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Meta-analysis in schizophrenia trials: comparison of chlorpromazine versus every other antipsychotic drug for schizophrenia and assessment of an imputation technique for estimating response rates from means and standard deviations in schizophrenia.

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Table of contents

A. List of symbols and abbreviations 5

B. Abstract 7

C. Cumulative thesis 8

Introduction and motivation 8

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs 8

II. Imputation of response rate from means and standard deviations in schizophrenia 10

Methods 13

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs 13

a. Setting the research question and defining the study protocol 13

b. Search and selection of trials 14

c. Data extraction 15

d. Risk of bias assessment 16

e. Meta-analytical calculations 17

f. Assessment of publication bias 19

g. Presentation of results 19

II. Imputation of response rate from means and standard deviations in schizophrenia 20

a. Imputation strategy 21

1. Based on mean endpoint scores 23

2. Based on mean change scores 24

b. Assessment of the imputation method 25

1. The Concordance Correlation Coefficient (CCC) 25

2. Predictive accuracy 25

3. The “limits of agreement” method 26

Results 28

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs 28

II. Imputation of response rate from means and standard deviations in schizophrenia 29

1. The Concordance Correlation Coefficient (CCC) 29

2. Predictive accuracy 29

3. The “limits of agreement” method 30

Discussion and conclusions 32

Table of contents

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs 32

II. Imputation of response rate from means and standard deviations in schizophrenia 35

References 38

D. Publications 55

First publication 55

Appendix A. Online supplement 66

Second publication 180

Appendix A. Online supplement 187

E. Acknowledgements 194

F. Copyright permission 195

A. List of symbols and abbreviations

ANOVA: Analysis of Variance

BPRS: Brief Psychiatric Rating Scale

CC: Completer Cases

CCC: Concordance Correlation Coefficient

CGI: Clinical Global Impression

ECT: Electroconvulsive Therapy

EU: European Union

FGA: First Generation Antipsychotic

FINER: Feasible, Interesting, Novel, Ethical, Relevant

ICC: Intraclass Correlation Coefficient

ITT: Intention-to-treat

LOCF: Last Observation Carried Forward

MD: Mean Difference

MSE: Mean Squared Error

NNT: Number Needed to Treat

OR: Odds Ratio

PANSS Positive and Negative Syndrome Scale

PICOT: Population, Intervention, Comparison, Outcome, Time

A. List of symbols and abbreviations

RCT: Randomized Controlled Trial

RR: Risk Ratio

SD: Standardized Difference

SGA: Second Generation Antipsychotic

SMD: Standardized Mean Difference

WHO: World Health Organisation

WFSBP: World Federation of Societies of Biological Psychiatry

B. Abstract

Systematic reviews and meta-analyses can provide answers to long-standing dubious scientific statements. Thus, in my first project, I conducted a systematic review and meta-analysis in order to address one of the major psychiatric dogmas that all antipsychotic drugs are equally efficacious. Randomized controlled trials (RCTs) comparing the benchmark drug chlorpromazine to any other antipsychotic in the treatment of schizophrenia were assessed. Binary response to treatment, mean values in schizophrenia rating scales and drop-out rates were analyzed. 128, mostly small, RCTs with 10667 participants were included. Chlorpromazine was compared with 43 other antipsychotics and was shown more efficacious than five (butaperazine, mepazine, oxypertine, quetiapine and reserpine) and less efficacious than six antipsychotics (clomacran, clozapine, olanzapine, risperidone and zotepine). There were no statistically significant efficacy differences between chlorpromazine and the remaining 25 antipsychotics. Nevertheless, the main limitation of this meta-analysis was that most comparisons were underpowered; thus any conclusion that chlorpromazine is more or less efficacious than any other antipsychotic could not be driven.

Apparently, limited power is one of meta-analysis major drawbacks. As one of its causes is missing data, in my second project I assessed the performance of an imputation method in schizophrenia trials that has been previously applied with success in anxiety and depression trials. This imputation method converts continuous to binary data using means and standard deviations. To assess its performance in schizophrenia trials, I used individual patients' data from16 RCTs in schizophrenia. The imputed values were then compared to the observed ones concluding that the imputed values approximated the observed ones acceptably; however, in case of extreme risks and large treatment differences, the imputation method tended to introduce biases in a conservative direction. Therefore, meta-analyses applying the method should be accompanied by a sensitivity analysis excluding the imputed values.

C. Cumulative Thesis

Introduction and Motivation

Advances in the field of medical research grow exponentially and challenge researchers' and clinicians' ability of following them. With more than 500 medical trials being registered in a database every week (Bastian, Glasziou et al. 2010) and thousands of articles being published, keeping up with the current literature is almost impossible. Thus, appropriate summarization of the available information (e.g. a systematic review) is crucial. Nevertheless, contradictory results of single studies on the same research question further complicate the situation since a simple systematic review fails to clear the picture, it just captures it. The ultimate choice is the meta-analysis, an epidemiologic method which statistically synthesizes data from all studies included in a systematic review and produces a thorough summary estimate of an effect. In this context, my thesis has two parts. The first one is a meta-analysis on a critical clinical question highlighting the key role of systematic reviews and meta-analyses in providing evidence-based answers. The second one gives a solution to an important methodological problem when conducting a meta-analysis.

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs

Long before meta-analysis was introduced into research practice, all antipsychotic drugs used for schizophrenia treatment were considered equally efficacious based on narrative, unsystematic reviews that found no differences in efficacy between conventional antipsychotics available at that time (Klein and Davis 1969, Davis and Garver 1978). This unproven psychiatric assumption of equal efficacy was subsequently codified in numerous textbooks (Davis, Barter et al. 1989, Buchanan and Carpenter 2000, Stahl 2000) and

guidelines which make statements such as “comparable efficacy... among the different first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs)” (Patient Outcomes Research Team Psychopharmacological Treatment Recommendations and Summary Statements) (Buchanan, Kreyenbuhl et al. 2010), “with the possible exception of clozapine … antipsychotics have similar efficacy” (American Psychiatric Association Practice Guidelines) (Lehman, Lieberman et al. 2004), “all conventional antipsychotics if adequately dosed have comparable efficacy” (German National Schizophrenia Guideline (Gaebel, Falkai et al. 2006); or “FGAs and SGAs are effective…and in general no differences between drugs could be detected” (World Federation of Societies of Biological Psychiatry Guidelines) (Hasan, Falkai et al. 2012). However, apart from a methodologically insufficient ‘vote count’ approach in 1989 (Davis, Barter et al. 1989), the origins of this statement have never been systematically addressed despite contrasting with the clinical impression that not all antipsychotic drugs are equally efficacious.

So where does the truth lie? Nowadays, with hundreds of available trials comparing different antipsychotics, only meta-analytical synthesis of data can shed some light on the topic. Recent meta-analyses have challenged the dogma of equal efficacy founding small, but robust superiorities of some SGAs (Davis, Chen et al. 2003, Leucht, Wahlbeck et al. 2003, Martin, Perez et al. 2006, Leucht, Davis et al. 2009, Rabinowitz, Levine et al. 2009, Hartling, Abou-Setta et al. 2012, Zhang, Gallego et al. 2012, Kishimoto, Agarwal et al. 2013). But the older literature from which the dogma of “equal efficacy of all antipsychotic drugs” was originated has never been updated since then. The older literature is based on FGAs which are still the mainstay of treatment in low or middle-income countries (Chong, Tan et al. 2004,

Karagianis, Novick et al. 2009) – i.e. the largest part of the world - and they maintain a relatively high market share in industrialised countries such as the United States, United Kingdom and Germany (Hamann, Ruppert et al. 2003, Sernyak and Rosenheck 2008, Koranek, Smith et al. 2012, Prah, Petersen et al. 2012). Moreover, chlorpromazine, together with haloperidol and fluphenazine depot, is the only antipsychotic listed as an "essential drug" by the World Health Organisation (WHO). As it was the first developed antipsychotic drug, it has served as a benchmark for many other compounds.

The aim of my first study was to compare the efficacy of the benchmark antipsychotic chlorpromazine with all others, following the general approach of a pivotal Cochrane review comparing the benchmark antidepressant amitriptyline with all other antidepressants (Leucht, Huhn et al. 2012). As the "equal efficacy of all antipsychotics" is one of the major dicta in psychopharmacology, we decided to proceed to this large meta-analysis whose results, albeit mainly based on old trials, could have a direct major impact on revisions and future textbooks and guidelines. If chlorpromazine were shown to be more or less effective than other conventional antipsychotics, the long-standing dogma of equal efficacy could not be maintained.

II. Imputation of response rates from means and standard deviations in schizophrenia

In my second study, I focused on an important methodological limitation when conducting a meta-analysis. Meta-analysis can be performed with the use of established statistical techniques as long as the data of interest are available. Unfortunately, the results of a trial are usually reported inadequately so that they cannot be entered in the meta-analysis. For

example, it may be that only the mean scores of groups are presented (continuous outcome) and not the number of subjects that responded to treatment (dichotomous outcome) or vice versa. Subsequently studies are excluded from the meta-analysis, leading to loss of precision and power as well as potentially biased estimates.

