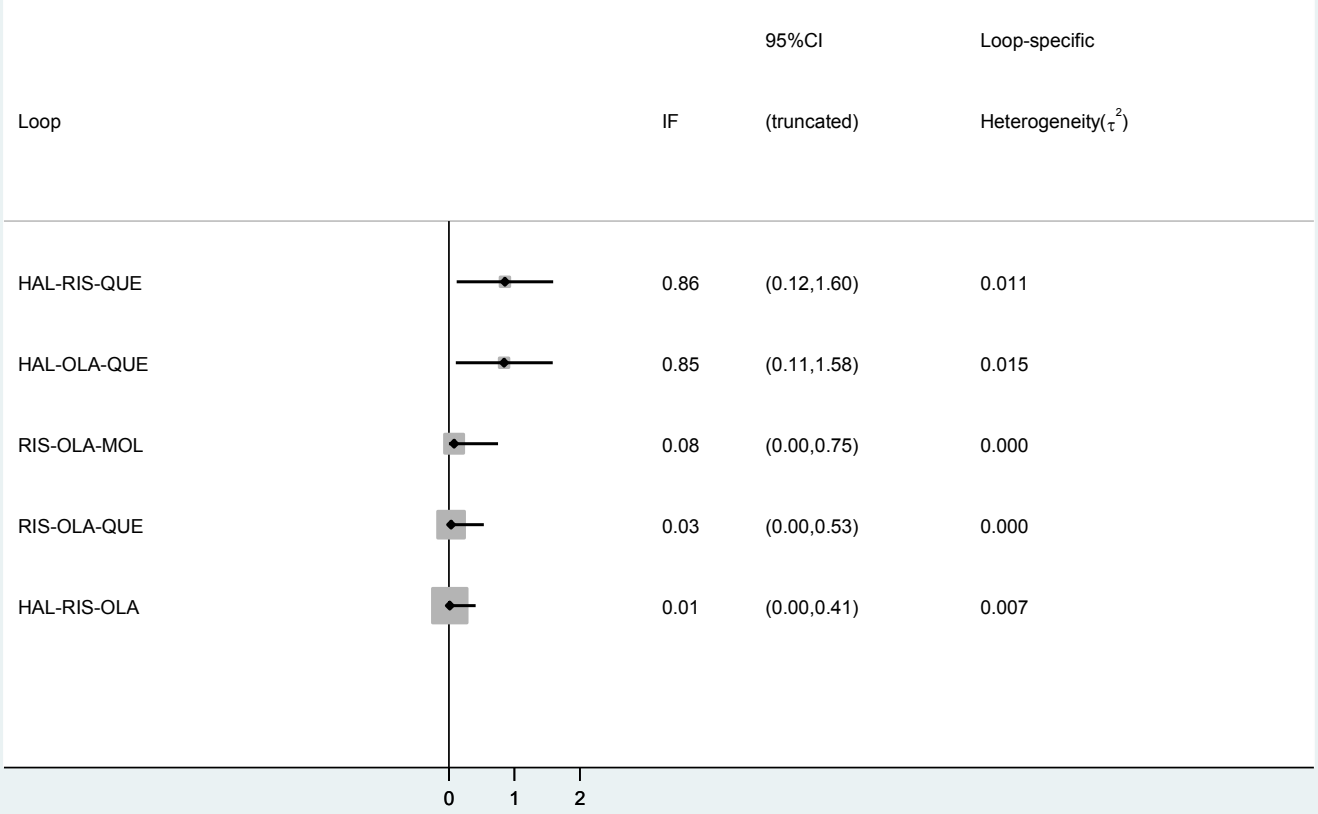
ARI = aripiprazole

SER = sertindole

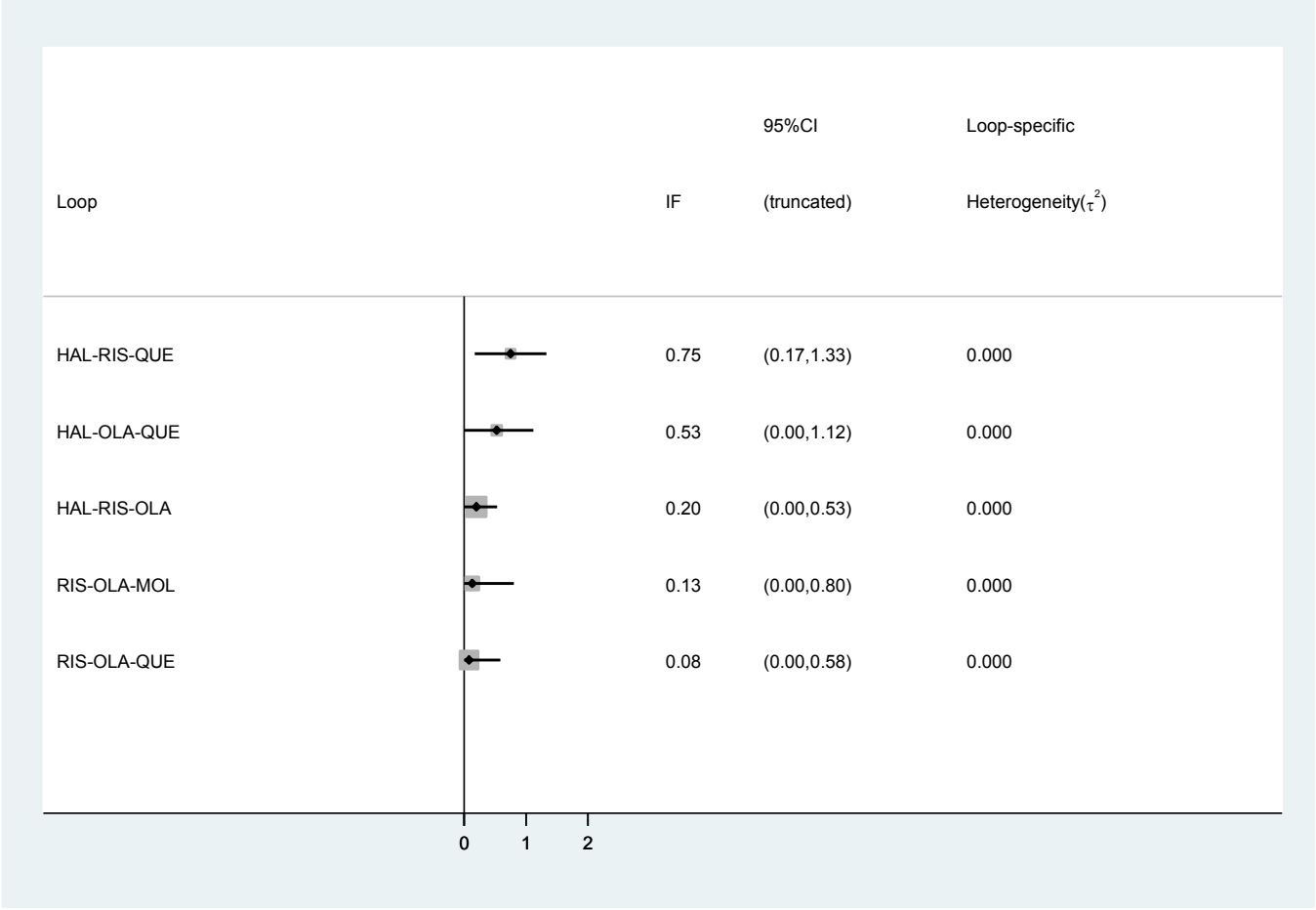
eFigure 24: Inconsistency plot for the primary outcome 'Overall symptoms change'



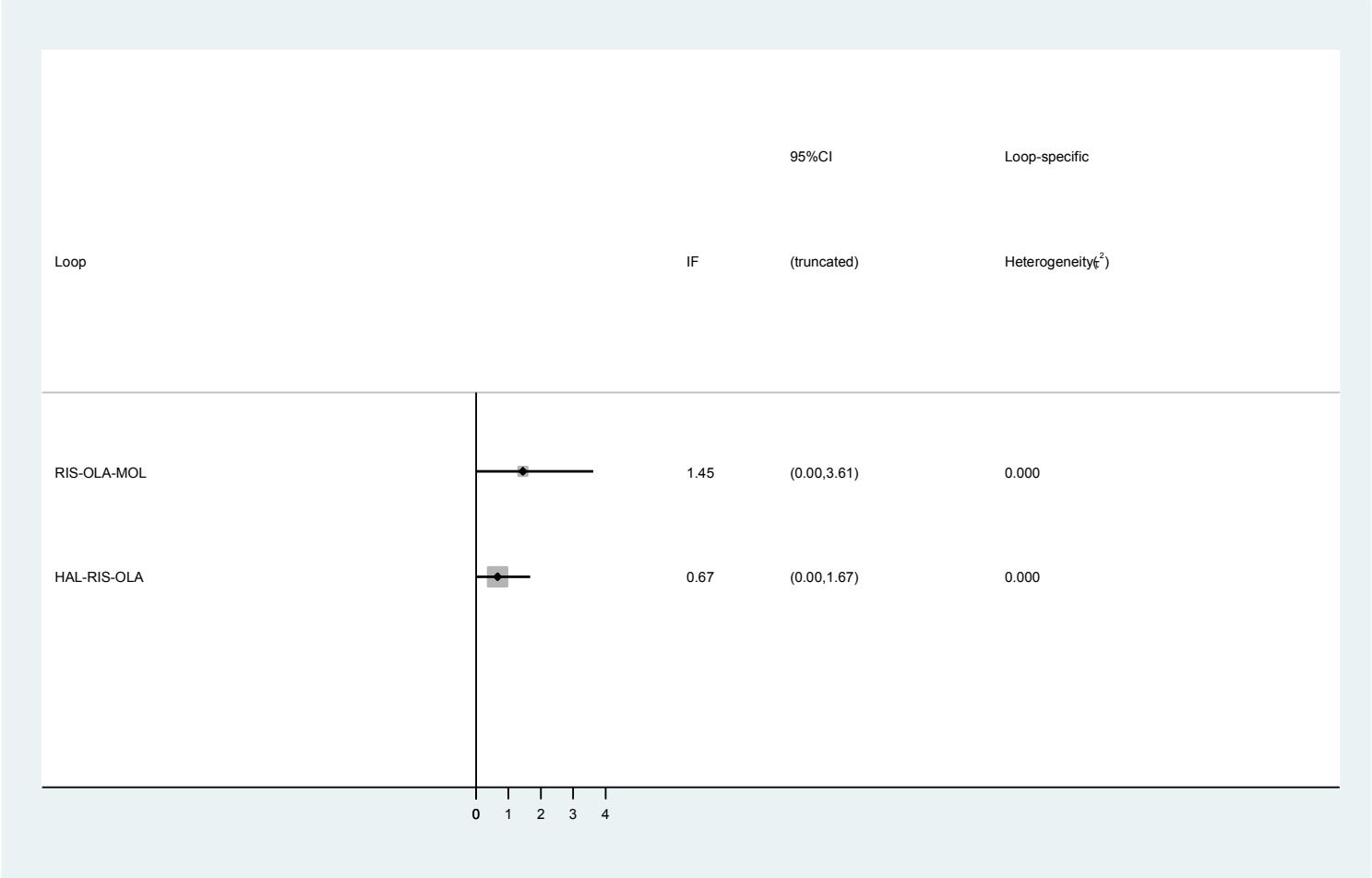
eFigure 25: Inconsistency plot for the secondary outcome ‘Positive symptoms’



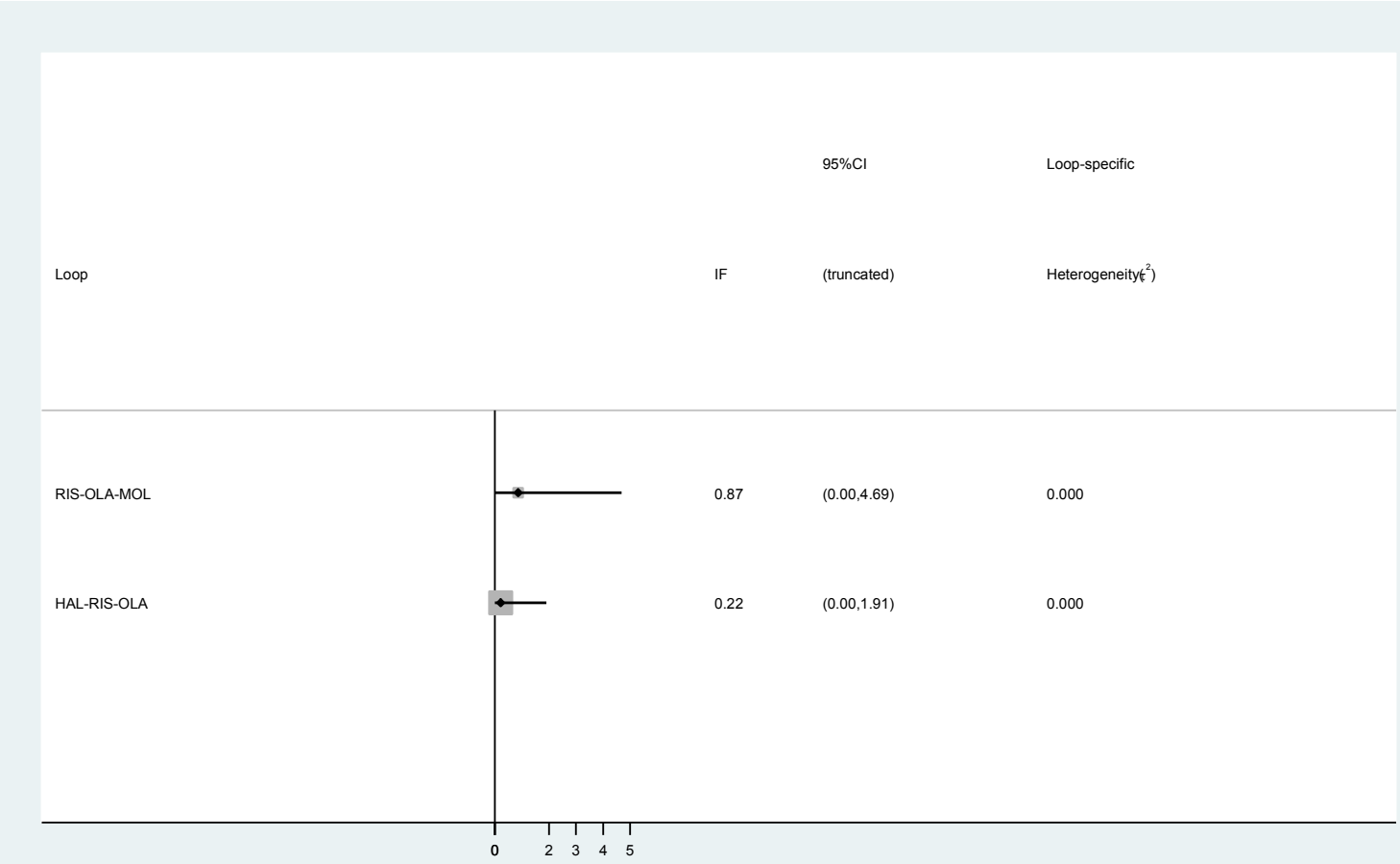
eFigure 26: Inconsistency plot for the secondary outcome ‘Negative symptoms’