Dichotomous outcomes present several advantages, both clinical and statistical. From a clinical point of view, dichotomisation allows for a simple interpretation of results and risk classification, assists in making treatment recommendations, estimating prognosis and setting diagnostic criteria. For example, the percentage of responders in two groups (e.g. 10% and 20%) and the resulting response ratio (two times more responders in the second group) can be understood more intuitively than a difference of e.g. 10 points on the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein et al. 1987) total score despite recent efforts to translate the results of such rating scales in clinical terms (Schennach-Wolff, Obermeier et al. , Leucht, Kane et al. 2005, Leucht, Kane et al. 2005, Levine, Rabinowitz et al. 2008). Simple interpretation of results is important for single randomized controlled trials (RCTs), but even more so for meta-analyses which aim to summarise all RCT data and present clinically useful indices based on dichotomous outcomes such as the number-needed-to-treat (NNT). From a statistical point of view, the use of dichotomous data eliminates the need for the linearity assumption, and, although it decreases statistical power, it makes data summarisation more efficient (Altman, Lausen et al. 1994, Royston, Sauerbrei et al. 2000, Streiner 2002, Mazumdar, Smith et al. 2003, Altman and Royston 2006).

To the best of our knowledge, limited literature exists and limited investigation has been done on how to convert continuous to dichotomous data. Suissa (1991) presented a

parametric method in order to estimate the risk of an event without resorting to dichotomization. He concluded that this method is more efficient, is not subjected to large biases because of the numerical discreteness of the continuous outcome and overcomes the problem of 100% and 0% of events in the sample (this can never be the case in a population) compared to the binomial model. Furukawa et al. (2005) used this approach and empirically explored its appropriateness for estimating response rates from means and standard deviations at endpoint in depression and anxiety trials when studies fail to report them.

The aim of my second study was to determine whether Furukawa's method for depression and anxiety trials, and one of its expansions based on the mean change rather than the endpoint data, could be also applied to schizophrenia trials since this would be very useful for meta-analytic projects. Meta-analysis is expected to use and summarize the best available evidence allowing regulatory and health authorities to develop guidelines and draw health policies, clinicians to have a comprehensive understanding of the data that would facilitate decision-making, and researchers to design future studies. Thus finding and synthesizing as much as possible original evidence is crucial.

C. Cumulative Thesis

Methods

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs

In the first project, all the essential meta-analytical steps were followed: a) definition of the research question and the study protocol, b) systematical search of trials, c) data extraction, d) risk of bias assessment, e) data analysis, f) assessment of publication bias and g) presentation of results.

a. Setting the research question and defining the study protocol

The research question answered the PICOT criteria (specification of the examined Population, the type of Intervention and Control, the Outcome measures, and the Timeframe) (Fineout-Overholt and Johnston 2005) and fulfilled the FINER criteria (Feasibility, Interesting, Novel, Ethical, Relevant) (Hulley, Cummings et al. 2007). The research question, together with the rationale of setting it, was presented in the study protocol. The study protocol also reported the statistical approach for analysing the data as well as any sub-group or meta-regression analysis for investigating the effect of specific moderators. The a priori written study protocol was published in the PROSPERO database (Registration No. CRD42012002084). As defined in the protocol, all randomised controlled trials that compared oral formulations of chlorpromazine with any other oral antipsychotic for the treatment of schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder, irrespective of the diagnostic criterion used) were included.

C. Cumulative Thesis

Methods

Intramuscular routes of antipsychotic delivery were excluded as these are mainly used for short-term sedation. Quasi-randomised studies (e.g. randomised by the day of the week) and studies in which allocation was clearly not concealed (e.g. alternate allocation) were also excluded (Higgins and Green 2011). No restrictions in terms of age, gender, chronicity of illness, duration of trial and dose range were applied. Post-hoc it was decided i) to include comparisons of chlorpromazine with second-generation antipsychotics (and not only with first-generation antipsychotics) in order to examine comprehensively all the available literature, and ii) to exclude Chinese studies in order to avoid a systematic bias as many of them neither use appropriate randomization procedures nor report their methods (Bian, Li et al. 2006, Wu, Li et al. October 23-26, 2006) and tend to overestimate differences between FGAs and SGAs (Leucht, Corves et al. 2009).

b. Search and selection of trials

For the systematic search of trials, the Cochrane Schizophrenia Group's Register was thoroughly examined up to August 2009 using the term "chlorpromazin*" (later versions of the register were not available to us). The Schizophrenia Group's Register is compiled by regular systematic searches of more than 15 databases, clinical trial registers, hand searches and conference proceedings. The electronic databases like MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov and PsychInfo were also searched using the specific key words "chlorpromazin* AND schizophrenia". RCTs comparing chlorpromazine with second-generation antipsychotics were identified through the comprehensive searches made for a recent network meta-analysis of our group (Leucht, Cipriani et al. 2013). Moreover, the search was supplemented by inspection of the reference

lists of included studies and of other reviews on chlorpromazine (Adams, Awad et al. 2007, Levine, Rabinowitz et al. 2008, Ahmed, Jones et al. 2010). No language restriction was applied apart from excluding Chinese trials (Gregoire, Derderian et al. 1995, Moher, Fortin et al. 1996, Egger, Zellweger-Zahner et al. 1997, Moher, Pham et al. 2000).

c. Data extraction

At least two investigators independently selected the reports and extracted data from all studies on standard extraction forms. The double selection and extraction process aimed to minimize the risk of errors or subjective decisions (Buscemi, Hartling et al. 2006). If disagreements between the two investigators were not solved in a conversation between them, a third investigator was involved. All reports based on the same initial study were retrieved and reviewed for additional information. Pharmaceutical companies producing chlorpromazine (SanofiAventis, GlaxoSmithKline, Bayer) as well as all first authors of initially selected studies were contacted requesting additional or missing information and a possibility for corrections. In the case of missing data, efforts were made to obtain them indirectly, based on their algebraic relationship to other values e.g. standard errors from standard deviations, confidence intervals or p-values. Imputation techniques were also employed when no other source of information was available (indirect or from authors of original studies).

The primary outcome was response to treatment (dichotomous). It was a priori defined in our protocol as at least 50% reduction of rating scales such as the PANSS (Kay, Fiszbein et al. 1987) , the BPRS (Overall and Gorham 1962) or at least “much improved” on the Clinical

Global Impressions Scale (CGI) (Guy 1976) because these cut-offs have been demonstrated to be clinically meaningful (Leucht, Kane et al. 2005, Leucht and Engel 2006, Levine, Rabinowitz et al. 2008, Leucht, Engel et al. 2012), but as these were rarely indicated, the authors' definitions were often used which has been found to be appropriate as long as relative risks or odds ratios are the effect size measures (Furukawa, Akechi et al. 2011). The mean overall change in symptom rating was also analysed, based on the following hierarchy: change in PANSS total score, change in BPRS total score, values of these scales at study endpoint, and then, if any of the previous measures were not available, other scales for overall schizophrenic symptomatology as long as the instrument had been published in a peer-reviewed journal since it has been suggested that unpublished rating scales tend to overestimate differences (Marshall, Lockwood et al. 2000). Intention-to-treat (ITT) datasets were used whenever available. Other outcomes were drop-out due to any reason, due to inefficacy and due to adverse events.

Except of data directly related to the primary and secondary outcomes of the meta-analysis, data on study design and patient characteristics such as blinding, mean dose of chlorpromazine, sex, mean age of patients, whether or not patients suffered from their first episode of schizophrenia or from treatment-resistant schizophrenia (as defined by the original studies) were extracted.

d. Risk of bias assessment

The quality of all included studies was independently assessed using the Cochrane Collaboration's risk of bias tool (Higgins and Green 2011). Five fields were examined as

possible sources of bias: the randomisation method, the allocation concealment, the blinding procedure in terms of performance and detection, the incomplete outcome data and the selective reporting of outcomes. There was also the possibility for assessing sources of other, not predefined bias such as baseline imbalance, replacement of dropouts during the trial, use of chlorpromazine or electroconvulsive therapy (ECT) as rescue treatment, no predetermined trial duration etc. (6^{th} item of the tool).

e. Meta-analytical calculations

The primary effect size measure for dichotomous outcomes was the relative risk (RR) together with corresponding 95% confidence intervals. The advantage of the RR is that it can be understood more intuitively than odds ratios which are often interpreted as relative risks leading to an overestimation of treatment effects (Davies, Crombie et al. 1998). The numbers-needed to treat (NNT) or numbers-needed to harm (NNH) were also calculated as reciprocals of absolute risk differences. The effect size for continuous data was the standardised mean difference expressed as Hedges' adjusted g. Standard inverse of the variance weighting was used for pooling the studies. Unreported standard deviation (SD) values were calculated from other statistics or from the average of the other studies.

As considerable heterogeneity between studies was expected, the Der-Simonian and Laird random-effects model (DerSimonian and Laird 1986) was applied throughout the meta-analysis, but ,in a sensitivity analysis of the primary outcome, it was examined whether a fixed-effects model would lead to substantial differences. The fixed-effect model is based on the hypothesis that there is one true effect size for all studies and any variation among them

is only because of sampling error. But this hypothesis is rarely valid. On the other hand, the random-effect model allows for effect sizes to vary between studies for reasons other than sampling error alone like patients' characteristics, study design and interventions. The aim is not to estimate the true, common effect size (which does not exist under this statistical hypothesis) but the mean from a normal distribution of effect sizes which are randomly represented in the meta-analysis. Fixed- and random-effect models produce identical results when there is no heterogeneity between the studies.

Heterogeneity was assessed by the chi-squared statistic (χ^2) and the I^2 statistic (Higgins and Thompson 2002). The χ^2 test examines the null hypothesis that all studies have the same effect in the population by comparing the observed effects of the studies with the pooled effect estimate. The expected χ^2 test should equal to the degrees of freedom ($df = number\ of\ studies - 1$) if the null hypothesis is true. Nevertheless, not detecting statistical heterogeneity with the test is not an evidence of homogeneity; heterogeneity may still exist but not being detected due to the test's low power. To deal with the low power of the χ^2 test, a higher level of statistical significance was set at $p - value < 0.1$. Moreover, the χ^2 test cannot quantify the heterogeneity. For that reason, the I^2 statistic was used (Higgins and Thompson 2002). The I^2 measures how much of the total variation is attributed to heterogeneity rather than chance and ranges between 0% and 100%. Values of I^2 above 50% were considered reflecting significant heterogeneity (Higgins and Green 2011).

To investigate sources of heterogeneity, subgroup and meta-regression analyses were performed. Subgroup analysis estimates the summary effect of specific subsets of patients or

studies and makes comparisons between them. Meta-regression analysis relates the effect size of single studies to their continuous characteristics. The subgroup and meta-regression analyses were pre-specified to avoid bias. Also, since both are observational techniques, the interpretation of results was careful. The following potential reasons for heterogeneity were explored: chlorpromazine dose, age, first episode of schizophrenia and treatment-resistant schizophrenia (as defined by the original studies). Meta-analytic calculations were done with RevMan 5.2 (Centre 2012), Comprehensive Meta-Analysis version 2 (Borenstein, Hedges et al. 2005) and STATA 12 (StataCorp 2011). Two-sided α test was set at $p<0{\cdot}05$.

f. Assessment of publication bias

Publication bias refers to the fact that studies with statistically significant results are more likely to be submitted and published than studies with null or non-significant results. To assess publication bias, funnel plots (scatter plots of study's effect size against its precision or size) were used. As funnel-plots are based on visually examined symmetry, they can only detect publication bias when a reasonable number of studies are available. This was defined as a minimum of ten (Higgins and Green 2011). The Egger's regression test (Egger, Davey Smith et al. 1997), which measures the degree of funnel plot asymmetry, was also applied. Finally, to both detect and correct any asymmetry caused by publication bias, the 'trim and fill' method was used (Taylor 1998, Duval 2000). According to that method, the asymmetric part of the funnel plot is removed, the centre of the symmetric part is estimated and then the omitted studies together with their missing mirror ones are replaced.

g. Presentation of results

C. Cumulative Thesis

Methods

Several figures and tables were used to present the results of this meta-analysis. Search results were presented in the PRISMA Flow Diagram which illustrates the selection of studies through the different phases of the search (Moher, Liberati et al. 2009) . Important individual characteristics of all included studies were presented in an online table. Two graphs presenting the risk of bias, one for every included study and one summary, accompanied the manuscript. Forest plots displaying the pooled RRs or SMDs (with their confidence intervals) for comparisons of chlorpromazine versus all other antipsychotics were presented in the manuscript for all outcomes (primary and secondary); the effect estimates (RRs or SMDs) of individual studies were shown in the online supplement. Moreover, results from the meta-regression analysis were presented graphically in the online supplement with a simple scatter plot (meta-regression plot) in which the moderating covariate was displayed on the horizontal axis and the effect estimate on the vertical axis whereas the precision of the effect estimates was indicated by the size of the bubbles (Thompson and Higgins 2002). Finally, a funnel plot was also included in the online supplement.

II. Imputation of response rates from means and standard deviations in schizophrenia

In the second project, in order to assess the performance of Furukawa et al. imputation method (Furukawa, Cipriani et al. 2005) in schizophrenia trials, original, individual patients' data from 16 previously published RCTs were used (Beasley, Sanger et al. 1996, Beasley, Hamilton et al. 1997, Moller, Boyer et al. 1997, Tollefson, Beasley et al. 1997, Tran, Hamilton et al. 1997, Puech, Fleurot et al. 1998, Wetzel, Grunder et al. 1998, Peuskens, Bech et al. 1999, Carriere, Bonhomme et al. 2000, Colonna, Saleem et al. 2000, Sechter, Peuskens et al. 2002, Lieberman, Phillips et al. 2003, Lieberman, Tollefson et al. 2003, Breier, Berg et

al. 2005, Keefe, Young et al. 2006, Kinon, Noordsy et al. 2006) that compared the efficacy of olanzapine or amisulpride with other antipsychotics or placebo in schizophrenia. Altogether 6276 patients from 37 arms were included.

The actual response rates and odds ratios (ORs) were compared to the ones imputed by the Furukawa et al. method. The scale in the olanzapine studies was the PANSS (Kay, Fiszbein et al. 1987) and in the amisulpride studies the BPRS (Overall and Gorham 1962). Four frequently used response cut-offs (at least 20%, 30%, 40%, and 50% reduction of the PANSS/BPRS total score from baseline) were applied leading to 148 response rate- and 116 OR-comparisons. Every possible combination was examined by sub-group analyses. As the PANSS and BPRS were rated on the 1-7 scale for each single item, the 30 and 18 minimum points respectively were subtracted for the calculation of percentage reduction from baseline to endpoint (Obermeier, Mayr et al. 2010, Furukawa, Akechi et al. 2011). All cut-offs were included in the primary analysis, but every cut-off was examined separately in a sensitivity analysis. All studies were analysed at endpoint using intention-to-treat (ITT) data with the last-observation-carried forward method (LOCF).

a. Imputation strategy

The imputation method converts continuous to binary data such as number of responders using the mean total score of the rating scale (μ) and its standard deviation (SD) at endpoint. Alternatively, the mean change and its SD from baseline to endpoint can be used. The statistical model is based on an assumption of normality of the rating scale's scores. Based on that assumption, the percentage of patients P (response rate) with an endpoint or

change score under a theoretical raw threshold of response (x) can be easily calculated since it is the same as the sub-area under the normal curve left to x (see figure 1). It is widely known that the percentage (or probability) P is directly derived with the use of the standard normal Z-table after having calculated the z-score according to the formula:

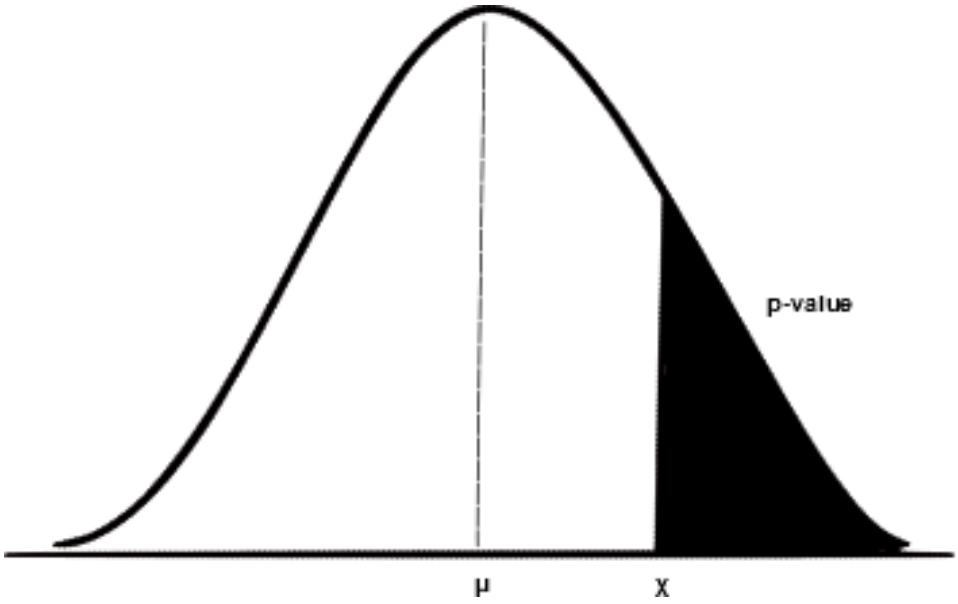
$$z - score = (x - \mu)/SD \quad (1)$$

Subsequently, in order to estimate the OR between groups 1 and 2, the below well-known formula was used:

$$OR = \frac{P1/(1-P1)}{P2/(1-P2)} \quad (2)$$

where $P1, P2$ are the response rates in groups 1 and 2 respectively.

Figure 1: The normal distribution



C. Cumulative Thesis

Methods

The theoretical response threshold x corresponds to the endpoint (or change) score that a patient with baseline score μ should at least have in order to be considered a responder (see below). It should be noted that, when the rating of single items is on 1-7 scale, any PANSS or BPRS mean score at baseline or endpoint should be reduced by 30 or 18 points respectively before being entered in the formulas (Leucht, Kissling et al. 2010, Obermeier, Mayr et al. 2010). For mean change scores, no subtraction is needed. Moreover, when the rating of single items is on 0-6 scale, no subtraction is needed for any PANSS/BPRS mean score (baseline, change, endpoint). The two cases of imputation, based on mean endpoint and mean change score, are presented, accompanied with examples, for better comprehension.

1. Based on mean endpoint scores

In schizophrenia trials, response is usually defined as a specific percentage reduction $a\%$ from baseline to endpoint score ($a\%$ is commonly 20%, 30%, 40% or 50%). When the mean endpoint score is used, the response threshold x corresponds to

$$(100\% - a\%) * baseline\ score$$

and the response rate equals to the probability derived from the Z table after having found the z-score. For example, let's assume that the response criterion of at least 20% reduction from baseline to endpoint is applied and the mean baseline value of the rating scale is 100 points (on PANSS, rating system 1-7) and the mean endpoint value is 85 with SD 15. Then, the approximate raw threshold of response would be

$(100\% - a\%) * baseline\ score = (100\% - 20\%) * (100 - 30) = 56$ points

The resultant z-score, based on formula (1) would be $(56 - (85 - 30))/15 = -0.0667$ corresponding to a probability of 52.7% derived from the Z-table (in other words 52.7% of the patients would have approximately an endpoint score lower than 56 which is the theoretical response threshold and could be considered responders).