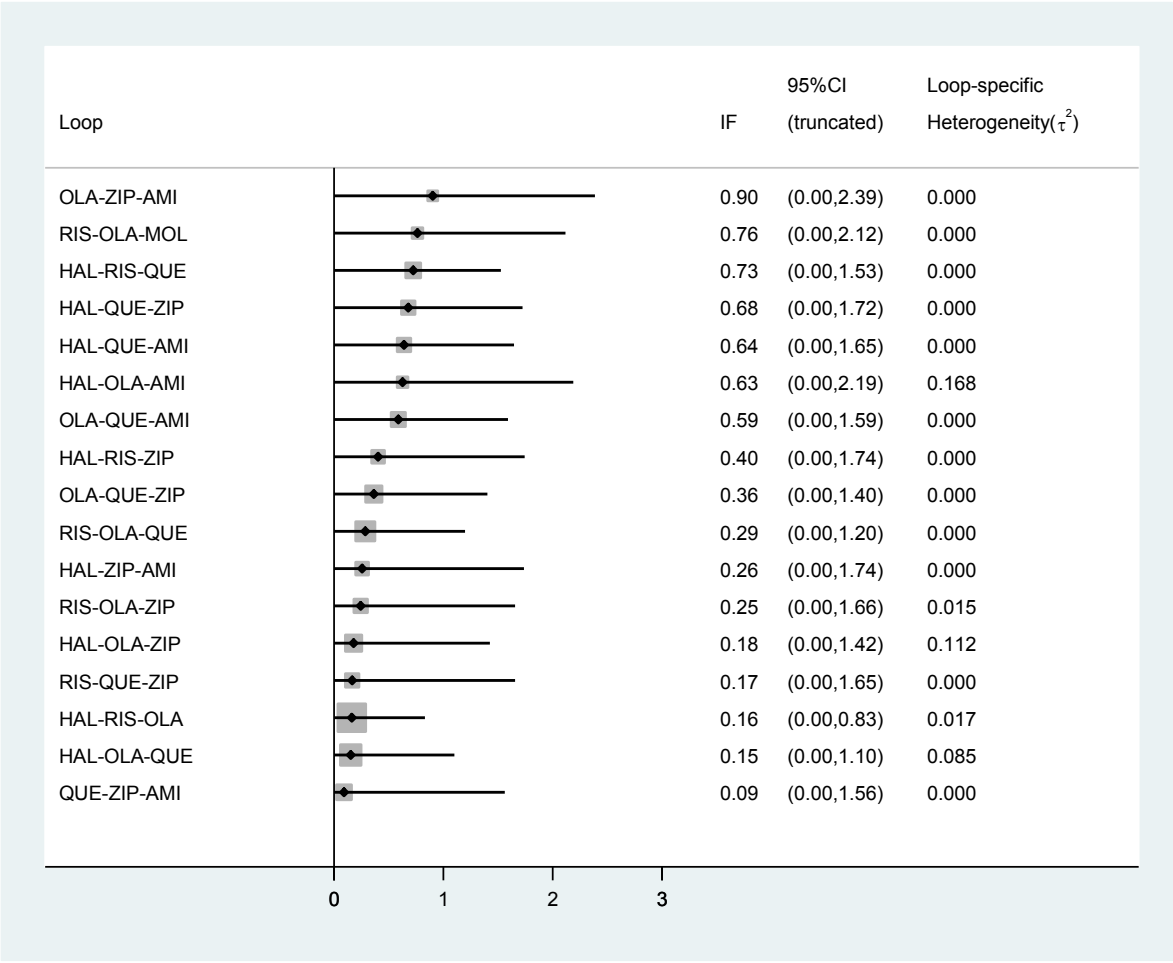
eFigure 27: Inconsistency plot for the secondary outcome ‘Discontinuation due to any reason’



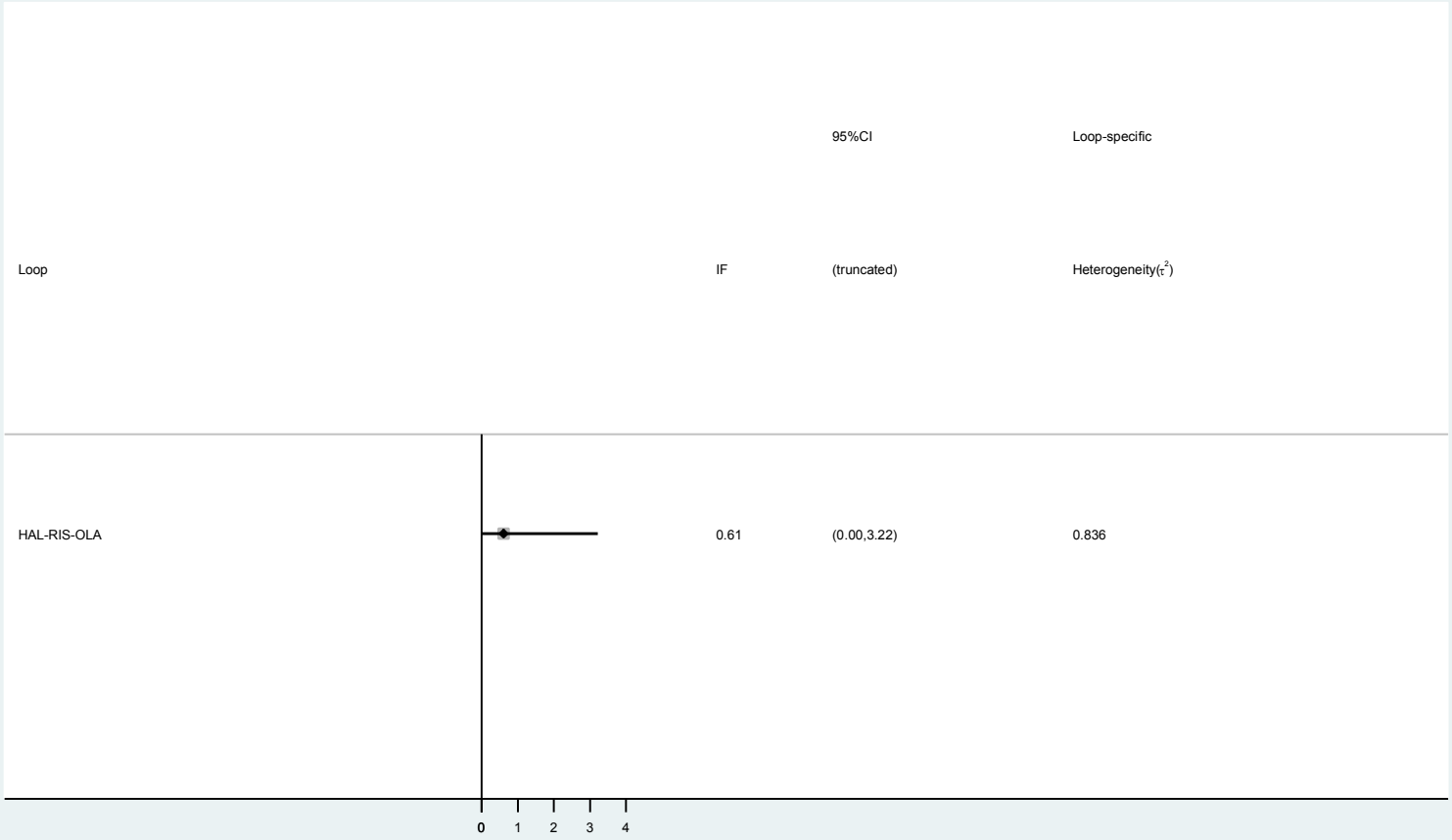
eFigure 28: Inconsistency plot for the secondary outcome ‘Discontinuation due to inefficacy’



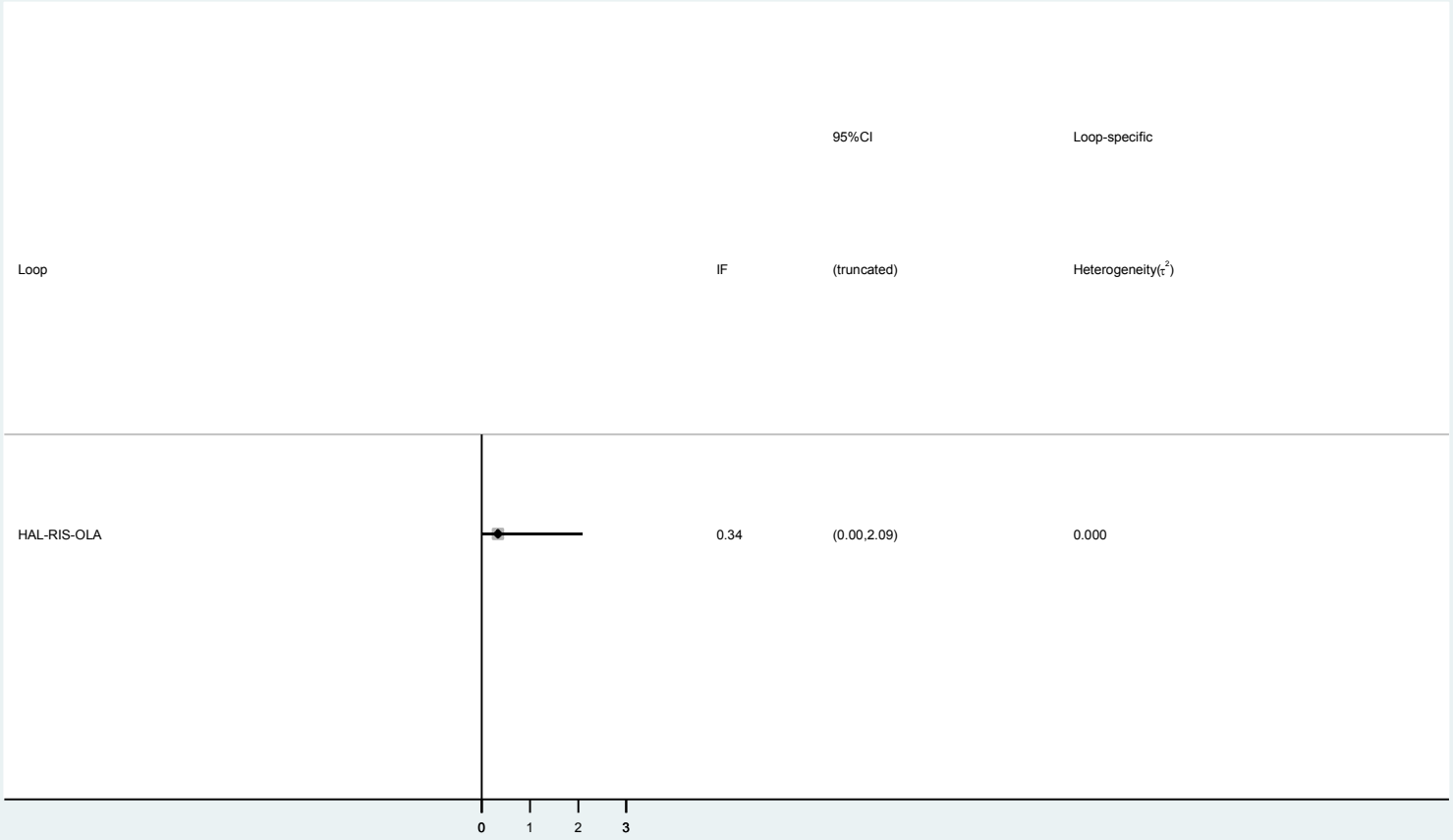
eFigure 29: Inconsistency plot for the secondary outcome ‘Response rate’



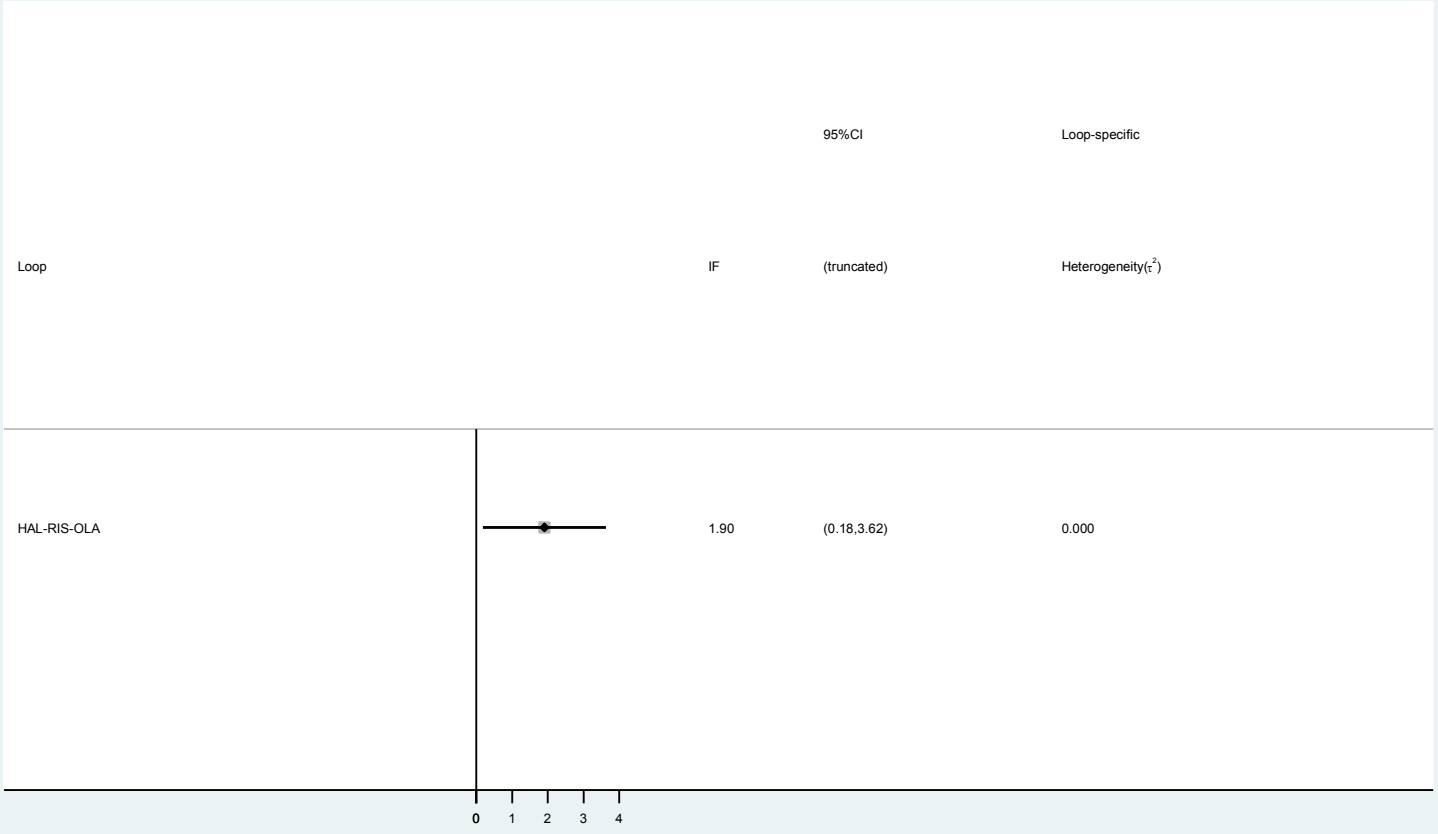
eFigure 30: Inconsistency plot for the secondary outcome ‘Antiparkinson medication’



eFigure 31: Inconsistency plot for the secondary outcome ‘Akathisia’



eFigure 32: Inconsistency plot for the secondary outcome ‘Sedation’



Design-by-treatment interaction model

We assessed the assumption of consistency in the entire network using the design-by treatment interaction model in Stata.

Outcome	P value
Overall symptom change	0.6457
Positive symptom	0.2823
Negative symptom	0.1752
All-cause discontinuation	0.0826
Dropout due to inefficacy	0.7435
Response	0.7708
Antiparkinson medication use	0.1812
Akathisia	0.6467
Sedation	0.0114*
Prolactin increase	0.0000*
Weight gain	0.7762

*p>0.05 means the data fits consistency model better, p<0.05 means it fits inconsistency model better.

Summary: The results showed that there was some inconsistency only in sedation and prolactin increase which did not fit the consistency model.

Side-splitting method

We also assessed the assumption of consistency using the side-splitting model in Stata.