2. Based on mean change scores

When the mean change score is used, the point x equals directly to $a\%$ of the baseline score. Thus, for a mean baseline value of 100, a mean change of -15 with SD 15 and the same response criterion of at least 20% reduction from baseline to endpoint, the approximate raw threshold of response would be

$-a\% * baseline\ score = 20\% * (100 - 30) = -14$ points

and the resultant z-score, based on formula (1) would be

$\frac{[-14-(-15)]}{15} = \frac{1}{15} = 0.0667$

corresponding to a probability of 52.7% derived from the Z-table (in other words 52.7% of the patients would have a mean reduction score higher than the defined raw cut-off; thus, they would be responders).

b. Assessment of the imputation method

To assess the performance of the imputation method, three criteria were applied: the concordance correlation coefficient by Lin (1989), the predictive accuracy by Euredit project (Chambers 2001) and the "limits of agreement" method by Bland and Altman (1986).

1. The **Concordance Correlation Coefficient (CCC)** by Lin (1989) is commonly used for the evaluation of agreement between two methods when the data are measured repeatedly (King, Chinchilli et al. 2007). The CCC is equivalent to the ANOVA Intraclass Correlation Coefficient (ICC), a general relative measurement of consistency and agreement (Shrout and Fleiss 1979), frequently used in the medical literature (Furukawa, Cipriani et al. 2005, Furukawa and Leucht 2011, da Costa, Rutjes et al. 2012). But, as ICC fails to incorporate the effect of the repeated measurements in the random error, CCC was applied in the primary analysis of the pooled cut-offs whereas ICC was applied in the subgroup analysis of each cut-off separately. The Correlation Coefficient ranges from -1 (perfect negative agreement) to 1 (perfect positive agreement). Nevertheless, its appropriateness has been contested, among other reasons, by the claim that it does not distinguish between random error and bias (Bland and Altman 1990, Rankin and Stokes 1998).

2. **Predictive accuracy** measures the maximal preservation of true values and implies other forms of accuracy such as ranking accuracy (maximal preservation of true ordering relationship), distributional accuracy (maximal preservation of distribution), estimation

accuracy (maximal preservation of analytic results and conclusions) and imputation plausibility. The Euredit project, an European Union sponsored project with the objective to develop tests for the validation of imputation methods (Chambers 2001), has identified predictive accuracy as a key parameter for assessing methods of imputation. Predictive accuracy is assessed by a regression approach which examines how close the imputed value ($\hat{Y}_i$) is to the true value (Y_i^*). A linear model of the form $Y_i^* = b \times \hat{Y}_i + \varepsilon$ is fitted to the imputed and true values, followed by testing whether the slope b equals to 1. If the t-test does not result in a significant difference, then the weighted regression mean square error (MSE) is calculated according to the below formula:

$$MSE = \frac{1}{n-1} \sum_{i=1}^{n} w_i \, (Y_i^* - b \times \hat{Y}_i)^2 \quad (3)$$

A good imputation method will have a non-significant p-value for the test of $b = 1$ as well as a low value of MSE. An additional regression-based measure is the coefficient of determination R^2 which is defined as the proportion of the variance in Y_i^* "explained" by the variation in $\hat{Y}_i$ (best result is 1).

3. In the **"limits of agreement" method** by Bland and Altman, the differences of imputed and observed values were plotted on the y-axis and their means on the x-axis, taking into account the repetition of measurements for each cut-off point (Bland and Altman 1986, Bland and Altman 1999). This plot allowed us to investigate any possible relationship between the error introduced by the imputation method and the true values and, unlike CCC, distinguished between random error and bias. Provided that the differences were

normally distributed, the agreement between the true and the imputed values could be considered reasonable if the 95% confidence interval of their difference was clinically acceptable.

C. Cumulative Thesis

Results

This section presents the main results obtained from the two projects, highlighting the scientific contributions of my thesis. Full length results including supplementary analyses and detailed information are presented in the published articles (see section VI).

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs

In the systematic review and meta-analysis on the efficacy of chlorpromazine versus any other antipsychotic in the treatment of schizophrenia, 128 mainly small (median sample size of 50 patients), randomized controlled trials with 10667 participants were included. The studies were published over a period of 55 years, from 1956 to 2011. Chlorpromazine was compared with 43 other antipsychotics. In the primary outcome, categorical response to treatment (dichotomous), chlorpromazine was found more efficacious than four antipsychotics (butaperazine, mepazine, oxypertine and reserpine) and less efficacious than other four antipsychotics (clomacran, clozapine, olanzapine and zotepine). In the outcome 'mean overall efficacy', measured by mean values in validated rating scales, chlorpromazine was found better than quetiapine and reserpine but worse than clozapine, levomepromazine, olanzapine, risperidone and zotepine. There were no statistically significant efficacy differences between chlorpromazine and the remaining antipsychotics. As for the all-cause discontinuation rates, clozapine and haloperidol groups were discontinued by fewer patients compared to chlorpromazine. Drop-outs because of adverse events were more in the zuclopenthixol group and fewer in the quetiapine group compared to chlorpromazine

whereas drop-outs because of inefficacy were more in the acetophenazine group and fewer in the clozapine and risperidone groups. Regarding the potential effect moderators, none was found significant apart from antipsychotic dose when chlorpromazine was compared with clozapine; higher chlorpromazine doses and chlorpromazine/clozapine ratios were associated with a more pronounced superiority of clozapine. Overall, the most important finding of the meta-analysis was that, due to the low numbers of participants, most comparisons were underpowered.

II. Imputation of response rates from means and standard deviations in schizophrenia

In the second part of my thesis, I examined the performance of the Furukawa et al. imputation method for dealing with missing dichotomous outcome data when conducting a meta-analysis. The performance was assessed in terms of response rates and odds ratios (ORs) separately using the three predefined criteria:

1. The **Concordance Correlation Coefficient (CCC)** for response rates in natural logarithms was 0.93 (CI: 0.91-0.95) for both scales (PANSS and BPRS) and all cut-offs (best value is 1). For ORs, again in natural logarithms, the CCC was 0.87 (CI: 0.77-0.93), demonstrating a strong association of the observed and imputed values.

2. For assessing **predictive accuracy**, a linear regression model was fitted to imputed and true response rates resulting in a regression coefficient of 1.24 (CI: 1.19-1.29) which was significantly different from 1 although the value R^2 was high (0.95). For

ORs, the linear regression model produced a regression coefficient of 1.25 (CI: 1.14-1.36) which was again significantly different from 1; the value R^2 was 0.86.

3. In the **"limits of agreement" method** (Bland and Altman 1999), the visual inspection of the Bland–Altman plot for response rates revealed that the direction and the quantity of the error introduced by the imputation method were related to the magnitude of response rates; when observed response rates were high, the imputation method underestimated the response rates and, vice versa, when the observed response rates were low, the imputation method overestimated them. Bland and Altman have argued that such a relationship produces artifactually wider limits of agreement than they should be (here the mean difference was 0.7% and the classical limits of agreement were −8.4% to 9.8%) and recommended a regression of the differences on their average in natural logarithms. In our case, this technique produced non-parallel, linear regression lines as limits of agreement since the SD of differences was not reasonably constant over the mean response rates. The mean difference in log scale was 0.02 ± 0.09 and the regression based 95% limits of agreement were: upper limit $= -0.07 - 0.18 \times log(P_{Im} \times P_{Ob})$ to lower limit $= -0.27 - 0.06 \times log(P_{Im} \times P_{Ob})$ where P_{Im} and P_{Ob} represent the imputed and observed percentage of responders (responder rate) respectively. After back transformation of the logarithmic values, the analysis showed that the average imputed values could differ from the observed ones by 1.05 times.

C. Cumulative Thesis

Results

For ORs, the same relationship between the direction and the quantity of the error introduced by the imputation method and the magnitude of ORs in the Bland–Altman plot was observed; when the observed ORs were larger than 1, the imputation method tended to underestimate the ORs, whereas, when the observed ORs were lower than 1, the imputation method tended to overestimate them, leading to conservative estimates regarding the efficacy comparison of two interventions. In addition, the plot suggested that the imputation method performed better when the observed differences between treatment effects were not large resulting in log OR around 0 (meaning OR around 1). According to the classical limits of agreement approach (without addressing the above relationship between the differences and the magnitude of log ORs by applying a regression model), the log transformed data produced a mean difference of −0.06 and limits of agreement of −0.35 to 0.24, which by back-transformation provided a geometric mean ratio of 0.94 with limits of agreement of 0.71 to 1.27. When the regression approach was applied, two parallel linear regression lines were produced as limits of agreement, the mean difference in log scale was -0.06 ± 0.12 and the regression based 95% limits of agreement were: lower limit $= -0.25 - 0.15 \times log(OR_{Im} \times POR_{Ob})$ and upper limit $= -0.22 - 0.15 \times log(OR_{Im} \times OR_{Ob})$ where OR_{Im} and POR_{Ob} represent the imputed and observed odds ratio respectively. After back-transformation of the logarithmic values, the average imputed values could differ from the observed ones by 0.93 times.