Overall symptom change

Side	P>z
HAL RIS	0.276
HAL OLA	0.719
HAL QUE	0.224
HAL ZIP	0.823
HAL AMI	0.51
RIS OLA	0.619
RIS QUE	0.147

RIS ZIP	0.579
RIS MOL	0.906
OLA QUE	0.949
OLA ZIP	0.451
OLA MOL	0.906
OLA AMI	0.118
QUE ZIP	0.338
QUE AMI	0.482
ZIP AMI	0.572

Positive symptom

Side	**P>z**
HAL RIS	0.282
HAL OLA	0.397
HAL QUE	0.002*
RIS OLA	0.815
RIS QUE	0.055
RIS MOL	0.89
OLA QUE	0.064
OLA MOL	0.891

Negative symptom

Side	**P>z**
HAL RIS	0.056
HAL OLA	0.577
HAL QUE	0.019*
RIS OLA	0.266
RIS QUE	0.024*
RIS MOL	0.429
OLA QUE	0.324
OLA MOL	0.429

All-cause discontinuation

Side	**P>z**
HAL RIS	0.059
HAL OLA	0.142
RIS OLA	0.196

RIS MOL	0.048*
RIS ARI	0.991
OLA MOL	0.048

Dropout due to inefficacy

Side	**P>z**
HAL RIS	0.993
HAL OLA	0.788
RIS OLA	0.751
RIS MOL	0.938
RIS ARI	0.997
OLA MOL	0.938

Response

Side	**P>z**
HAL RIS	0.125
HAL OLA	0.869
HAL QUE	0.244
HAL ZIP	0.656
HAL AMI	0.324
RIS OLA	0.763
RIS QUE	0.089
RIS ZIP	0.615
RIS MOL	0.143
RIS ARI	0.995
OLA QUE	0.543
OLA ZIP	0.613
OLA MOL	0.143
OLA AMI	0.195
QUE ZIP	0.856
QUE AMI	0.971
ZIP AMI	0.638

Antiparkinson med

Side	**P>z**
HAL RIS	0.25
HAL OLA	0.948

RIS OLA	0.425
RIS ZUC	1
RIS ARI	0.988

Akathisia

Side	**P>z**
HAL RIS	0.647
HAL OLA	0.997
RIS OLA	0.647
RIS ARI	0.997

Weight gain

Side	**P>z**
HAL OLA	0.993
RIS OLA	0.994
RIS QUE	0.996
RIS MOL	0.995
RIS ARI	0.997
OLA MOL	0.993

Sedation

Side	**P>z**
HAL RIS	0.398
HAL OLA	0.437
RIS OLA	0.986
RIS ARI	1.000

*P<0.05 means there is inconsistency between direct and indirect evidence for this comparsion.

Summary: The results showed that there was some inconsistency in positive symptom, negative symptom and all-cause discontinuation.

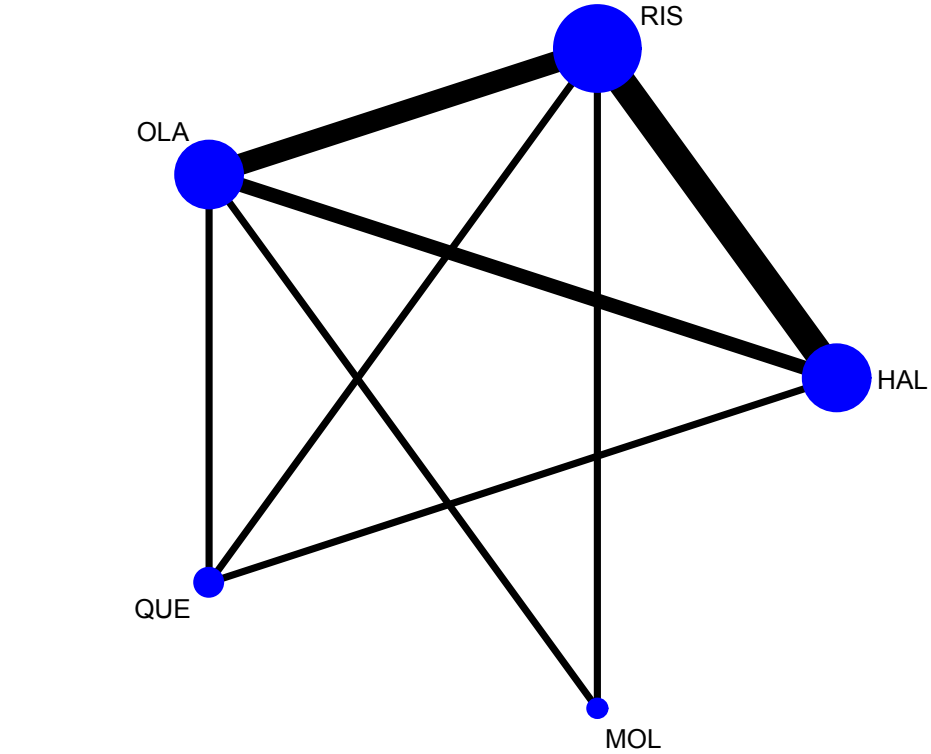
eAppendix 8

Sensitivity Analyses

Sensitivity Analysis by excluding open-label studies

As sensitivity analysis, we excluded the four open-label trials and performed pairwise and a network meta-analysis for the primary outcome “Overall symptoms change”. Overall 15 studies were included in the sensitivity analysis.

eFigure 33: Network plot for the primary outcome ‘Overall symptoms change’ when excluding open-label studies



eTable 6. Pairwise (upper triangle) and NMA (lower triangle) results for the primary outcome 'Overall symptoms change' when excluding open-label trials. For pairwise results, standardized mean differences (SMDs) lower than 0 indicate that the treatment specified in the row is more efficacious. For NMA results, SMDs lower than 0 indicate that the treatment specified in the column is more efficacious. Bold underlined results indicate statistical significance.

OLA	0.02 (-0.43, 0.48) (1 study, 75 patients)	-0.07 (-0.30, 0.16) (3 studies, 289 patients)	-0.25 (-0.55, 0.04) (1 study, 181 patients)	**-0.36 (-0.58, -0.14)** **(2 studies, 333 patients)**
0.00 (-0.39,0.40)	MOL	-0.15 (-0.58, 0.29) (1 study, 81 patients)		
-0.16 (-0.34,0.01)	-0.17 (-0.56,0.22)	RIS	-0.20 (-0.49, 0.10) (1 study, 182 patients)	-0.07 (-0.24, 0.10) (4 studies, 521 patients)
-0.24 (-0.48,-0.00)	-0.25 (-0.69,0.20)	-0.08 (-0.32,0.16)	QUE	-0.29 (-0.75, 0.17) (1 study, 73 patients)
-0.30 (-0.48,-0.13)	-0.31 (-0.71,0.10)	-0.14 (-0.29,0.01)	-0.06 (-0.30,0.18)	HAL

Sensitivity Analysis including Robinson 2006

Response (lower triangle) and weight gain (upper triangle) NMA results for sensitivity analysis by including Robinson 2006. For response, odds ratios (ORs) lower than 1 indicate that the treatment specified in the column is more efficacious. For weight gain, standardized mean differences (SMDs) higher than 0 indicate that the treatment specified in the row is more efficacious. Bold underlined results indicate statistical significance. Overall, including this study did not change the result much.

MOL	MOL	0.84 (-0.07,1.74)	**0.88 (0.10,1.66)**	**0.91 (0.08,1.74)**	**1.01 (0.39,1.63)**	**1.53 (0.89,2.17)**	
1.12 (0.41,3.08)	ARI	QUE	0.04 (-0.87,0.95)	0.07 (-0.78,0.93)	0.17 (-0.48,0.83)	0.69 (-0.10,1.49)	
1.20 (0.50,2.91)	1.07 (0.52,2.22)	QUE	HAL	0.03 (-0.81,0.87)	0.13 (-0.50,0.76)	**0.65 (0.21,1.09)**	
1.26 (0.48,3.30)	1.12 (0.49,2.56)	1.05 (0.60,1.81)	AMI	ARI	0.10 (-0.45,0.65)	0.62 (-0.09,1.33)	
1.39 (0.61,3.15)	1.24 (0.63,2.43)	1.15 (0.79,1.69)	1.10 (0.65,1.88)	OLA	RIS	**0.52 (0.07,0.97)**	
1.46 (0.57,3.79)	1.31 (0.58,2.93)	1.22 (0.72,2.06)	1.16 (0.63,2.15)	1.05 (0.63,1.76)	ZIP	OLA	
1.49 (0.66,3.36)	1.33 (0.73,2.43)	1.24 (0.83,1.85)	1.18 (0.67,2.08)	1.07 (0.79,1.45)	1.02 (0.59,1.75)	RIS	
2.02 (0.87,4.71)	1.80 (0.92,3.53)	1.68 (1.16,2.43)	1.60 (0.94,2.72)	1.45 (1.07,1.97)	1.38 (0.83,2.28)	1.35 (1.00,1.83)	HAL

eAppendix 9

Subgroup analyses

The network meta-regression analyses planned a priori severity of illness at baseline, duration of untreated psychosis (DUP) and gender ratio turned out to be not feasible, because too few data were available. The subgroup analysis on drug naive patients versus not naive patients and haloperidol dose did not show clear difference. Bold underlined results indicate statistical significance.

Drug naive subgroup (NMA):

OLA	_QUE_	_ZIP_	_RIS_	_HAL_
OLA	0.29 (-0.29,0.87)	0.33 (-0.27,0.94)	0.43 (-0.09,0.95)	0.61 (0.08,1.15)
-0.29 (-0.87,0.29)	QUE	0.05 (-0.56,0.66)	0.14 (-0.38,0.67)	0.33 (-0.22,0.87)
-0.33 (-0.94,0.27)	-0.05 (-0.66,0.56)	ZIP	0.10 (-0.46,0.65)	0.28 (-0.29,0.85)
-0.43 (-0.95,0.09)	-0.14 (-0.67,0.38)	-0.10 (-0.65,0.46)	RIS	0.18 (-0.14,0.51)
-0.61 (-1.15,-0.08)	-0.33 (-0.87,0.22)	-0.28 (-0.85,0.29)	-0.18 (-0.51,0.14)	HAL

The network meta-analysis results of overall symptom change for drug naive subgroup suggested that olanzapine was more efficacious than haloperidol in drug-naive patients.

Not naive subgroup (NMA):

AMI	_ZIP_	_MOL_	_OLA_	_RIS_	_QUE_	_HAL_
AMI	0.10 (-0.19,0.39)	0.09 (-0.36,0.55)	0.14 (-0.10,0.37)	0.23 (-0.03,0.50)	0.26 (0.02,0.51)	0.37 (0.13,0.61)
-0.10 (-0.39,0.19)	ZIP	-0.01 (-0.47,0.45)	0.03 (-0.23,0.29)	0.13 (-0.15,0.41)	0.16 (-0.11,0.43)	0.26 (0.00,0.52)
-0.09 (-0.55,0.36)	0.01 (-0.45,0.47)	MOL	0.04 (-0.35,0.43)	0.14 (-0.25,0.53)	0.17 (-0.25,0.59)	0.27 (-0.13,0.67)
-0.14 (-0.37,0.10)	-0.03 (-0.29,0.23)	-0.04 (-0.43,0.35)	OLA	0.10 (-0.06,0.26)	0.13 (-0.05,0.30)	0.23 (0.09,0.37)
-0.23 (-0.50,0.03)	-0.13 (-0.41,0.15)	-0.14 (-0.53,0.25)	-0.10 (-0.26,0.06)	RIS	0.03 (-0.16,0.23)	0.13 (-0.02,0.29)
-0.26 (-0.51,-0.02)	-0.16 (-0.43,0.11)	-0.17 (-0.59,0.25)	-0.13 (-0.30,0.05)	-0.03 (-0.23,0.16)	QUE	0.10 (-0.08,0.28)
-0.37 (-0.61,-0.13)	-0.26 (-0.52,-0.00)	-0.27 (-0.67,0.13)	**-0.23 (-0.37,-0.09)**	-0.13 (-0.29,0.02)	-0.10 (-0.28,0.08)	HAL

The network meta-analysis results of overall symptom change for not naive subgroup suggested that amisulpride and olanzapine were more efficacious than haloperidol in not naive patients, and amisulpride was superior to quetiapine.

Haloperidol low dose subgroup (NMA):

AMI	0.09 (-0.37,0.54)	0.13 (-0.15,0.40)	0.14 (-0.11,0.38)	0.22 (-0.05,0.48)	0.27 (0.02,0.52)	0.34 (0.09,0.59)
-0.09 (-0.54,0.37)	MOL	0.04 (-0.41,0.49)	0.05 (-0.35,0.45)	0.13 (-0.26,0.52)	0.18 (-0.24,0.60)	0.25 (-0.16,0.67)
-0.13 (-0.40,0.15)	-0.04 (-0.49,0.41)	ZIP	0.01 (-0.23,0.25)	0.09 (-0.17,0.35)	0.14 (-0.10,0.39)	0.21 (-0.03,0.46)
-0.14 (-0.38,0.11)	-0.05 (-0.45,0.35)	-0.01 (-0.25,0.23)	OLA	0.08 (-0.10,0.26)	0.13 (-0.05,0.32)	0.20 (0.01,0.40)
-0.22 (-0.48,0.05)	-0.13 (-0.52,0.26)	-0.09 (-0.35,0.17)	-0.08 (-0.26,0.10)	RIS	0.05 (-0.15,0.25)	0.12 (-0.05,0.30)
-0.27 (-0.52,-0.02)	-0.18 (-0.60,0.24)	-0.14 (-0.39,0.10)	-0.13 (-0.32,0.05)	-0.05 (-0.25,0.15)	QUE	0.07 (-0.13,0.27)
-0.34 (-0.59,-0.09)	-0.25 (-0.67,0.16)	-0.21 -0.46,0.03)	**-0.20 (-0.40,-0.01)**	-0.12 (-0.30,0.05)	-0.07 (-0.27,0.13)	HAL

The network meta-analysis results of overall symptom change for haloperidol low dose subgroup suggested that amisulpride and olanzapine were more efficacious than low dose haloperidol, and amisulpride was also superior to quetiapine.

Haloperidol high dose subgroup (NMA):

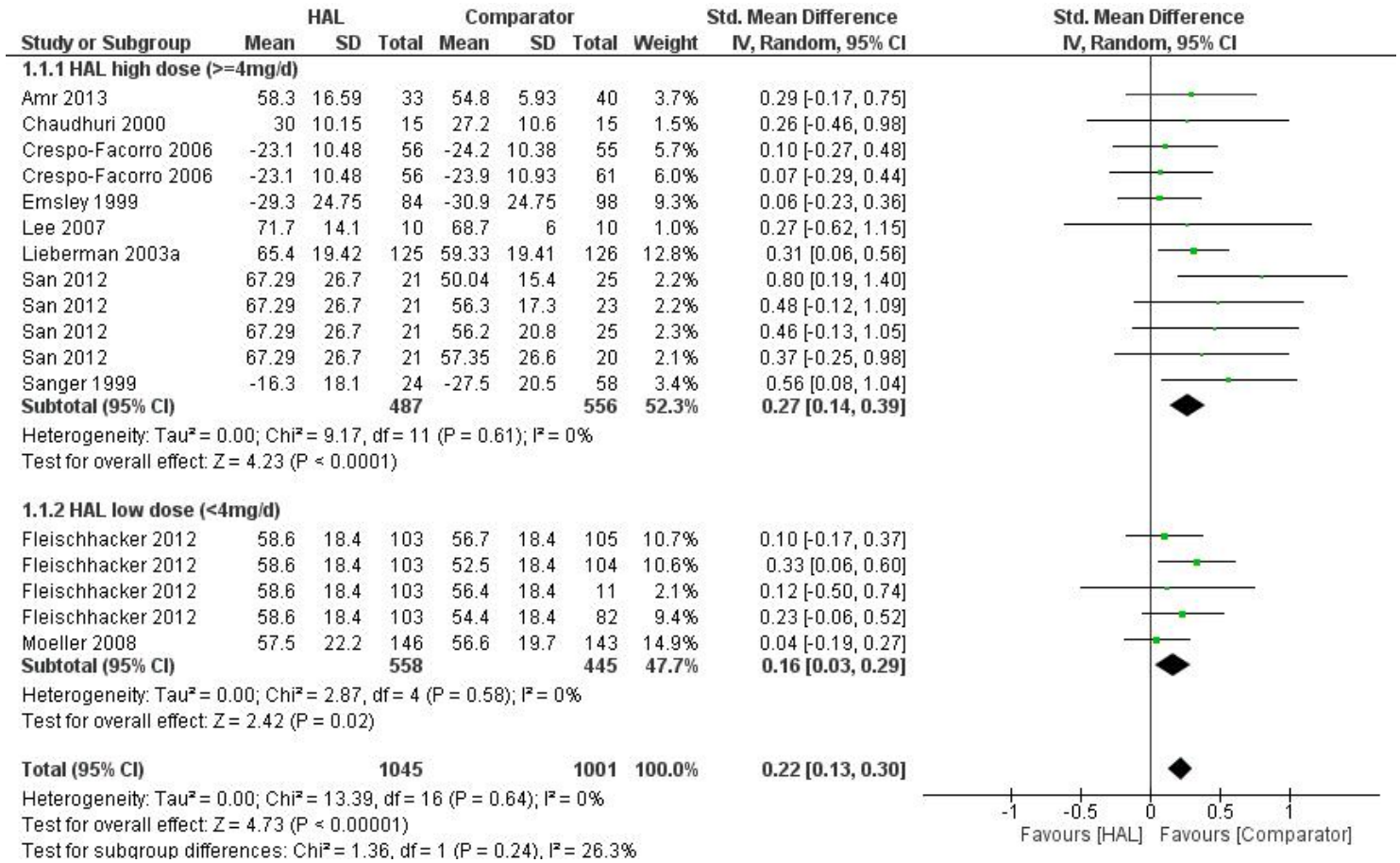
OLA	-0.03 (-0.43,0.36)	0.11 (-0.06,0.28)	0.22 (-0.02,0.46)	0.29 (0.13,0.45)
0.03 (-0.36,0.43)	MOL	0.14 (-0.25,0.54)	0.25 (-0.19,0.70)	0.32 (-0.08,0.73)
-0.11 (-0.28,0.06)	-0.14 (-0.54,0.25)	RIS	0.11 (-0.13,0.35)	0.18 (0.01,0.35)
-0.22 (-0.46,0.02)	-0.25 (-0.70,0.19)	-0.11 (-0.35,0.13)	QUE	0.07 (-0.18,0.32)
-0.29 (-0.45,-0.13)	-0.32 (-0.73,0.08)	**-0.18 (-0.35,-0.01)**	-0.07 (-0.32,0.18)	HAL

The network meta-analysis results of overall symptom change for haloperidol high dose subgroup suggested that olanzapine and risperidone were superior to high dose haloperidol.

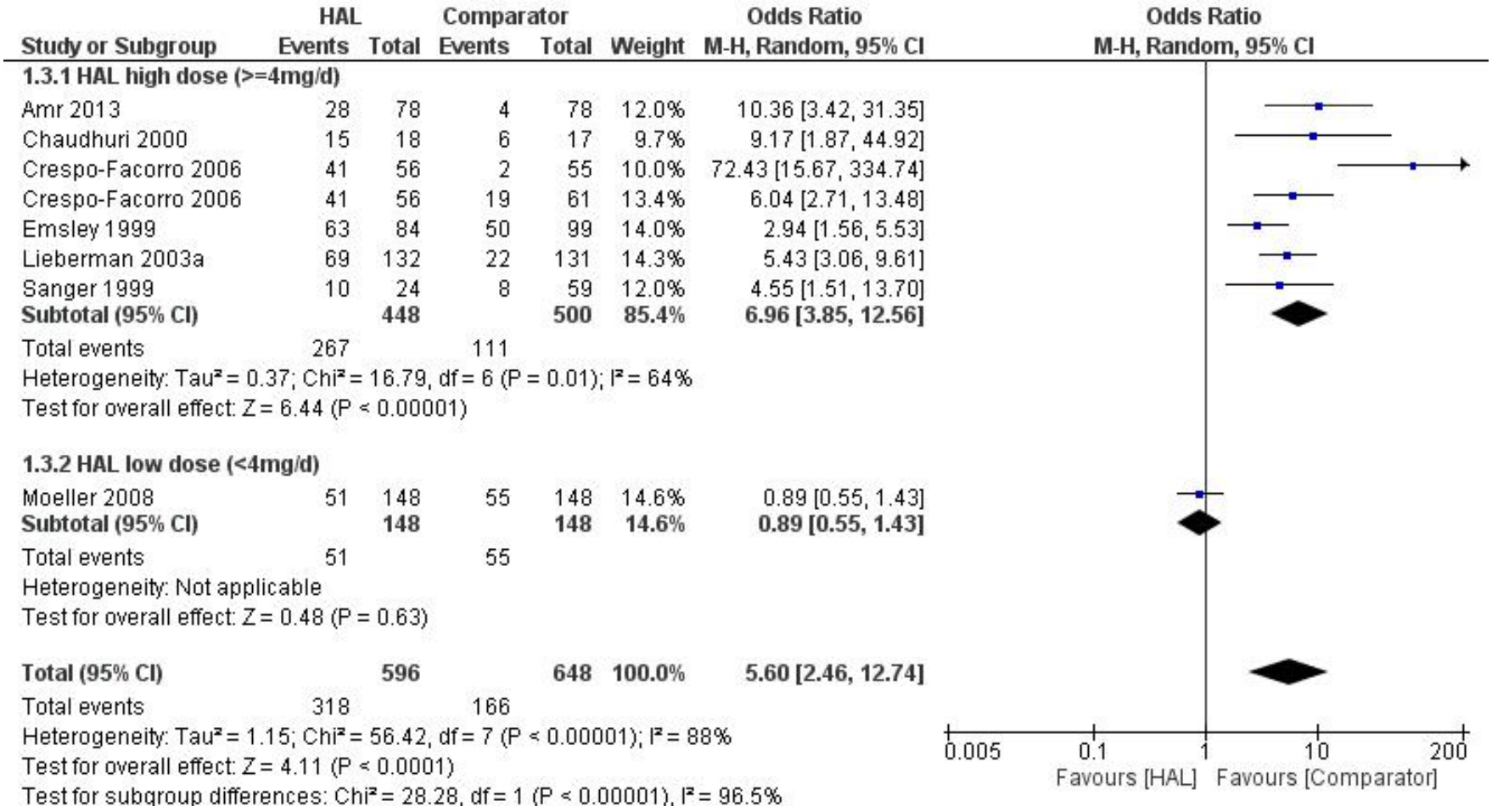
We further conducted subgroup analysis of pairwise meta-analysis for overall symptom change and at least one use of antiparkinson medication regarding haloperidol and risperidone dose. We defined high does group was >=4mg/d, while low does group was <4mg/d (for these two outcomes, there were no study in which the dose of haloperidol or risperidone was lower than 2mg/d).

We only found subgroup differences of at least one use of antiparkinson medication for haloperidol dose ($P<0.001$), but no differences of overall symptom change either for haloperidol or risperidone dose.

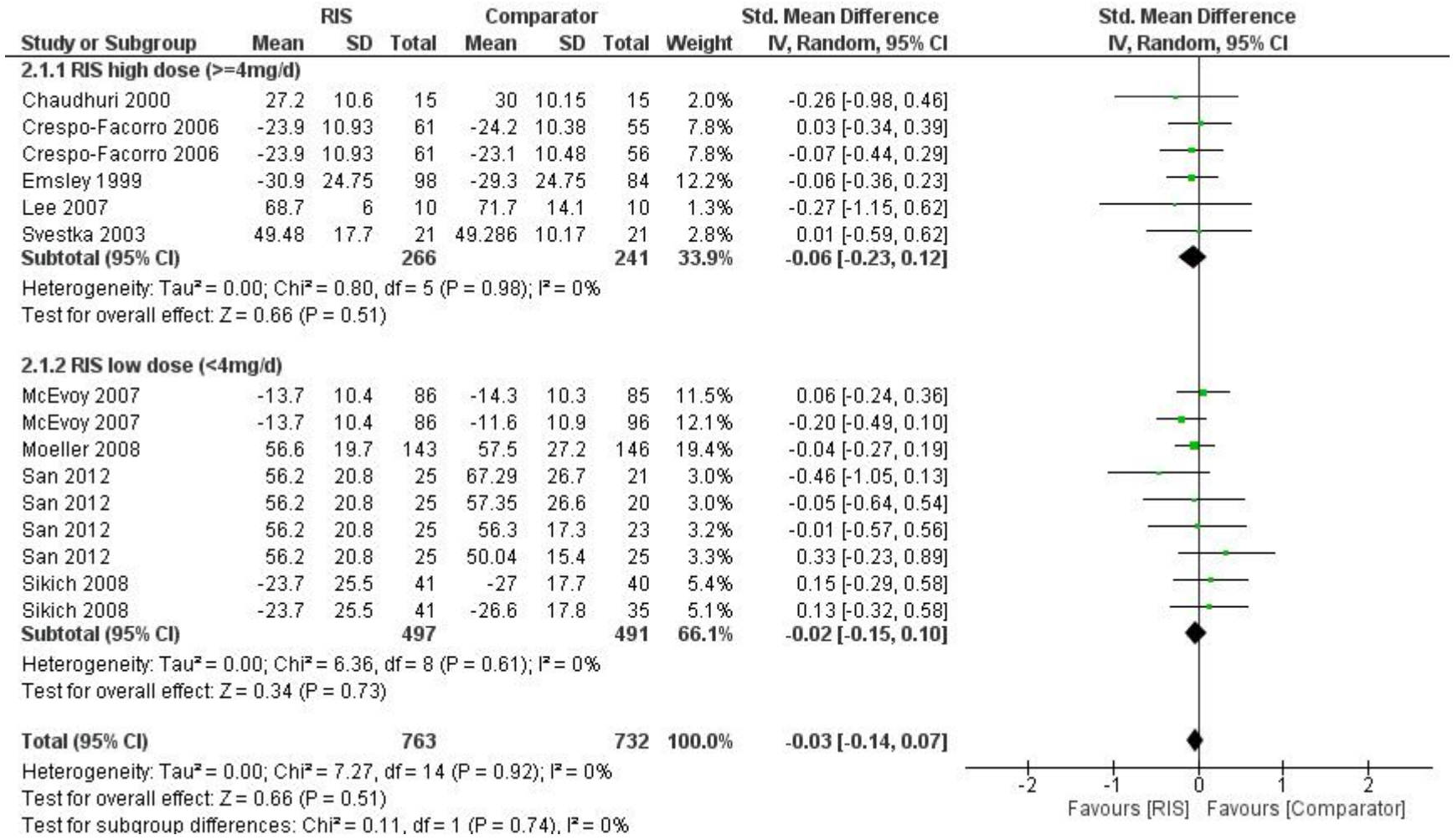
eFigure 34: Forest plot for subgroup analysis of pairwise meta-analysis in overall symptom change for haloperidol dose



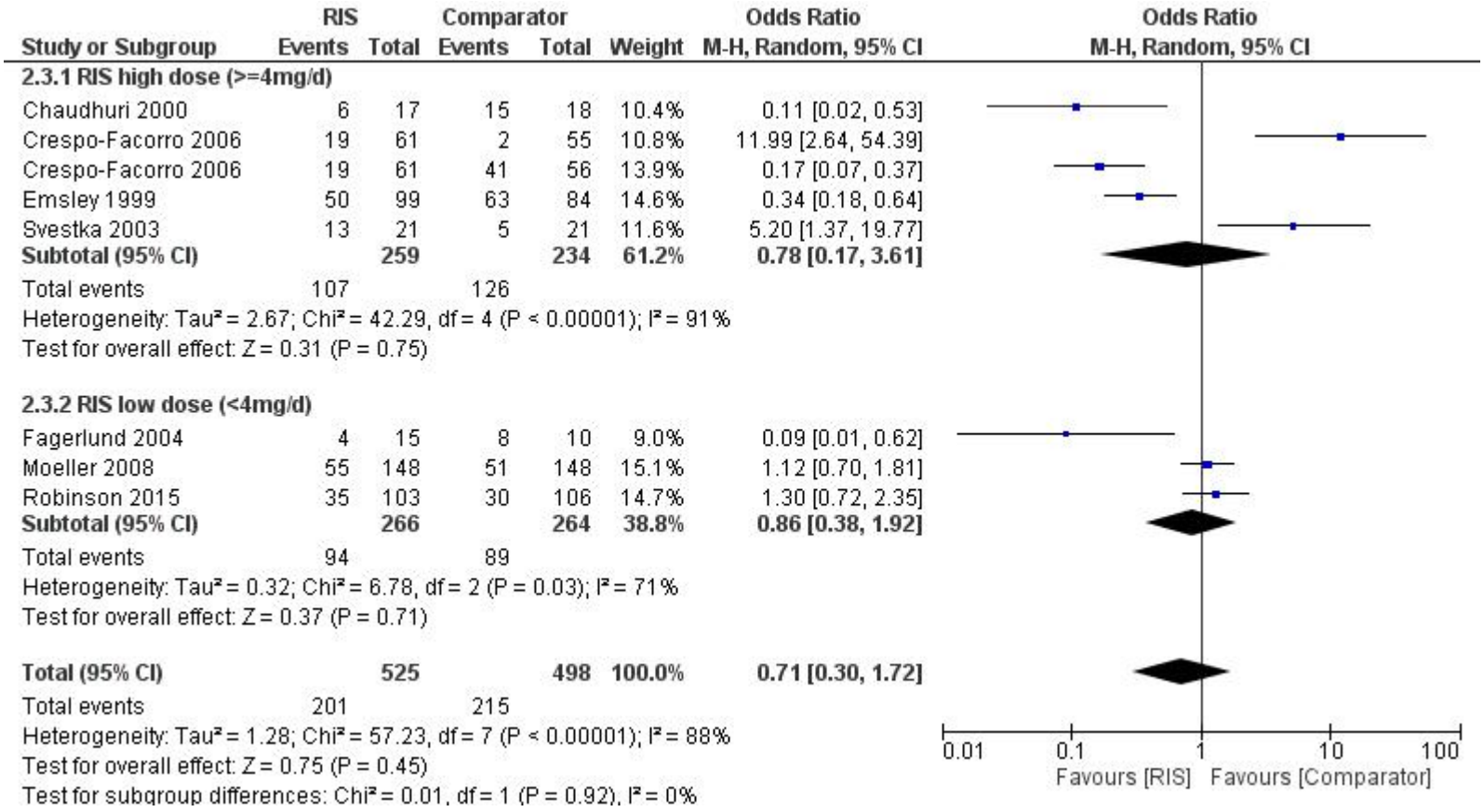
eFigure 35: Forest plot for subgroup analysis of pairwise meta-analysis in at least one use of antiparkinson medication for haloperidol dose



eFigure 36: Forest plot for subgroup analysis of pairwise meta-analysis in overall symptom change for risperidone dose