C. Cumulative Thesis

Discussion and conclusions

I. Chlorpromazine versus every other antipsychotic for schizophrenia: a systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs

The dogma that all antipsychotic drugs are equally efficacious originated from old, narrative reviews on first generation antipsychotics. In the first part of the present thesis, this dogma was addressed by conducting a systematic review and meta-analysis of 128 RCTs with 10667 participants comparing chlorpromazine versus any other antipsychotic ever marketed. Eleven comparisons presented statistically significant efficacy difference from chlorpromazine. All comparisons except the one versus quetiapine were underpowered, not reaching the benchmark of 1000 included participants suggested by Trikalinos (Trikalinos, Churchill et al. 2004). According to Trikalinos, the results of a meta-analysis in psychiatry are not robust if less than 1000 participants have been included since the publication of new trials could still change the effect sizes considerably.

Butaperazine, mepazine, oxypertine, quetiapine and reserpine were found less efficacious than chlorpromazine but the comparisons of chlorpromazine with the first three drugs were based on few patients (20-100) making any conclusion uncertain. Nevertheless, evidence that butaperazine, mepazine and oxypertine may be less effective than other FGAs were presented as early as in the 1960s (Rajotte, Bordeleau et al. 1965, Klein and Davis 1969). The comparison of chlorpromazine versus quetiapine had a better sample size (1092 patients) and the provided result was consistent with a previous meta-analysis that found lower efficacy of quetiapine compared to other FGAs on positive symptoms (Leucht, Corves et al. 2009). As for reserpine, it is rarely used nowadays, mainly because of its side effects,

although it has been suggested as an option in treatment-refractory schizophrenia (Christison, Kirch et al. 1991).

Clomacran, clozapine, levomepromazine, olanzapine, risperidone and zotepine were found more efficacious than chlorpromazine. The comparisons with clomacran, levomepromazine and risperidone were underpowered (20-100 participants). Clomacran was marketed only in the UK and was withdrawn after 60 months of use (1982) because of serious hepatotoxicity (Abraham and Davis 2005). Levomepromazine (also called methotrimeprazine) was found significantly more efficacious than chlorpromazine but the results were based on only one study in treatment-resistant patients (Lal, Thavundayil et al. 2006). Similarly, the superiority of risperidone was based on only one study but risperidone has already been found more efficacious than typical antipsychotics (Hunter, Joy et al. 2003) and chlorpromazine (Leucht, Cipriani et al. 2013). The comparisons versus clozapine, olanzapine and zotepine had better sample sizes (824, 194 and 218 participants respectively). According to our subgroup analysis, clozapine was more efficacious for both treatment-resistant and non-treatment-resistant patients, a consistent result to a recent network meta-analysis (Leucht, Cipriani et al. 2013). Results for olanzapine were also concordant with the same network meta-analysis (Leucht, Cipriani et al. 2013), the results of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) (Lieberman, Stroup et al. 2005) and a previous pooled analysis of 4 open label studies (Dossenbach, Treuer et al. 2007). Finally, zotepine, which is used in Japan and Europe (Green 2009), but still not in the USA, was found more effective than chlorpromazine; nevertheless, our results were based on two studies (Nishizono 1994, Cooper, Tweed et al. 2000), weakening the body of evidence. Regarding the comparisons that demonstrated no significant differences, the number of included studies and the sample

sizes were also limited (only loxapine reached Trikalinos' threshold), making most results inconclusive.

The small sample sizes were not the only limitation of our meta-analysis. Most of the included studies were old, lacking of modern standards and presenting high level of bias in all domains. Methods of randomization and allocation concealment were inadequately described and completer case data (CC) instead of ITT were usually presented, corrupting randomization, although a recent study found no significant difference in the results from ITT and CC data (Bohnke and Lutz 2012). The blinding procedures, outcomes and dropouts were also poorly reported. Despite having a priori defined response as a reduction of at least 50% in PANSS or BPRS, no study used that definition. In most of the cases, the response criterion of "much improved" in CGI-Improvement scale was applied or, when not available, authors' definition of response. However, Furukawa and Leucht have showed that the application of different response criteria does not lead to significant meta-analytical differences as long as relative risks or odds ratios are used as measures of the effect size (Leucht, Davis et al. 2007, Furukawa, Akechi et al. 2011). Many RCTs were so poorly reported, that no outcome could be used, leading to exclusion from our analysis. Finally, despite efforts to contact the first authors of all included studies, few responses were obtained, mainly because of the age of the publications.

Conclusively, despite the large total number of trials and patients, the number of patients per comparison was so small that no definite answers could be drawn, highlighting the importance of including as much available information as possible, even by imputing data, when a meta-analysis is conducted.

C. Cumulative Thesis

Discussion and conclusions

II. Imputation of response rates from means and standard deviations in schizophrenia

In the second part of my thesis, I addressed the aforementioned limitation when conducting a meta-analysis: missing outcome data. When full data sets of single trials are provided, meta-analysis can be performed using established techniques. However, single trials investigating treatments in schizophrenia usually report their results as means of symptom scales such as PANSS and BPRS, leading to exclusion of these trials from the meta-analysis of response (binary) data. Unfortunately, up to date, imputation methods for missing binary data are limited.

Suissa (1991) was the first who attempted to estimate the risk of an event from means and standard deviations based on an assumption of normal distribution of the outcome values. His objective was not to provide an imputation method for missing binary data but to avoid dichotomization of the continuous outcomes. Furukawa et al. (2005) used the same assumption of normal distribution and proposed an imputation method for depression and anxiety trials. Apart from Suissa's and Furukawa's methods, there are only three available conversion methods by Cox and Snell (1989), Hasselblad and Hedges (1995) and Kraemer and Kupfer (2006). Cox and Snell's method and Hasselblad and Hedges' method allow the direct conversion of SMDs into odds ratios (Cox and Snell 1989, Hasselblad and Hedges 1995) whereas Kraemer and Kupfer's method allows the direct conversion of SMDs into risk differences (Kraemer and Kupfer 2006). Practically, these methods are less useful than Furukawa's one since meta-analytic software such as the Cochrane Collaboration's RevMan (Centre 2012) do not allow entering odds ratios directly.

C. Cumulative Thesis

Discussion and conclusions

The performance of Furukawa's imputation method in schizophrenia trials was examined. Our results showed that the imputed values re-captured reasonably the original properties of the observed (true) values providing a simple and practical imputation method of missing binary data in schizophrenic trials. However, the method tended to introduce bias in the direction of overestimation for low values and underestimation for high values leading to conservative estimates when two interventions were compared. The imputation method performed better for medium degrees of percentage response, but was biased in very high and very low response rates. Therefore, it is suggested that meta-analyses applying the method should also perform a sensitivity analysis excluding the imputed values.

The main strength of my second study was its empirical design; I used a large, empirical dataset of individual patient data to examine the performance of the imputation method. Most of the earlier studies assessing imputation methods had used simulated data, thus have been depended on inherently untestable assumptions (Horton, White et al. 2010). We assumed a normal distribution of the continuous outcome measure which indeed is the case for all four measures from the PANSS (composite, positive, negative and general psychopathology scales) according to the American (Kay, Fiszbein et al. 1987) and the Swedish standardization of that scale (von Knorring and Lindstrom 1992) as well as the Greek version of PANSS and the results of one Spanish trial (Peralta and Cuesta 1994).

However, it is not possible to draw definite conclusions on the appropriateness of one imputation method under all circumstances. Several factors affect the performance of different imputation approaches in meta-analysis including the sample size, the proportion of

data imputed and the distribution of the outcome measure (Anzures-Cabrera, Sarpatwari et al.). When a meta-analysis attempts to account for missing data, a sensitivity analysis should always accompany it.

C. Cumulative Thesis

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C. Cumulative Thesis

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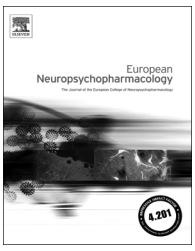

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Chlorpromazine versus every other antipsychotic for schizophrenia: A systematic review and meta-analysis challenging the dogma of equal efficacy of antipsychotic drugs

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Abstract
It is one of the major psychiatric dogmas that the efficacy of all antipsychotic drugs is same. This statement originated from old, narrative reviews on first-generation antipsychotics, but this old literature has never been meta-analysed. We therefore conducted a meta-analysis of randomised controlled trials on the efficacy of chlorpromazine versus any other antipsychotic in the treatment of schizophrenia. If the benchmark drug chlorpromazine were significantly more or less effective than other antipsychotics, the notion of equal efficacy would have to be rejected. We searched the Cochrane Schizophrenia Group's specialized register, MEDLINE, EMBASE, PsychInfo and reference lists of relevant articles. The primary outcome was response to treatment. We also analyzed mean values of schizophrenia rating scales at endpoint and drop-out rates. 128, mostly small, RCTs with 10667 participants were included. Chlorpromazine was compared with 43 other antipsychotics and was more efficacious than four (butaperazine, mepazine, oxypertine and reserpine) and less efficacious than other four antipsychotics (clomacran, clozapine, olanzapine and zotepine) in the primary outcome. There were no statistically significant efficacy differences between chlorpromazine and the remaining 28 antipsychotics. The most important finding was that, due to low numbers of participants (median 50, range 8–692), most comparisons were underpowered. Thus we infer that the old

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antipsychotic drug literature was inconclusive and the claim for equal efficacy of antipsychotics was never evidence-based. Recent meta-analyses on second-generation antipsychotics were in a better position to address this question and small, but consistent differences between drugs were found.