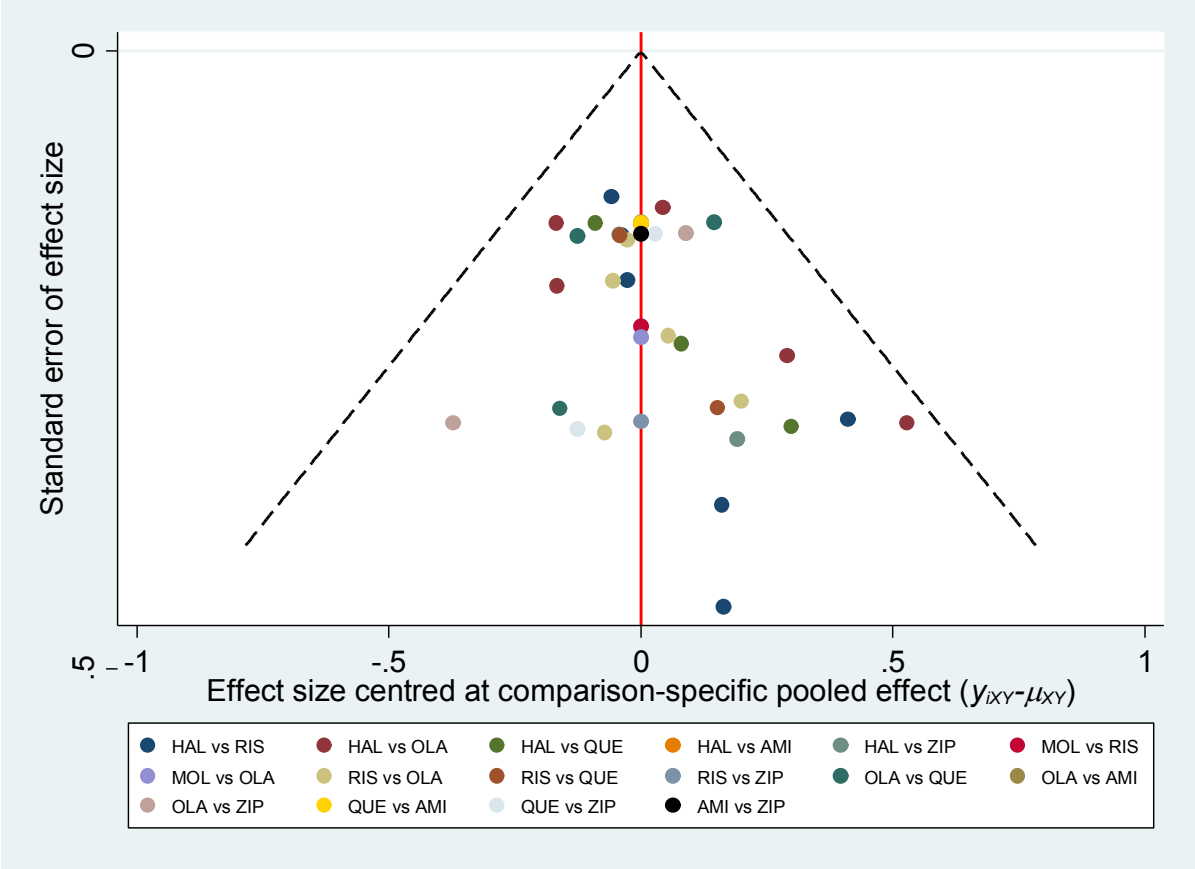
eFigure 37: Forest plot for subgroup analysis of pairwise meta-analysis in at least one use of antiparkinson medication for risperidone dose



eAppendix 10

Investigation of Small Study Effects

eFigure 38: Comparison-adjusted funnel plot for the primary outcome. Comparisons have been defined as newer vs older drug based on the time of FDA approval

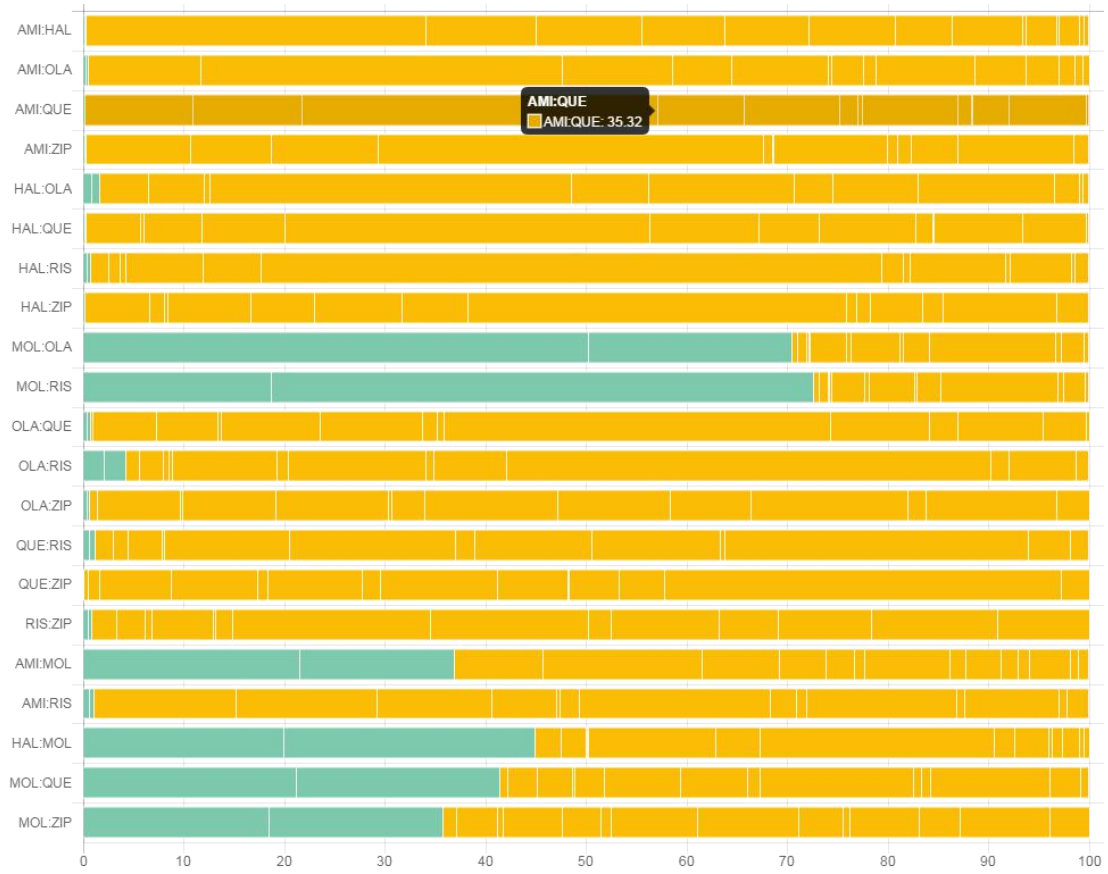


eAppendix 11

Evaluation of the Quality of evidence

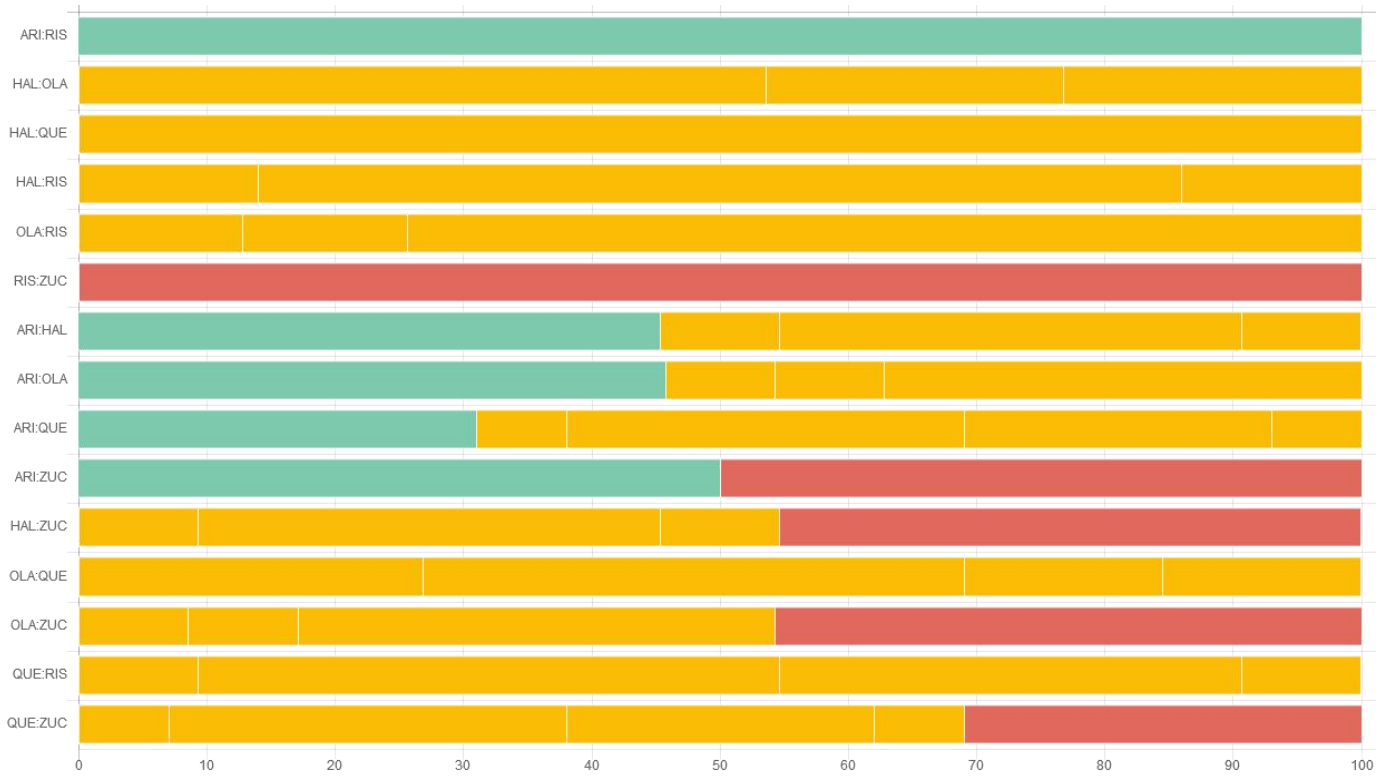
We evaluated the quality of evidence of primary outcome and the major adverse event outcome ‘use of antiparkinson medication at least once’ based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in line with the framework for evaluating suggested in Salanti 2014. Following this publication, we assessed the following five domains for confidence in a specific pairwise effect and in treatment ranking estimated in NMA: Study limitations, Indirectness, Inconsistency, Imprecision and Publication bias. For this purpose, we also used an under-development online tool CINeMA (http://ec2-35-156-97-18.eu-central-1.compute.amazonaws.com:8004/ocpu/library/contribution/www/#welcome) for the assessment of the domains study limitations.

eFigure 39: Contribution bar graph for overall symptom change



In the graph, each bar shows the relative contribution of the various pieces of evidence. The colors represent the risk of bias (green: low, yellow: moderate, red: high).

eFigure 40: Contribution bar graph for at least one use of antiparkinson medication



In the graph, each bar shows the relative contribution of the various pieces of evidence. The colors represent the risk of bias (green: low, yellow: moderate, red: high).

Summary of confidence by GRADE assessment in effect estimates and ranking of treatments in overall symptom change

Comparison	Nature of the evidence	Confidence	Downgrading due to
HAL vs RIS	Mixed	Low	Study limitations[1],Indirectness[2],
HAL vs OLA	Mixed	Moderate	Study limitations[1]
HAL vs QUE	Mixed	Very low	Study limitations[1],Indirectness[2],Imprecision[3]
HAL vs ZIP	Mixed	Low	Study limitations[1],Indirectness[2],
HAL vs MOL	Indirect	Low	Study limitations[1],Imprecision[3]
HAL vs AMI	Mixed	Low	Study limitations[1],Indirectness[2],
RIS vs OLA	Mixed	Low	Study limitations[1],Imprecision[3]
RIS vs QUE	Mixed	Very low	Study limitations[1],Indirectness[2], Imprecision[3]
RIS vs ZIP	Mixed	Very low	Study limitations[1],Indirectness[2], Imprecision[3]
RIS vs MOL	Mixed	Low	Indirectness[2], Imprecision[3]
RIS vs AMI	Indirect	Low	Study limitations[1], Imprecision[3]
OLA vs QUE	Mixed	Low	Study limitations[1], Imprecision[3]
OLA vs ZIP	Mixed	Very low	Study limitations[1],Indirectness[2], Imprecision[3]
OLA vs MOL	Mixed	Low	Indirectness[2], Imprecision[3]
OLA vs AMI	Mixed	Very low	Study limitations[1],Indirectness[2], Imprecision[3]
QUE vs ZIP	Mixed	Very low	Study limitations[1],Indirectness[2], Imprecision[3]
QUE vs MOL	Indirect	Low	Study limitations[1],Imprecision[3]
QUE vs AMI	Mixed	Low	Study limitations[1],Indirectness[2],
ZIP vs MOL	Indirect	Low	Study limitations[1],Imprecision[3]
ZIP vs AMI	Mixed	Very low	Study limitations[1],Indirectness[2], Imprecision[3]
MOL vs AMI	Indirect	Low	Study limitations[1], Imprecision[3]
Ranking of treatments		Low[6]	Study limitations[4],Indirectness[5]

[1]Dominated by evidence at moderate risk of bias.

[2]No convincing evidence for the plausibility of the transitivity assumption, because this comparison included no more than 2 studies.

[3]Confidence intervals include values favouring either treatment.

[4]90% of the information is from studies at moderate risk of bias.

[5]Lack convincing evidence for the plausibility of the transitivity assumption due to few studies included in the network

[6]No evidence of inconsistency in the network and low level of heterogeneity

Summary of confidence by GRADE assessment in effect estimates and ranking of treatments in at least one use of antiparkinson medication

Comparison	Nature of the evidence	Confidence	Downgrading due to
HAL vs RIS	Mixed	Very low	Study limitations[1],Inconsistency[3],Imprecision[4]
HAL vs OLA	Mixed	Low	Study limitations[1],Inconsistency[3]
HAL vs QUE	Mixed	Low	Study limitations[1],Indirectness[2]
HAL vs ZUC	Indirect	Very low	Study limitations[1],Inconsistency[3]Imprecision[4]
HAL vs ARI	Indirect	Very low	Study limitations[1],Inconsistency[3],Imprecision[4]
RIS vs OLA	Mixed	Low	Study limitations[1],Indirectness[2]
RIS vs QUE	Indirect	Very low	Study limitations[1],Inconsistency[3]Imprecision[4]
RIS vs ZUC	Mixed	Very low	Study limitations[1],Indirectness[2],Imprecision[4]
RIS vs ARI	Mixed	Low	Indirectness[2],Imprecision[4]
OLA vs QUE	Indirect	Very low	Study limitations[1],Inconsistency[3],Imprecision[4]
OLA vs ZUC	Indirect	Low	Study limitations[1],Inconsistency[3]
OLA vs ARI	Indirect	Very low	Study limitations[1],Inconsistency[3],Imprecision[4]
QUE vs ZUC	Indirect	Low	Study limitations[1],Inconsistency[3]
QUE vs ARI	Indirect	Very low	Study limitations[1],Inconsistency[3],Imprecision[4]
ZUC vs ARI	Indirect	Very low	Study limitations[1],Inconsistency[3],Imprecision[4]
Ranking of treatments		Low	Study limitations[5],Inconsistency[3]

[1]Dominated by evidence at high or moderate risk of bias.

[2]No convincing evidence for the plausibility of the transitivity assumption, because this comparison included no more than 2 studies.

[3]Moderate to high level of heterogeneity, but no other evidence of inconsistency.

[4]Confidence intervals include values favouring either treatment.

[5]90% of the information is from studies at moderate risk of bias.

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REVIEW

How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis

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Response;
Antipsychotics;
First-episode schizophrenia

Abstract
It is often stated that first-episode patients tend to respond better to antipsychotics than chronic patients, but the exact numbers and moderators of response in this population are unclear. We, therefore, present the first systematic review on response rates of first episode patients with schizophrenia in randomized trials. We searched multiple databases for randomized-controlled trials of antipsychotics in acutely ill patients with a first episode of schizophrenia (last search: November 17, 2016). The outcomes were response rate based on two criteria, at least 50% PANSS or BPRS total score reduction from baseline and at least 20% reduction. Data were pooled in a single-group summary meta-analysis using Comprehensive Meta-Analysis software. Moreover, several potential moderators of response to antipsychotics were examined by meta-regression. We included 17 studies with a total of 3156 participants. On the average, 81.3%/51.9% of the first-episode patients reached an at least 20%/50% PANSS or BPRS reduction from baseline, respectively. Meta-regressions revealed a better treatment response in female patients, in more severely ill patients at baseline, in antipsychotic naïve patients, in patients with a shorter illness duration and in open studies. Study duration and dosage were no significant moderators of

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response. Our finding suggest that more than 80% of first-episode patients achieved 20% PANSS/BPRS reduction from baseline and around 50% achieved a 50% PANSS/BPRS reduction. Several patient characteristics moderated response rates.
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1. Introduction

Schizophrenia is a severe disorder, and a leading cause of disability according to the World Health Report (DALYs and Collaborators, 2016). Schizophrenia typically onsets in early adulthood, between the ages of 15 and 25 (Buchanan and Carpenter, 2005). Men tend to have earlier age of onset than women, and women have a second peak after menopause (Sham et al., 1994). The course is variable but often chronic (Jaaskelainen et al., 2013). The effectiveness of antipsychotic drugs has been proven by many randomized clinical trials, but most studies have been conducted in chronic patients (Leucht et al., 2017). The first episode of schizophrenia is widely viewed as a critical phase of treatment in schizophrenia, because gaining optimum improvement at this stage may determine the long-term outcome. First episode patients have been shown to be different from chronic patients in various aspects such as age, symptom patterns (Sanger et al., 1999), cognitive impairment (McCleery et al., 2014), brain volume loss (Torres et al., 2016) and functional changes (Li et al., 2017). It also seems to be generally accepted that people with a first episode of schizophrenia tend to respond better to antipsychotics than chronic patients (Gaebel et al., 2002; Lieberman et al., 1996; Ohlsen et al., 2004). For example, studies have shown that the time needed to reach a remission is considerably longer already after a second episode of schizophrenia compared to a first psychotic break (Emsley et al., 2013; Lieberman, 1996). Or in a meta-analysis of chronic patients only 53% reached at least 20% Positive and Negative Syndrome Scale (PANSS) total score or Brief Psychiatric Rating Scale (BPRS) total score reduction from baseline (Leucht et al., 2017), and only 23% of chronic patients reached at least 50% PANSS or BPRS total score reduction from baseline (Leucht et al., 2017). The hypothesis is that the improvement of first episode patients is much better, but a systematic assessment is not available. To fill this gap, we present the first systematic review of response rates in patients with a first episode of schizophrenia who participated in randomized controlled trials. The purpose of the meta-analysis was twofold: i) how well do patients with a first episode of schizophrenia respond to antipsychotics; ii) what are determinants of antipsychotic response in this population.

2. Experimental procedures

2.1. Search strategy and study inclusion criteria

We searched MEDLINE, EMBASE, PsycINFO, Cochrane Library, PubMed, Biosis, and ClinicalTrials.gov for reports published up to Nov 17, 2016 for randomized controlled trials that compared antipsychotic drugs with each other or with placebo in people with schizophrenia, and we inspected the reference lists of previous reviews (Crossley et al., 2010; Leucht et al., 2013; Zhang et al., 2013). Quasi-randomized studies (e.g. allocation by day of the week) were excluded. Due to the limited number of RCTs in first-episode schizophrenia, we also included open-label RCTs. In cross-over trials only data up to the point of the first cross-over were used to avoid carryover effects (Elbourne et al., 2002). Cluster-randomized trials were generally excluded. We excluded studies from mainland China to avoid a systematic bias because serious quality concerns have been raised (Woodhead, 2016). The exception was a Chinese study conducted by international renowned international researchers so that we were confident that international standards had been applied (Lieberman et al., 2003a). For reasons of consistency, this study was excluded in a sensitivity analysis, however.

We included people (no age limit, no restriction in setting, gender, ethnicity) with a first-episode of schizophrenia or related disorders (such as schizophreniform, or schizoaffective disorders). We allowed all definitions of “first episode” by the original authors. We excluded studies in treatment resistant patients, in patients with predominant negative symptoms, in patients with concomitant medical or psychiatric illness (e.g. studies in which all patients also had concomitant cannabis abuse), and studies in stable patients (mainly relapse prevention studies), because the response rates of such patients may be very different, while we focused on “typical” patients with acute exacerbations so that meta-analytic pooling with the rest of the studies would have been problematic. (Except one study in patients with co-occurring cannabis use and several relapse prevention studies, no RCTs had to be excluded on this basis, in particular there were neither RCTs in patients with predominant negative symptoms nor RCTs in treatment resistant patients). Following the rules of the Cochrane Schizophrenia Group we included trials irrespective of the diagnostic criteria used (Adams et al., 2011). We included studies of any orally administered antipsychotics (SGAs and FGAs) that are licensed in at least one country. In fixed-dose studies we followed the International Consensus Study on Antipsychotic dose (Gardner et al., 2010) which recommends 25–30% lower doses for first-episode patients than for chronic patients. We included all flexible-dose studies, because these allow the investigators to titrate to the adequate dose for the individual patient.

2.2. Screening and data extraction

Two reviewers out of YZ, MH, MK independently inspected all abstracts identified in the searches based on the inclusion criteria. Disagreement was resolved by discussion, and where doubt still remained, we acquired the full article for further inspection. Once the full articles were obtained, two reviewers out of YZ, MH, MK independently decided whether the studies met the review criteria. If disagreement could not be resolved, we discussed with the team leader SL and also contacted the authors per e-mail for seeking further information. Again, two reviewers YZ and PR independently reviewed the main reports and supplementary materials, extracted the relevant data from the included trials on electronic forms, and assessed risk of bias in terms of sequence generation, allocation concealment,

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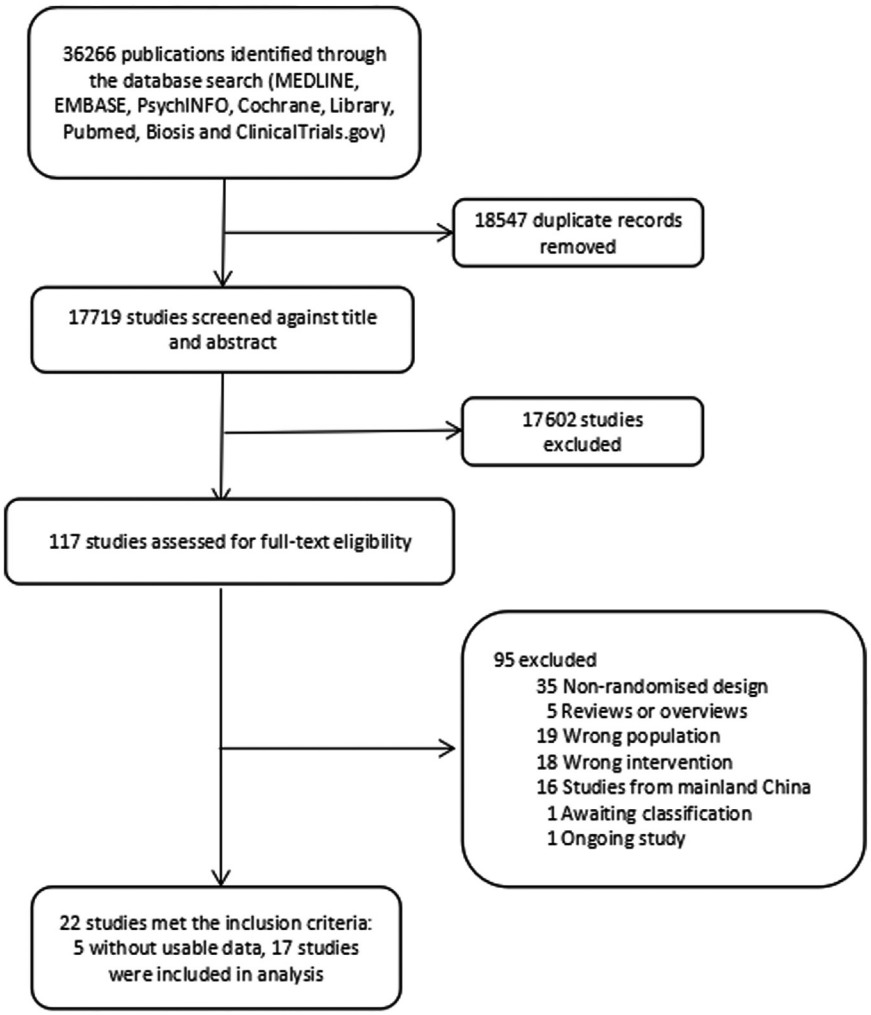

Figure 1 PRISMA Diagram.

blinding, the completeness of outcome data, selective reporting and other biases with the Cochrane risk of bias tool (Higgins and Green, 2011).

2.3. Definitions of response

In schizophrenia trials response is usually defined as a minimum percentage reduction of the PANSS/BPRS total score from baseline to endpoint, but different response cut-offs have been used in the literature (for example at least 20%, 25%, 30%, 40%, 50%) (Leucht et al., 2007). Equipercentile linking studies comparing BPRS/PANSS ratings with simultaneous CGI ratings (Guy, 1976) have revealed that at least 20% reduction from baseline roughly means minimally improved according to the Clinical Global Impressions of the raters, while 50% reduction from baseline corresponds to much improved according to the CGI (Leucht et al., 2005b, 2005c; Levine et al., 2008; Schennach-Wolff et al., 2010). We presented results on both cut-offs, but 50% was our primary one based on the assumption of high response rates in first-episode patients. If results based on other cut-offs were reported (e.g. 30% or 40%) or if responder rates were not presented, we used the imputation method first proposed by Furukawa et al. (2005) and replicated by Samara et al. (2013) to estimate at least 20% and at least 50% reduction from baseline based on means and standard deviations at endpoint of the PANSS/BPRS or their change scores from baseline (Furukawa et al., 2005; Samara et al., 2013). Moreover, response rates were often miscalculated (Obermeier et al., 2011), because the 30/18 minimum scores of the PANSS/BPRS were not subtracted, which results in an underestimation of response rates (Leucht et al., 2007; Obermeier et al., 2010) when the 1–7 scoring system is used. Therefore, the 30/18 minimum scores of the PANSS/BPRS were appropriately subtracted for this procedure (Leucht et al., 2005b', 2005c; Schennach-Wolff et al., 2010).

2.4. Analysis

Different from most meta-analyses focusing on relationships between interventions, the goal of the current meta-analysis was to examine the response rate in a single population (first episode patients). In this case the index is simply a single group summary, not a between-group difference, but the meta-analytic calculations for obtaining an average of all studies are in essence the same (Borenstein et al., 2009). To obtain an average response rate, a single-group summary meta-analysis was performed using Comprehensive Meta-Analysis software (version 2.0) (Biostat, Inc., Englewood, NJ. USA), for both cutoffs, at least 20% and at least 50% reduction from baseline, separately, and using the intention-to-treat datasets. For this purpose the response rates of the individual arms were pooled, but we examined in a sensitivity analysis

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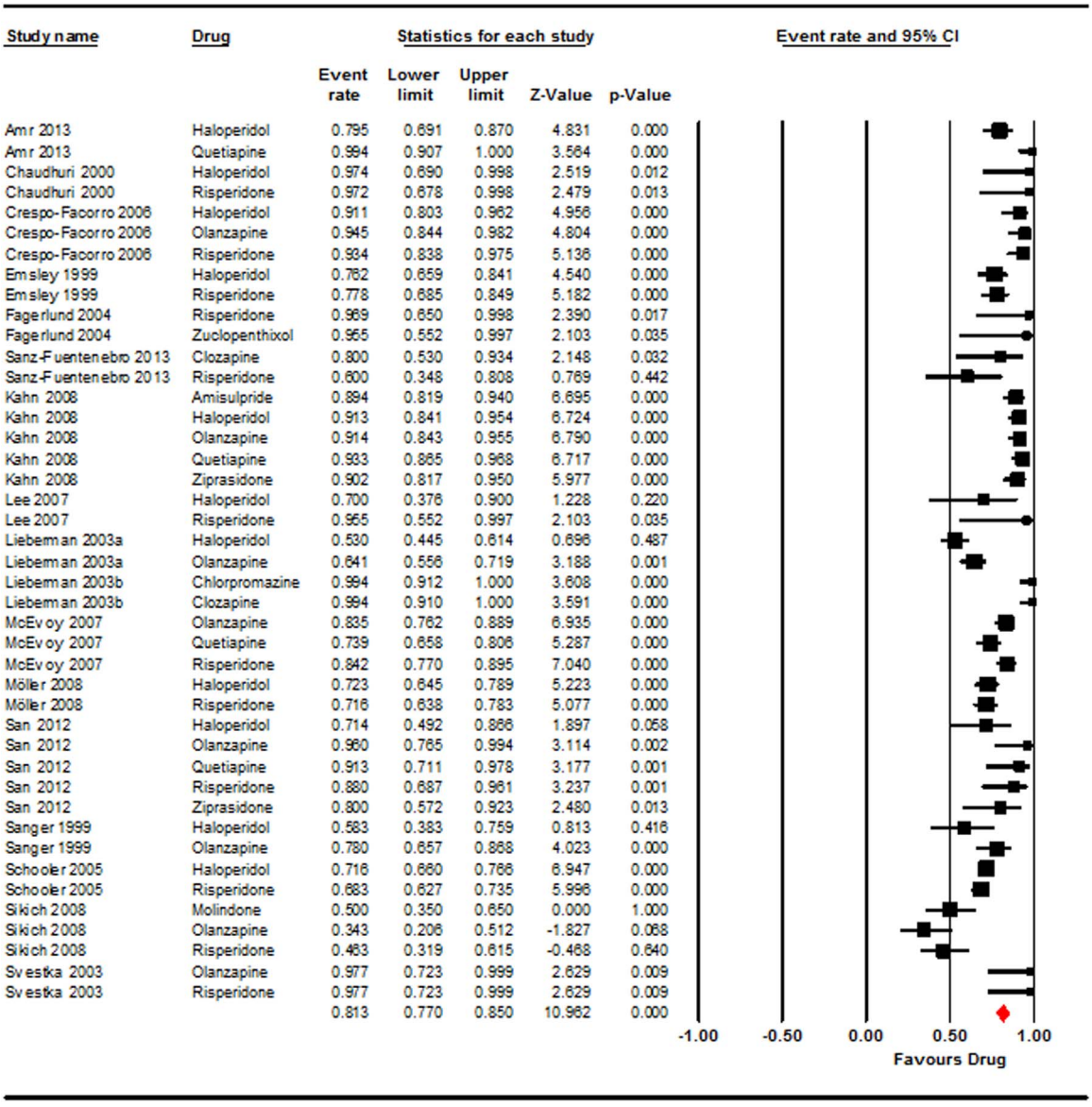

Figure 2 Pooled results for response rate of 20% reduction from baseline (random-effects model).

whether the results were robust if first the arms of each study were combined and then the studies were pooled. In another sensitivity analysis studies with imputed response rates were excluded (Samara et al., 2013). Heterogeneity was assessed using the I-square statistic (values >50% were considered as considerable heterogeneity) (Higgins et al., 2003). Subgroup (dichotomous outcomes) and meta-regression (continuous outcomes) analyses were conducted on our primary cut-off 50% PANSS/BPRS reduction using a random-effects model to explore which study characteristics may explain heterogeneity. The following moderators were chosen a priori: mean age, duration of illness, study duration, gender ratio, severity of illness at baseline and dose of antipsychotics in olanzapine equivalents (Gardner et al., 2010). Subgroup analyses were performed by grouping studies according to type of study design (blinded or open-label) and type of participants (drug naive or pre-treated). We did not examine the effects of single drugs, because too few studies were available for each compound so that such an analysis would not have been meaningful, and because differences between drugs should rather be the focus of standard meta-analyses based on differences between drug arms. We also assessed small-study effects by visual examination of funnel plots.