1. Introduction

Despite more than four decades of research one of the major questions of psychopharmacology remains unanswered: do antipsychotic drugs differ in efficacy? The dogma of equal efficacy of antipsychotic drugs probably goes back to an influential narrative review by Klein and Davis who in 1969 found no efficacy differences between the predominantly phenothiazine-based antipsychotics available at that time (Klein and Davis, 1969). This dogma of equal efficacy has been since then codified in numerous textbooks (Buchanan and Carpenter, 2000; Davis et al., 1989; Stahl, 2000) and guidelines which make statements such as "comparable efficacy… among the different first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs)" (PORT Psychopharmacological Treatment Recommendations and Summary Statements) (Buchanan et al., 2010) or "with the possible exception of clozapine … antipsychotics have similar efficacy" (APA Practice Guidelines) (Lehman et al., 2004). However, apart from a methodologically insufficient 'vote count' approach in 1989 (Davis et al., 1989), the question on efficacy differences between first-generation ("typical") antipsychotics has never again been systematically addressed. The dogma has been challenged by meta-analyses which consistently found small, but robust efficacy superiorities of some SGAs compared to some FGAs and other SGAs (Davis et al., 2003; Kishimoto et al., 2013; Leucht et al., 2009, 2003; Zhang et al., 2012). These meta-analyses (Leucht et al., 2013, 2009) and the effectiveness studies CATIE (Lieberman et al., 2005b; McEvoy et al., 2006; Stroup et al., 2006) and CUtLASS (Jones et al., 2006; Lewis et al., 2006) have questioned the classification into 'typical' and 'atypical' antipsychotics and pointed out to the fact that older drugs should not just be abandoned. But the older literature on first-generation antipsychotics – on which the dogma of equal efficacy was originally based – has never been summarised by a systematic review and meta-analysis.

Chlorpromazine, together with haloperidol and fluphenazine depot, are the only antipsychotics listed as "essential drugs" by the World Health Organisation (WHO), (2011). Since chlorpromazine was the first antipsychotic drug developed, it has served as a benchmark for many other compounds. We, therefore, conducted a systematic review comparing the efficacy of chlorpromazine with every other antipsychotic drug, following the general approach of a pivotal Cochrane review comparing the benchmark antidepressant amitriptyline with all other antidepressants (Guaiana et al., 2007). If chlorpromazine were shown to be more or less effective than other antipsychotics, the long-standing dogma of equal eficacy would have to be rejected. As "equal efficacy of all antipsychotics" is one of the major dicta in psychopharmacology, we found it important to systematically address its origin, i.e. the old literature on first-generation antipsychotics, but we also decided to include comparisons with second-generation antipsychotics for completeness.

2. Experimental procedures

2.1. Inclusion criteria

We included all randomised controlled trials that compared oral formulations of chlorpromazine with any other oral antipsychotic for the treatment of schizophrenia or related disorders (schizoaffective, schizophreniform, or delusional disorder, irrespective of the diagnostic criterion used). We did not include trials of intramuscular chlorpromazine as it is mainly used for short-term sedation. Quasi-randomised studies (e.g. randomised by the day of the week) and studies in which allocation was clearly not concealed (e.g. alternate allocation) were excluded (Higgins and Green, 2011). We excluded Chinese studies to avoid a systematic bias as many of them do not use appropriate randomization procedures and do not report their methods (Bian et al., 2006; Wu et al., 2006). Moreover, we found in another meta-analysis that Chinese studies tended to overestimate differences between FGAs and SGAs (Leucht et al., 2009). The quality of all included studies was independently assessed by two out of three reviewers (MS, HC, and BH) using the Cochrane Collaboration's risk of bias tool (Higgins and Green, 2011). No restrictions in terms of age, gender, chronicity of illness, duration of trial and dose range were applied.

2.2. Search

The Cochrane Schizophrenia Group's Register was searched up to August 2009 using the term "chlorpromazin*" (later versions of the register were not available to us). The Schizophrenia Group's Register is compiled by regular systematic searches of more than 15 databases, clinical trial registers, hand searches and conference proceedings. We also searched MEDLINE, EMBASE, PsychInfo and Cochrane Central Register of Controlled Trials up to June 2013 using the term "chlorpromazin* AND schizophrenia". RCTs comparing chlorpromazine with second-generation antipsychotics were also identified through the comprehensive searches made for a recent network meta-analysis of our group (Leucht et al., 2013). Moreover, we inspected the reference lists of included studies and of other reviews on chlorpromazine (Adams et al., 2007; Ahmed et al., 2010; Leucht et al., 2008). No language restriction was applied apart from excluding Chinese trials (Egger et al., 1997b; Gregoire et al., 1995; Moher et al., 1996, 2000).

2.3. Data extraction and outcome variables

At least two of the following three reviewers (MS, HC, BH) independently extracted data from each trial on standard forms. We contacted pharmaceutical companies producing chlorpromazine

(SanofiAventis, GlaxoSmithKline, Bayer) and sent our data extraction forms to first authors of each included study with a request for missing information and a possibility for corrections. The primary outcome was response to treatment, a priori defined in our protocol as at least 50% reduction of rating scales such as the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) or at least "much improved" on the Clinical Global Impressions Scale (CGI) (Guy, 1976) because these cut-offs have been demonstrated to be clinically meaningful (Leucht and Engel, 2006; Leucht et al., 2012, 2005; Levine et al., 2008), but as these were rarely indicated, we often used the authors' definitions which is appropriate as long as relative risks or odds ratios are the effect size measures (Furukawa et al., 2011). We also analysed the mean overall change in symptom rating scales, based on the following hierarchy: change in PANSS total score, change in BPRS total score, values of these scales at study endpoint, and then, if any of the previous measures were not available, other scales for overall schizophrenic symptomatology as long as the instrument had been published in a peer-reviewed journal, because unpublished rating scales tend to overestimate differences (Marshall et al., 2000). Intention-to-treat (ITT) datasets were used whenever available. Other outcomes were dropout due to any reason, due to inefficacy and due to adverse events.

2.4. Meta-analytic calculations

The primary effect size measure for dichotomous outcomes was the relative risk (RR) with corresponding 95% confidence intervals. The advantage of the RR is that it can be understood more intuitively than odds ratios. They are often interpreted as relative risks leading to an overestimation of treatment effects (Davies et al., 1998). We also calculated numbers-needed to treat (NNT) or numbers-needed to harm (NNH) as reciprocals of absolute risk differences. As we expected considerable heterogeneity between studies, we applied the DerSimonian and Laird random-effects model throughout (DerSimonian and Laird, 1986). In a sensitivity analysis of the primary outcome we examined whether a fixed effects model would lead to substantial differences. The effect size for continuous data was the standardised mean difference expressed as Hedges' adjusted g. Standard inverse of the variance weighting was used for pooling the studies. Unreported SD values were calculated from other statistics or from the average of the other studies. The degree of heterogeneity was estimated by the I^2 statistics (Higgins and Green, 2011) (I^2 values $>50\%$ reflecting considerable heterogeneity), and a chi-square test of homogeneity (α set at $p<0.1$). The following a priori defined potential reasons for heterogeneity were explored with meta-regression and subgroup analyses: chlorpromazine dose, age, first episode of schizophrenia and whether or not the patients had treatment-resistant schizophrenia (as defined by the original studies). RCTs which were open, single-blind, or where blinding was unclear were excluded in a sensitivity analysis. We assessed publication bias with funnel plots, Egger's regression test (Egger et al., 1997a) and the Trim and Fill method (Duval and Tweedie, 2000). As funnel-plots are based on symmetry, they can only detect publication bias when a reasonable number of studies are available. We defined this as a minimum of ten (Higgins and Green, 2011). Meta-analytic calculations were done with RevMan 5.2 (Centre, 2012), Comprehensive Meta-Analysis version 2 (Borenstein et al., 2005) and STATA 12 (StataCorp, 2011). Two-sided α test was set at 0·05 level.

The a priori written study protocol has been published in the PROSPERO database (Registration no. CRD42012002084, also see Supplement, e-Initial protocol). We post-hoc decided to include comparisons of chlorpromazine with second-generation antipsychotics (and not only with first-generation antipsychotics) to be comprehensive, and to exclude Chinese studies for the reasons explained above. Moreover, as meta-analyses can be considered to be descriptive rather than confirmatory, we had originally not planned to adjust for multiple testing, but we post-hoc applied a Bonferroni correction (Bland and Altman, 1995) to see how much this changed the primary outcome in a sensitivity analysis.

3. Results

3.1. Search

We identified 128 randomized trials (179 publications) which met our inclusion criteria. Fig. 1 presents the PRISMA flow diagram (Moher et al., 2009) of the search.