3. Results

3.1. Description of included studies

We identified 36,266 citations through the literature search and 17,602 references were left after duplication. After excluding irrelevant reports by reviewing the titles and abstracts, 117 potentially eligible articles were retrieved in full text. 17 studies (Amr et al., 2013; Chaudhuri et al., 2000; Crespo-Facorro et al., 2006; Emsley, 1999; Fagerlund et al., 2004; Kahn et al., 2008; Lee et al., 2008; Lieberman et al., 2003a, 2003b; McEvoy et al., 2007; Moller et al., 2008; San et al., 2012; Sanger et al., 1999; Sanz-Fuentenebro et al., 2013; Schooler et al., 2005; Sikich et al., 2008; Svestka et al., 2003) with a total of 3156 participants were included in the analysis. A PRISMA flow-chart is presented in Figure 1. Description of included studies is presented in eAppendix. Seven studies (Chaudhuri et al., 2000; Emsley, 1999; Fagerlund et al.,

2004; Lee et al., 2008; Lieberman et al., 2003a; San et al., 2012; Sanz-Fuentenebro et al., 2013) examined drug-naive patients, and twelve studies (Amr et al., 2013; Chaudhuri et al., 2000; Emsley, 1999; Lee et al., 2008; Lieberman et al., 2003a', 2003b; McEvoy et al., 2007; Moller et al., 2008; Sanger et al., 1999; Schooler et al., 2005; Sikich et al., 2008; Svestka et al., 2003) were blinded. Of the 17 included studies, ten studies (Crespo-Facorro et al., 2006; Emsley, 1999; Kahn et al., 2008; Lieberman et al., 2003b; McEvoy et al., 2007; Moller et al., 2008; Sanger et al., 1999; Schooler et al., 2005; Sikich et al., 2008; Svestka et al., 2003) reported a response rate, but only five reported at least 20% or 50% PANSS/BPRS total score reduction from baseline. The median study duration was 12 week (range 4-104), and ten (Amr et al., 2013; Chaudhuri et al., 2000; Crespo-Facorro et al., 2006; Emsley, 1999; Lee et al., 2008; Lieberman et al., 2003b; Moller et al., 2008; Sanger et al., 1999; Sikich et al., 2008; Svestka et al., 2003) were classified as short-term studies ($<=$12 weeks), and seven (Fagerlund et al., 2004; Kahn et al., 2008; Lieberman et al., 2003a; McEvoy et al., 2007; San et al., 2012; Sanz-Fuentenebro et al., 2013; Schooler et al., 2005) as long-term studies ($>$12 weeks). The mean age of participants was 24.3 years SD$\pm$9.77. The mean baseline severity (PANSS equivalent) was 81.6 SD$\pm$20.49. The mean duration of illness was 1.24 year SD$\pm$1.77. Eleven studies examined haloperidol, twelve risperidone, eight olanzapine, four quetiapine, two clozapine, two ziprasidone, one zuclopenthixol, one amisulpride, one chlorpromazine, and one examined molindone. It should be noted that the two clozapine studies were conducted in first-episode patients, not in treatment resistant patients (Lieberman et al., 2003a; Sanz-Fuentenebro et al., 2013). No study included a placebo group. The mean dosage of antipsychotics in olanzapine equivalents (Gardner et al., 2010) was 13.2 mg/d. Figures illustrating the risk of bias assessment are presented in the eAppendix. Overall, the reports often did not provide details about randomization procedures and

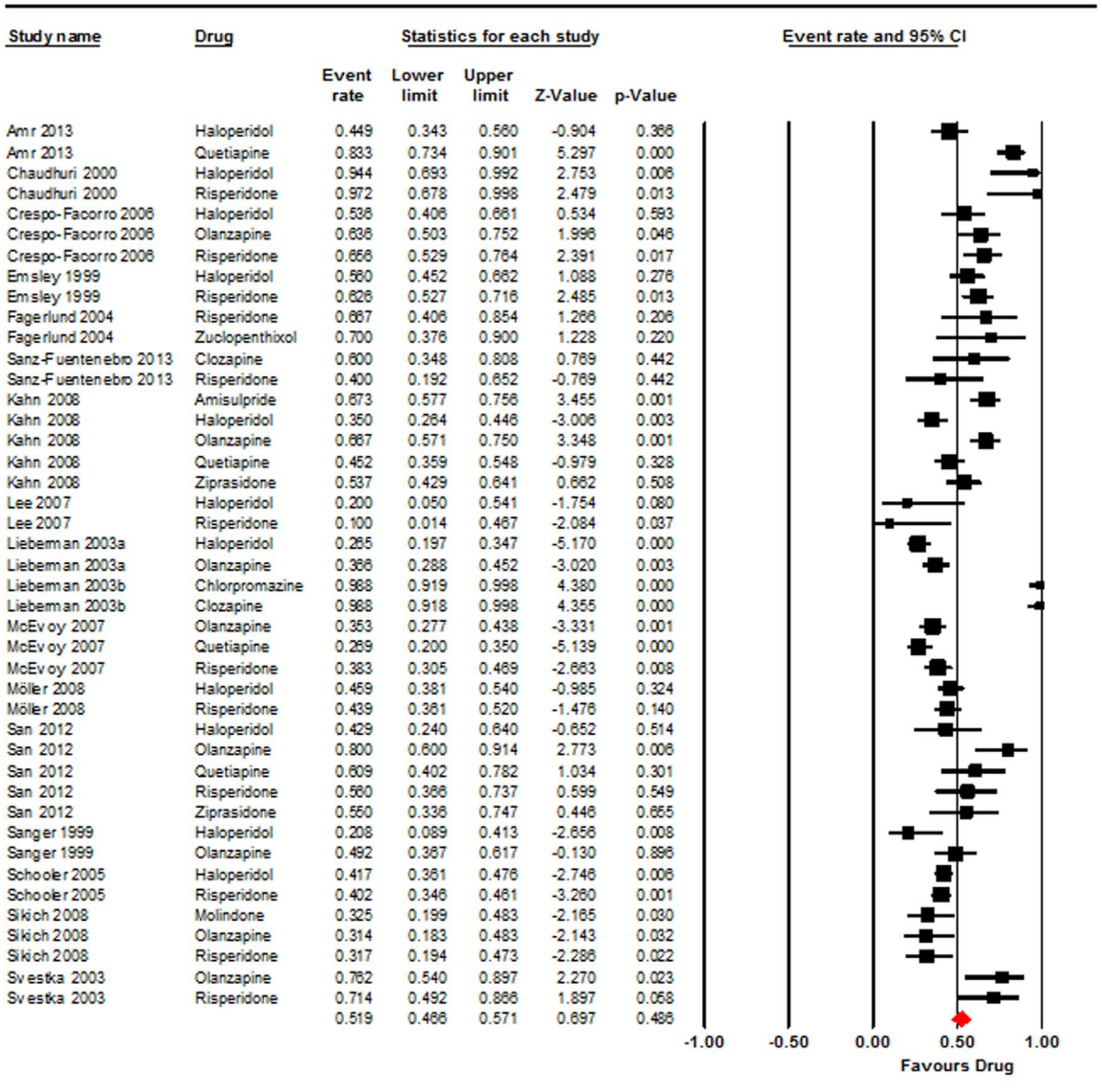

Figure 3 Pooled results for response rate of 50% reduction from baseline (random-effects model).

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allocation concealment, and the overall dropout rate was quite high (39.4%). There was no important selective reporting which would have been relevant for our research question and no important other bias.

3.2. Response rates

The pooled response rate for the cutoff at least 20% PANSS/BPRS reduction from baseline was 81.3% (17 RCTs (Amr et al., 2013; Chaudhuri et al., 2000; Crespo-Facorro et al., 2006; Emsley, 1999; Fagerlund et al., 2004; Kahn et al., 2008; Lee et al., 2008; Lieberman et al., 2003a', 2003b; McEvoy et al., 2007; Moller et al., 2008; San et al., 2012; Sanger et al., 1999; Sanz-Fuentenebro et al., 2013; Schooler et al., 2005; Sikich et al., 2008; Svestka et al., 2003), 3156 participants, 95% CI 77.0% to 85.0%), and the pooled response rate for the cutoff at least 50% reduction from baseline was 51.9% (17 RCTs (Amr et al., 2013; Chaudhuri et al., 2000; Crespo-Facorro et al., 2006; Emsley, 1999; Fagerlund et al., 2004; Kahn et al., 2008; Lee et al., 2008; Lieberman et al., 2003a', 2003b; McEvoy et al., 2007; Moller et al., 2008; San et al., 2012; Sanger et al., 1999; Sanz-Fuentenebro et al., 2013; Schooler et al., 2005; Sikich et al., 2008; Svestka et al., 2003), 3156 participants, 95% CI 46.6% to 57.1%). Results are presented in Figures 2 and 3.

3.3. Sensitivity analysis

In the sensitivity analysis first combining the arms of the individual studies and then pooling the studies, the results were virtually identical (50% cut-off: 51.8%, 20% cut-off: 80.1%). In the sensitivity analysis excluding imputed response data the average response rates for 20%/50% reduction in first-episode schizophrenia were 56.5% (2 RCTs (Schooler et al., 2005; Sikich et al., 2008), 675 participants, 95% CI 44.0% to 68.2% and 58.1% (3 RCTs (Emsley, 1999; Kahn et al., 2008; Svestka et al., 2003), 723 participants, 95% CI 49.4% to 66.3%), respectively. It should be noted, however, that these results were only based on five studies and the 30/18 minimum points of the PANSS/BPRS were not always subtracted, which would have underestimated the true response rates (Leucht et al., 2005b', 2005c; Schennach-Wolff et al., 2010). When excluding the single Chinese study (Lieberman et al., 2003a) in a sensitivity analysis, the average response rates for 20%/50% reduction were 80.3% and 49.8%, respectively.

3.4. Subgroup and meta-regression analyses (see Table 1).

3.4.1. Blinded vs open-label studies

The test for subgroup differences of response rate between blinded studies and open-label studies was just not statistically significant (48.0% vs 57.2%, p=0.055).

3.4.2. Drug naive vs treated patients

We found a statistically significantly higher response rate in studies in drug naive patients compared to studies allowing some pre-treatment (65.8% vs 46.7%, p=0.004).

3.4.3. Percentage male participants

The meta-regression with percentage of male as a moderator suggested that female patients might have a better clinical response than males (slope=−2.53, p<0.0001).

3.4.4. Baseline severity

The meta-regression with baseline severity as a moderator suggested that severe patients at baseline have a higher response rate than mild patients (slope=0.02, p=0.02).

3.4.5. Illness duration

The patients with shorter illness duration had a higher response rate than those with longer illness duration (slope=−0.43, p=0.047).

Table 1 Estimates of subgroup and meta-regression analysis.

Subgroup analyses (dichotomous moderators)					
Moderator	Percentage responders	Lower limit	Upper limit	*Z*-value for subgroup differences	*P*-value for subgroup differences
Subgroup: Blinded [*N*=12, *n*=1932]	0.48	0.41	0.55	3.70	0.06
Open-label [*N*=5, *n*=1224]	0.57	0.51	0.63		
Subgroup:Naive [*N*=7, *n*=566]	0.66	0.54	0.76	8.52	0.004
Treated [*N*=10, *n*=2590]	0.47	0.41	0.52		
Meta-regression (continuous moderators)					
Moderator	Coefficient	Lower limit	Upper limit	Z-value	*P*-value
Male percentage	−2.53	−3.71	−1.35	−4.21	<0.0001
Baseline severity	0.02	0.003	0.04	2.24	0.03
Mean age	0.12	0.01	0.24	2.06	0.04
Illness duration	−0.43	−0.85	−0.01	−1.99	0.05
Study duration	−0.001	−0.01	0.01	−0.12	0.90
Drug dosage	0.04	−0.01	0.09	1.58	0.11

N: number of studies, n: number of participants.

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3.4.6. Mean age

The meta-regression with mean age as a moderator suggested that older first-episode patients had a higher response rate than younger patients (slope=0.12, p=0.04).

3.4.7. Study duration

Response rates were not found to be associated with study duration (p=0.903).

3.4.8. Dosage (olanzapine equivalent)

Response rates were not found to be associated with antipsychotic dosage (p=0.114).

3.5. Small-study effects

There was no obvious asymmetry in the funnel plot that would have indicated small-study effects.

4. Discussion

To the best of our knowledge, this is the first systematic review that shows how well patients with a first episode of schizophrenia respond to antipsychotics in randomized trials. Our main findings were that 81.3%/51.9% of first-episode patients reached an at least 20%/50% PANSS/BPRS reduction from baseline, respectively. This contrasts with a meta-analysis of 29,087 mainly chronic patients where only 53%/23% reached 20%/50% PANSS/BPRS reduction from baseline (Leucht et al., 2017).

We also found that the patient characteristics age, gender, baseline severity, drug naivety, illness duration, and the methodological factor of blinding study personnel and patients were determinants of response to antipsychotics. The response rates in open-label studies were higher than in blinded RCTs. This finding maybe explained by the fact that in open studies efficacy is overestimated, because raters know the treatment patients are assigned to. A reason for the higher response rates in drug naive first episode patients can be that some pre-treatment with antipsychotics has already reduced symptoms so that the leeway for response was lower in patients who had already been exposed to some antipsychotics before study start. The same reason may explain why more severely ill patients at baseline had a higher response rate than less severely ill ones, a finding that has also been documented in chronic patients (Furukawa et al., 2015; Rabinowitz et al., 2014). In line with the findings by Rabinowitz et al. (2014), we also found increased treatment response in female patients compared to male patients, and in patients with a shorter illness duration. That women with schizophrenia have a better outcome than men has been hypothesized in the literature for many years (Angermeyer et al., 1989), but the reasons are unclear. The better response of patients with a shorter duration of illness may somehow be associated with duration of untreated psychosis (DUP), although DUP itself was only rarely reported and could therefore not be analysed as a separate factor. That older patients responded better than younger ones at first glance contradicts the finding of better response in patients with a shorter duration of illness. It is conceivable, however, that an early onset of schizophrenia is a marker of a more severe, less treatable form of the disorder. Finally, study duration was not associated with the number of responders. It has been well-documented that a substantial amount of the antipsychotic drug effect occurs during the first two weeks of treatment (Agid et al., 2003; Leucht et al., 2005a) and that response curves often already flatten after the third week of treatment (McMahon et al., 2008). Therefore, longer study duration may not be associated with substantially higher response rates. There was no significant correlation between dosage and response rates. It should be noted that doses of individual drugs had to be converted to olanzapine equivalents for this purpose. All methods of dose equivalents have serious limitations (Leucht et al., 2016, 2015, 2014).

Several limitations should be considered while interpreting our results. First, in many studies response data had to be imputed and it has been shown that the imputation method tended to underestimate extremely high values and to overestimate very low values (Samara et al., 2013). In particular the high response rates based on the 20% cutoff may thus in fact be even higher, while response rates based on 50% reduction scattered around 50% anyhow so that not much over- or underestimation should have occurred. Our sensitivity analysis excluding imputed values was not very useful in this regard, because only 5 studies presented actually observed response rates based on 20%/50% cutoffs making the results contradictory. Future studies should present responder rates based on several cutoffs and consistently take the 18/30 minimum points of the BPRS/PANSS into account (Leucht, 2014). Second, definitions of first episode in the studies varied, and diagnoses in the early stages of schizophrenia can be difficult, implying that first-episode patients might actually suffer from other psychiatric problems than schizophrenia-like disorders. Finally, not a single placebo-controlled first-episode trial was identified. As studies in chronic patients revealed substantial placebo effects in recent trials (Agid et al., 2013), it would be useful to know how much such effects accounted for the high response rates in our trials. This knowledge could also have implications for future clinical trials. If placebo response in first-episode studies were not extremely high, studies in first episode patients could provide better signal detection than trials in chronic patients. For instance, an early, large NIMH-sponsored trial from 1964 (Cole, 1964) showed a substantial difference between antipsychotics and placebo (61% versus 22% were at least much improved on a Clinical Global Impression), and in this study approximately 50% of the sample had a first-episode or was antipsychotic naïve. In a similar vein Rabinowitz et al. (2014) reported that drug-placebo differences are larger in patients with a shorter illness duration, and there is evidence that already in the second episode the time to remission is considerably larger than in the first episode (Emsley et al., 2013). However, due to issues such as the impact of duration of untreated psychosis and the subsequent ethical concerns about withholding effective treatment for prolonged periods of time, the conduct of a placebo-controlled first-

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episode study needs to be carefully weighted against its risks. Such trials might not be generally recommendable.

We conclude that the response rate of first-episode patients with schizophrenia to antipsychotics is rather high, and that female patients, more severely ill patients, drug naive patients, and patients with a short illness respond better than their counterparts.

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Contributors

The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SL and YZ designed this study. Samantha Roberts helped us to conduct the literature searches. YZ, CL, MH and MK performed study screening. YZ and PR extracted the data. YZ, IB and JST analyzed data. YZ and SL wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

In the last three years Stefan Leucht has received honoraria for lectures from EliLilly, Lundbeck (Institute), Pfizer, Janssen, BMS, Johnson and Johnson, Otsuka, Roche, SanofiAventis, ICON, Abbvie, AOP Orphan, Servier; for consulting/advisory boards from Roche, Janssen, Lundbeck, EliLilly, Otsuka, TEVA; for the preparation of educational material and publications from Lundbeck Institute and Roche. EliLilly has provided medication for a clinical trial led by SL as principal investigator. The other authors have no conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2017.06.011.

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eAppendix 1. Description of included studies

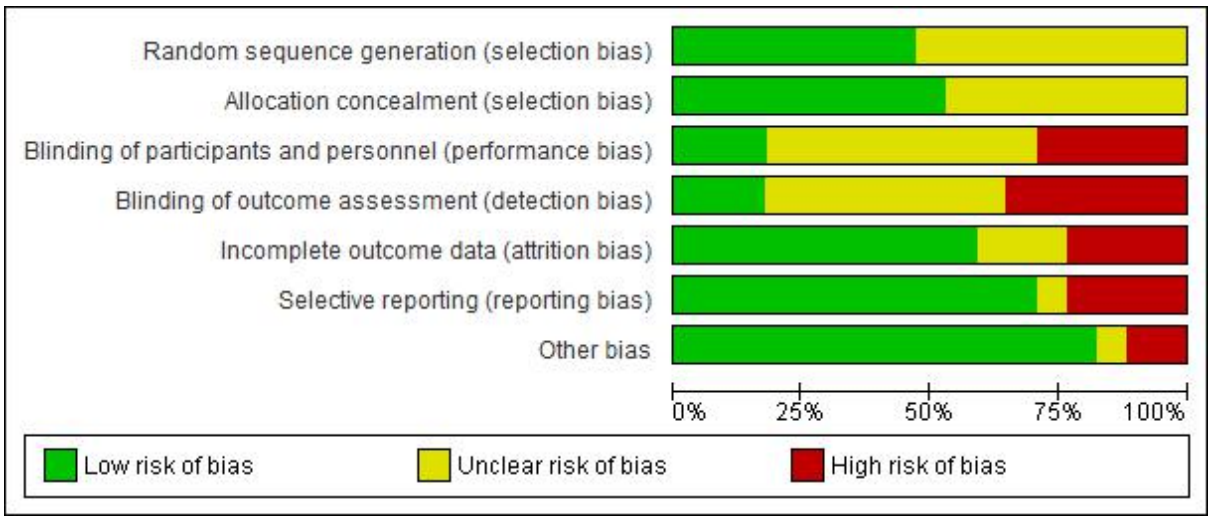
Study	Study groups /number of participants	Trial duration (weeks)	Mean antipsychotic doses (mg/d)	Diagnosis	Definition of first episode	Study design	Characteristics of included patients
Amr et al. 2013[29]	HAL: n=33 QUE: n=40	12	HAL: 14.2 QUE: 705.8	Schizophrenia (DSM-IV-TR)	First-episode schizophrenia	SB-RCT	Setting: outpatients Sex: M 46 F 27 Age: mean 31.05 yrs SD 3.67 Duration of illness (month): 4.94 SD 1.93
Chaudhuri et al. 2000[30]	HAL: n=15 RIS: n=15	4	HAL: 15 RIS: 4	acute and transient psychotic disorder (ICD-10)	Treatment-naïve first-episode schizophrenia	SB-RCT	Setting: inpatients Sex: M 15 F 15 Age: 24 cases between 16-25 ages, 5 cases between 26-35 ages, 1 case between 46-55 ages History: drug naive, no psychiatric morbidity
Crespo-Facorro et al. 2006[31]	HAL: n=56 OLA: n=55 RIS: n=61	6	HAL: 5.4 OLA: 15.3 RIS: 4	schizophrenifrom disorder, schizophrenia, schizopaffective disorder, brief reactive psychosis, schizotypal personality disorder or psychosis not otherwise specified (DSM-IV)	First-episode, no prior or less than 6 weeks antipsychotic treatment	OL-RCT	Setting: inpatients and outpatients Sex: M 107 F 65 Age: mean 27.3 yrs SD 7.8 Duration of illness (month): 27.9 SD 36.7. Baseline psychotic symptoms of moderate severity or greater assessed by 1 of the 5 items of SAPS
Emsley et al. 1999[32]	HAL: n=84 RIS: n=99	6	HAL: 5.6 RIS: 6.1	schizophreniform disorder or schizophrenia (DSM-III-R)	Treatment-naïve first-episode schizophrenia	DB-RCT	Setting: inpatients and outpatients Sex: M 122 F 61 Age: median 26 yrs for Risperidone, median 24 yrs for Haloperidol History: drug naive
Fagerlund et al. 2004[33]	RIS: n=15 ZUC: n=10	13	RIS: 3.6 ZUC: 9.6	Schizophrenia (ICD-10)	Treatment-naïve first-episode schizophrenia	OL-RCT	Setting: inpatients Sex: not reported Age: mean 27.3 yrs SD 5.9 History: duration of untreated psychosis median 14 months, drug naive
Kahn et al. 2008[34]	HAL: n=103 AMI: n=104 OLA: n=105 QUE: n=104 ZIP: n=82	52	HAL: 3 AMI: 450.8 OLA: 12.6 QUE: 498.6 ZIP: 107.2	schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV)	First-episode schizophrenia	OL-RCT	Setting: inpatients and outpatients Sex: M 298 F 200 Age: mean 26 yrs SD 5.6 History: baseline PANSS total 88.5 SD 20.6

Lee et al. 2007[35]	HAL: n=10 RIS: n=10	8	HAL: 7.6 RIS: 4.1	schizophrenia (DSM-IV)	Treatment-naïve schizophrenia	DB-RCT	Setting: inpatients Sex: M 20 F 0 Age: mean 26.6 yrs SD 8.8 History: baseline PANSS total 92.3 SD 12.2, drug naive
Lieberman et al. 2003a[36]	OLA: n=131 HAL: n=132	12	OLA: 9.1 HAL: 4.4	schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV)	First-episode schizophrenia	DB-RCT	Setting: inpatients and outpatients Sex: M 215 F 48 Age: mean 23.8 yrs SD 4.8 History: had onset of psychotic symptoms before age 35 yrs, scored >=4 on at least two PANSS psychosis items or scored >=5 on one psychosis item, CGI severity score >=4 (moderately ill)
Lieberman et al. 2003b[44]	CLO: n=81 CHL: n=83	52	CLO: 300 CHL: 400	schizophrenia or schizophreniform disorder (DSM-IV)	First-episode schizophrenia	DB-RCT	Setting: inpatients Sex: M 85 F 79 Age: mean 28.7 yrs SD 6.9 History: baseline CGI 5.6, drug naive
McEvoy et al. 2007[37]	OLA: n=133 QUE: n=134 RIS: n=133	52	OLA: 11.7 QUE: 506 RIS: 2.4	schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV)	First episode schizophrenia, continuously ill for at least 1 month and no more than 5 years	DB-RCT	Setting: inpatients and ourpatients Sex: M 292 F 108 Age: mean 24.5 yrs SD 5.8 History: duration of illness (months) 12.9 SD 17.29, score >=4 on at least one PANSS psychosis item and score >=4 (moderately ill) on the severity item of CGI
Moeller et al. 2008[38]	RIS: n=143 HAL: n=146	8	RIS: 3.8 HAL: 3.7	schizophrenia (ICD-10)	First-episode schizophrenia	DB-RCT	Setting: inpatients Sex: M 172 F 117 Age: mean 30.1 yrs SD 9.8 History: baseline PANSS total 79.1 SD 24.0
San et al. 2012[39]	OLA: n=25 QUE: n=23 RIS: n=25 ZIP: n=20 HAL: n=21	52	OLA: 12 QUE: 572 RIS: 3.7 ZIP: 81 HAL: 4	schizophrenia, schizophreniform disorder, schizoaffective disorder, psychotic disorder NOS, brief psychotic disorder (DSM-IV-TR)	Treatment-naïve first-episode schizophrenia	OL-RCT	Setting: inpatients Sex: M 85 F 29 Age: mean 25.6 yrs SD 8.0 History: baseline PANSS total 91.0 SD 20.0, DUP (weeks) 52.5 SD 170.0, drug naive
Sanger et al. 1999[1]	HAL: n=24 OLA: n=59	6	HAL: 10.8 OLA: 11.6	schizophrenia, schizoaffective disorder,	First-episode schizophrenia,	DB-RCT	Setting: n.i. Sex: M 57 F 26

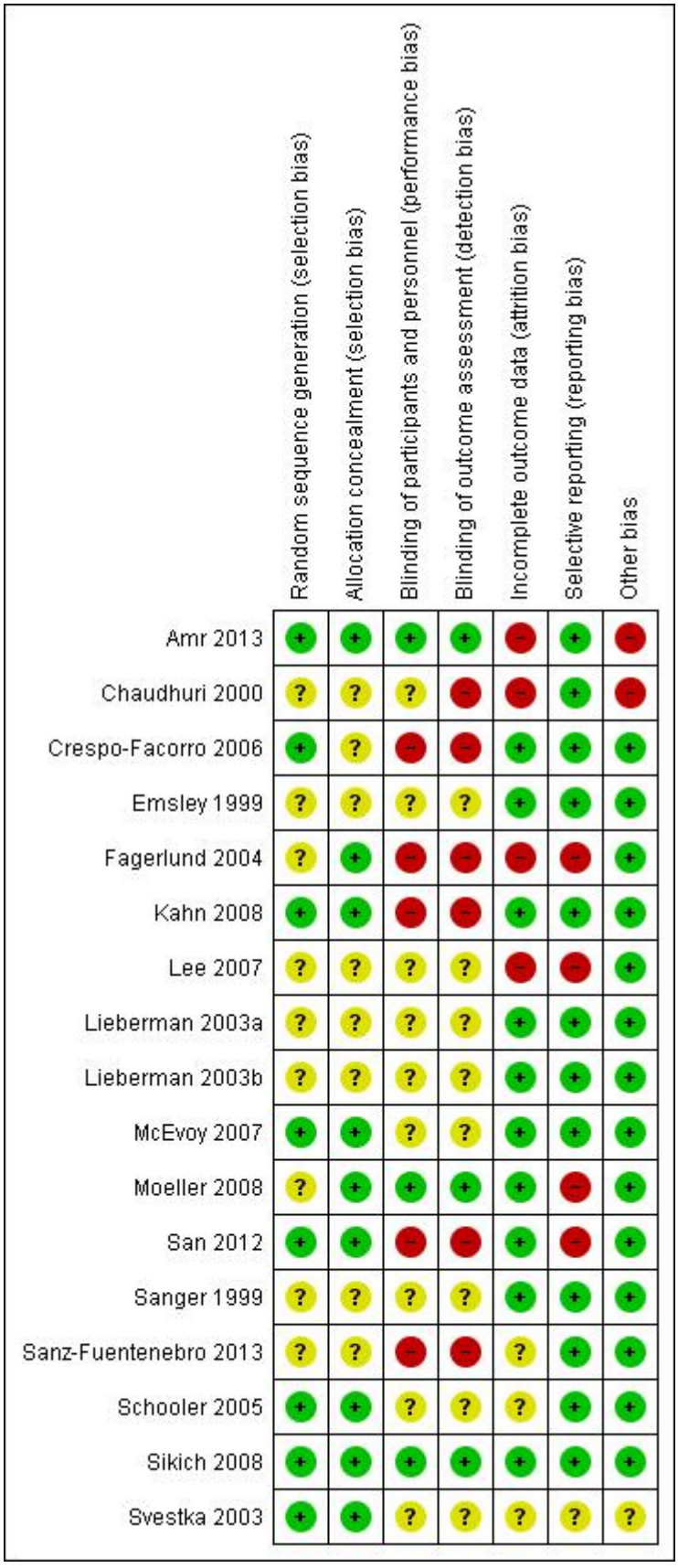
				or schizophreniform disorder (DSM-III-R)	current episode no more than 5 years		Age: mean 28.5 yrs SD 7.3 History: duration of illness (years): 1.3, length of current episode (days): 389.6 SD 422.8
Sanz-Fuentenebro et al. 2013[40]	CLO: n=15 RIS: n=15	52	CLO: 220.45 RIS: 5.43	schizophrenia or schizophreniform disorder (DSM-IV)	Treatment-naïve first-episode schizophrenia	OL-RCT	Setting: inpatients and outpatients Sex: M 21 F 9 Age: mean 24.5 yrs SD 5.3 History: DUP (months) 9.9 SD 22.5, baseline PANSS total 83.1 SD 20.3
Schooler et al. 2005[41]	RIS: n=278 HAL: n=277	104	RIS: 3.3 HAL: 2.9	schizophrenia, schizophreniform disorder, or schizoaffective disorder (DSM-IV)	First-episode schizophrenia	DB-RCT	Setting: outpatients Sex: M 396 F 159 Age: mean 25.4 yrs SD 6.86 History: a diagnosis for no more than 1 year during which period they had no more than two psychiatric hospitalizations for psychosis and had less than 12 weeks of cumulative exposure to antipsychotics
Sikich et al. 2008[42]	MOL: n=40 OLA: n=35 RIS: n=41	8	MOL: 59.9 OLA: 11.4 RIS: 2.8	schizophrenia, schizoaffective disorder, or schizophreniform disorder (DSM-IV(KID-SCID))	First-episode schizophrenia (early-onset)	DB-RCT	Setting: inpatients and outpatients Sex: M 75 F 41 Age: range 8-19 yrs History: had current positive psychotic symptoms of at least moderate intensity
Svestka et al. 2003[43]	OLA: n=21 RIS: n=21	6	OLA: 18 RIS: 4.9	schizophrenic and schizoform disorders (ICD-10)	First-episode schizophrenia	DB-RCT	Setting: inpatients Sex: M 0 F 42 Age: mean 28.37 yrs History: the current first episode lasted 14-725 days (mean 103.59)

HAL = haloperidol, RIS = risperidone, OLA = olanzapine, QUE = quetiapine, ZIP = ziprasidone, MOL = molindone, ARI = aripiprazole, AMI = amisulpride, SER = sertindole, ZUC = zuclopenthixol, FLU = flupentixol, PIM = pimozide, CLO = clozapine, CHL = chlorpromazine. DB-RCT = double blind randomized controlled trial, SB-RCT = single blind randomized controlled trial, OL-RCT = open label randomized controlled trial, n = numbers of participants, n.i. = not indicated, M = males, F = females, yrs = years, SD = standard deviation.

eAppendix 2. Risk of bias graph



eAppendix 3. Risk of bias summary



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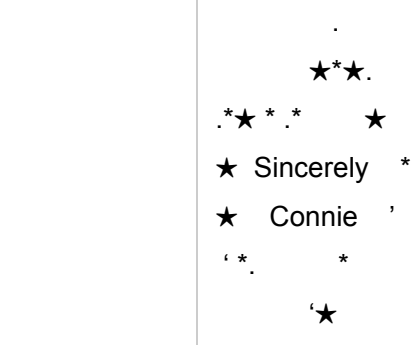

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7. Acknowledgment

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