3.2. Description of included studies

eTable 1 in the Supplement presents important characteristics of individual trials. The studies were published over a period of 55 years from 1956 to 2011 and had a median

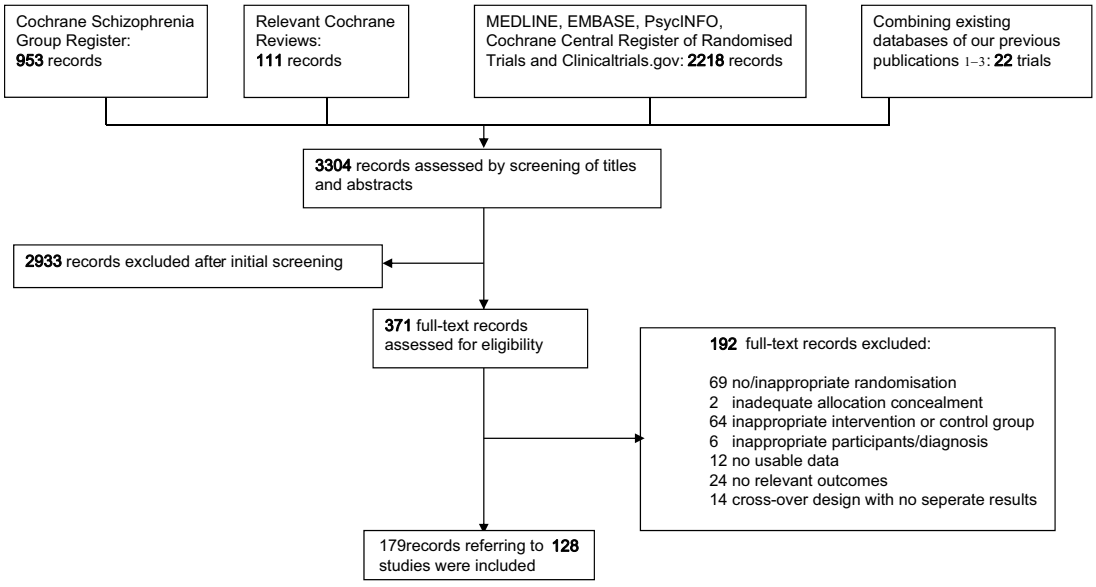

Fig. 1 Study flow diagram (PRISMA). Searches for chlorpromazine versus all other antipsychotics in schizophrenia.

sample size of 50 (range 8–692) per study. 101 (78.9%) studies lasted 12 weeks or less; 14 (10.9%) lasted up to 6 months; 11 (8.6%) were longer than 6 months; and 2 studies (0.02%) had unclear duration. Chlorpromazine was compared with 43 other antipsychotics. Clozapine was the comparator drug in 12 randomised controlled trials (RCTs), loxapine and thioridazine in 9, clomacran and trifluoperazine in 7, fluphenazine, haloperidol, pimozide and trifluprom azine in 6, promazine and reserpine in 5, mesoridazine, olanzapine, oxypertine, piperacetazine, prochlorperazine, quetiapine, sulpiride and thiothixene in 4, levomepromazine/methotrimeprazine, mepazine, metiapine, penfluridol, perphenazine and trifluperidol in 3, benzquinamide, butaperazine, clopenthixol, clotiapine, lenperone, molindone, periciazine, risperidone, thiopropazate and zotepine in 2, and all other drugs (acetophenazine, acetylpromazine, bromperidol, carperone, carphenazine, chlorprothixene, ziprasidone and zuclopenthixol) in one each. The mean/median doses in the chlorpromazine group ranged between 50 and 2000 mg, with a median of 525 mg (for doses of the comparator groups please see the table of included studies). Mean participants' age was 37.5 (SD 7.2) years and mean duration of illness was 12.5 (SD 7.6) years. One study included only first episode patients (Lieberman et al., 2003), one study antipsychotic naïve patients (Simon et al., 1958) and 19 studies treatment resistant patients (Amin et al., 1977; AstraZeneca, 2000, 2005; Bratfos and Haug, 1979; Conley et al., 1998; Fleming et al., 1959; Geller et al., 2005; Hamilton et al., 1960; Hong et al., 1997; Honigfeld et al., 1984; Howanitz et al., 1999; Kane et al., 1988, 2006; Lal et al., 2006; McCreadie and MacDonald, 1977; Mercer et al., 1997; Neal et al., 1969; Toru et al., 1972; Wilson et al., 1961).

3.3. Risk of bias assessment

Seven studies reported adequate randomisation methods and 22 adequate allocation concealment. 16 studies were implied randomisation as they were double-blind. The rest of the studies were said to be randomised without a description of methods. 112 studies were double-blind out of which 23 confirmed the success of blinding in terms of both performance and detection. 4 RCTs were only rater blind, 2 were stated as single blind and 4 were open label, whereas the degree of blinding remained unclear in the remaining 6 studies. Approximately half of the trials (63 out of 128) adequately addressed incomplete outcome data. Selective reporting was a source of bias in that many studies did not present means or standard deviations for rating scale outcomes. Sources of other bias in a few trials were baseline imbalance, replacement of dropouts during the trial, use of chlorpromazine or ECT as rescue treatment and no predetermined trial duration (see eFig. 1 in the Supplement).

3.4. Response to treatment (primary outcome)

Fig. 2 presents mean RRs and eFig. 2 (in the Supplement) presents the RRs of the individual studies (77 comparisons, 5897 patients). Chlorpromazine was significantly more efficacious than four antipsychotic drugs (butaperazine: number of RCTs $N=1$, number of participants $n=20$, RR 2.25, 95% CI 1.02–4.94, NNT 2, 95% CI 1–7; mepazine: $N=1$, $n=100$, RR 2.88, 95% CI 1.42–5.80, NNT 3, 95% CI 2–8; oxypertine: $N=2$, $n=80$, RR 1.73, 95% CI 1.07–2.79, NNT 5,

Comparator	N of studies	Chlorpromazine Total	Comparator Total	Risk Ratio M-H, Random, 95% CI	p-value
Acetylpromazine	1	14	11	1.96 [0.47, 8.27]	0.36
Benzquinamide	1	10	10	7.00 [0.41, 120.16]	0.18
Bromperidol	1	20	20	0.75 [0.19, 2.93]	0.68
Butaperazine	**1**	10	10	2.25 [1.02, 4.94]	**0.04**
Clomacran	**3**	44	45	0.64 [0.43, 0.95]	**0.03**
Clopenthixol	2	35	35	1.21 [0.78, 1.89]	0.39
Clotiapine	1	41	43	1.51 [0.73, 3.16]	0.27
Clozapine	**7**	421	403	0.60 [0.40, 0.91]	**0.02**
Fluphenazine	1	23	20	0.94 [0.59, 1.48]	0.78
Haloperidol	5	108	112	0.74 [0.47, 1.18]	0.21
Lenperone	2	30	33	1.07 [0.64, 1.79]	0.81
Levomepromazine	2	33	27	0.77 [0.44, 1.35]	0.36
Loxapine	8	195	194	0.94 [0.73, 1.20]	0.60
Mepazine	**1**	50	50	2.88 [1.42, 5.80]	**0.003**
Mesoridazine	2	57	57	0.88 [0.57, 1.37]	0.58
Metiapine	2	68	69	1.11 [0.82, 1.50]	0.50
Molindone	1	15	15	1.00 [0.24, 4.18]	1.00
Olanzapine	**4**	78	116	0.19 [0.06, 0.60]	**0.005**
Oxypertine	**2**	39	41	1.73 [1.07, 2.79]	**0.03**
Penfluridol	1	28	28	1.09 [0.88, 1.35]	0.45
Periciazine	1	21	21	5.00 [0.25, 98.27]	0.29
Pimozide	5	115	115	0.87 [0.64, 1.19]	0.38
Piperacetazine	1	13	13	2.00 [0.21, 19.44]	0.55
Promazine	1	14	10	1.19 [0.37, 3.87]	0.77
Quetiapine	4	543	549	0.95 [0.74, 1.20]	0.66
Reserpine	**3**	218	218	1.90 [1.43, 2.52]	**<0.00001**
Risperidone	1	12	15	2.92 [0.95, 8.93]	0.06
Sulpiride	3	102	95	0.77 [0.47, 1.27]	0.31
Thioridazine	4	82	85	0.92 [0.59, 1.43]	0.70
Thiothixene	2	50	49	0.94 [0.67, 1.33]	0.73
Trifluoperazine	3	56	56	1.24 [0.51, 3.03]	0.64
Trifluperidol	3	55	56	0.68 [0.38, 1.23]	0.20
Triflupromazine	2	29	29	1.22 [0.70, 2.15]	0.48
Ziprasidone	1	154	152	0.79 [0.53, 1.18]	0.26
Zotepine	**2**	105	113	0.64 [0.47, 0.87]	**0.004**
Zuclopenthixol	1	44	50	1.08 [0.93, 1.26]	0.31

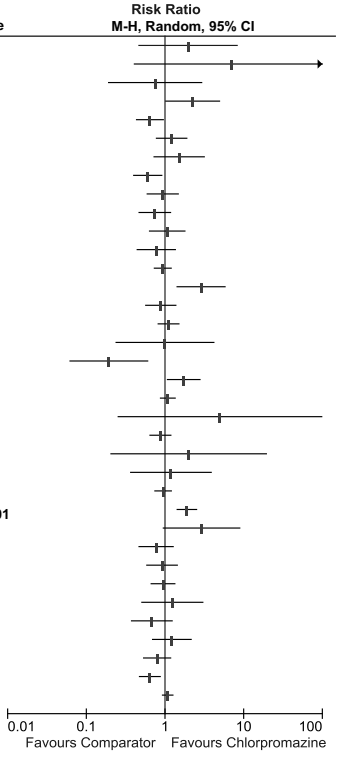

Fig. 2 Response ratio (primary outcome) of chlorpromazine versus all other antipsychotic drugs (effect sizes of the individual trials are shown in eFig. 2 in the Supplement). N=number, M-H=Maentel-Haenszel, CI=Confidence interval.

95% CI 3–27; and reserpine: $N=3$, $n=436$, RR 1.90, 95% CI 1.43–2.52, NNT 5, 95% CI 3–8). Chlorpromazine was significantly less efficacious than four antipsychotic drugs (clomacran: $N=3$, $n=89$, RR 0.64, 95% CI 0.43–0.95, NNH 5, 95% CI 2–26, clozapine: $N=7$, $n=824$, RR 0.60, 95% CI 0.40–0.91, NNH 5, 95% CI 3–10, olanzapine: $N=4$, $n=194$, RR 0.19, 95% CI 0.06–0.60, NNH 4, 95% CI 2–50, zotepine: $N=2$, $n=218$, RR 0.64, 95% CI 0.47–0.87, NNH 6, 95% CI 2 to ∞ to NNT 18). There were no statistically significant differences between chlorpromazine and the remaining 28 antipsychotics. After Bonferroni correction, only reserpine remained statistically less efficacious than chlorpromazine. The sensitivity analysis excluding single blind and open label studies as well as studies with unclear level of blindness confirmed the differences of chlorpromazine compared to butaperazine, clomacran, clozapine and zotepine. For mepazine no studies were available, whereas for olanzapine, oxypertine and reserpine, with one study remaining in each comparison, no result was significant. The sensitivity analysis with a fixed effects model did not substantially change the results (results of sensitivity analyses can be obtained from the authors upon request).

3.5. Mean overall efficacy

Fewer RCTs (59 comparisons, 4538 patients) presented usable mean values of rating scales than dichotomous responder data. Here, quetiapine and reserpine were significantly less efficacious than chlorpromazine (quetiapine: $N=4$, $n=989$, SMD -0.17, 95% CI -0.32 to -0.02, reserpine: $N=1$, $n=40$, SMD -0.84, 95% CI -1.49 to -0.19), whereas clozapine, levomepromazine, olanzapine, risperidone and zotepine were significantly more efficacious than chlorpromazine (clozapine: $N=10$, $n=778$, SMD 0.47, 95% CI 0.15 to 0.78, levomepromazine: $N=1$, $n=38$, SMD 0.69, 95% CI 0.03 to 1.34, olanzapine: $N=4$, $n=191$, SMD 0.80, 95% CI 0.11 to 1.49, risperidone: $N=1$, $n=100$, SMD 0.95, 95% CI 0.54 to 1.37, zotepine: $N=1$, $n=105$, SMD 0.73, 95% CI 0.33 to 1.12) (see Fig. 3 and eFig. 3 in the Supplement).

3.6. Drop-out rates

There was no statistically significant difference between chlorpromazine and any other antipsychotic in terms of all-cause discontinuation, except for clozapine and haloperidol which were discontinued by fewer participants (clozapine: $N=10$, $n=1046$, RR 1.34, 95% CI 1.08–1.67, haloperidol: $N=5$, $n=157$, RR 6.12, 95% CI 1.16–32.38) (see Fig. 4 and eFig. 4 in the Supplement). Significantly more participants in the zuclopenthixol group and fewer in the quetiapine group than in the chlorpromazine group dropped out due to adverse events. More participants in the acetophenazine group and fewer in the clozapine and risperidone groups dropped out due to inefficacy (see eFigs. 5 and 6 in the Supplement).

3.7. Sub-group and meta-regression analyses

There were no statistically significant effects of any potential effect moderators except when chlorpromazine was compared with clozapine (see eSubgroup and meta-regression analyses in the Supplement). Higher chlorpromazine doses or chlorpromazine/clozapine ratios were associated with a more pronounced superiority of clozapine (see eFig. 7 in the Supplement). This was probably explained by the use of higher chlorpromazine doses (but not clozapine doses) in studies including treatment resistant patients which also corroborated the increased superiority of clozapine. Nevertheless, clozapine was also more efficacious than chlorpromazine in non-refractory participants.

Comparator	N of studies	Chlorpromazine Total	Comparator Total	Std. Mean Difference IV, Random, 95% CI	p-value
Bromperidol	1	20	20	-0.38 [-1.00, 0.25]	0.24
Butaperazine	1	7	7	-0.49 [-1.56, 0.58]	0.37
Clomacran	2	68	60	-0.21 [-0.56, 0.14]	0.24
Clopenthixol	2	32	35	-0.18 [-0.67, 0.30]	0.45
Clotiapine	1	12	19	0.75 [-0.00, 1.50]	0.05
Clozapine	**10**	391	387	0.47 [0.15, 0.78]	**0.004**
Fluphenazine	1	20	18	-0.25 [-0.89, 0.39]	0.45
Haloperidol	2	19	24	0.57 [-1.16, 2.31]	0.52
Lenperone	1	10	10	-0.37 [-1.26, 0.52]	0.41
Levomepromazine	**1**	19	19	0.69 [0.03, 1.34]	**0.04**
Loxapine	6	130	127	-0.14 [-0.58, 0.30]	0.54
Mesoridazine	3	64	65	-0.00 [-0.35, 0.34]	0.98
Metiapine	2	68	69	0.06 [-0.27, 0.40]	0.71
Molindone	2	35	39	-0.06 [-0.52, 0.39]	0.79
Olanzapine	**4**	75	116	0.80 [0.11, 1.49]	**0.02**
Oxypertine	2	23	27	-0.55 [-1.45, 0.34]	0.23
Penfluridol	2	24	25	0.02 [-0.54, 0.58]	0.93
Pimozide	3	44	47	-0.06 [-0.77, 0.65]	0.87
Promazine	1	170	171	-0.21 [-0.43, -0.00]	0.05
Quetiapine	**4**	492	497	-0.17 [-0.32, -0.02]	**0.02**
Reserpine	**1**	20	20	-0.84 [-1.49, -0.19]	**0.01**
Risperidone	**1**	50	50	0.95 [0.54, 1.37]	**<0.00001**
Sulpiride	3	82	89	0.37 [0.07, 0.68]	0.02
Thioridazine	2	91	90	-0.04 [-0.33, 0.25]	0.79
Thiothixene	1	23	24	-0.18 [-0.75, 0.39]	0.54
Ziprasidone	1	154	152	0.11 [-0.12, 0.33]	0.36
Zotepine	**1**	52	53	0.73 [0.33, 1.12]	**0.0003**
Zuclopenthixol	1	38	45	-0.02 [-0.45, 0.41]	0.93

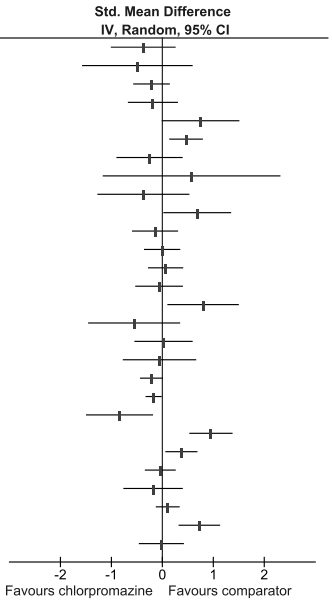

Fig. 3 Mean overall efficacy of chlorpromazine versus all other antipsychotic drugs (effect sizes of the individual trials are shown in eFig. 3 in the Supplement). N=number, Std.=Standardised, IV=Inverse variance, CI=Confidence interval.

Comparator	N of studies	Chlorpromazine Total	Comparator Total	Risk Ratio M-H, Random, 95% CI	p-value
Acetophenazine	1	160	164	0.74 [0.45, 1.20]	0.22
Benzquinamide	2	16	16	0.23 [0.05, 1.16]	0.07
Bromperidol	1	20	20	2.00 [0.20, 20.33]	0.56
Butaperazine	2	33	33	1.71 [0.48, 6.17]	0.41
Carperone	1	15	15	1.00 [0.42, 2.40]	1.00
Carphenazine	1	108	108	1.40 [0.65, 3.01]	0.39
Chlorprothixene	1	86	87	1.10 [0.90, 1.34]	0.35
Clomacran	2	38	40	1.86 [0.39, 8.89]	0.44
Clopenthixol	2	35	35	4.82 [0.88, 26.32]	0.07
Clotiapine	2	61	64	2.43 [0.83, 7.16]	0.11
Clozapine	**10**	535	511	1.34 [1.08, 1.67]	**0.007**
Fluphenazine	6	535	539	1.05 [0.88, 1.24]	0.60
Haloperidol	**5**	78	79	6.12 [1.16, 32.38]	**0.03**
Lenperone	2	30	33	0.70 [0.30, 1.66]	0.42
Levomepromazine	2	33	33	1.72 [0.54, 5.49]	0.36
Loxapine	7	173	168	0.97 [0.73, 1.28]	0.82
Mepazine	3	88	89	0.99 [0.81, 1.23]	0.96
Mesoridazine	4	97	97	3.92 [0.45, 34.46]	0.22
Metiapine	2	35	35	0.90 [0.43, 1.90]	0.78
Molindone	1	15	15	5.00 [0.26, 96.13]	0.29
Olanzapine	4	78	116	1.39 [0.52, 3.71]	0.51
Oxypertine	4	79	81	0.97 [0.45, 2.09]	0.93
Penfluridol	3	67	63	1.14 [0.80, 1.64]	0.47
Periciazine	1	15	15	5.00 [0.66, 37.85]	0.12
Perphenazine	3	90	94	0.90 [0.74, 1.10]	0.30
Pimozide	6	135	135	1.32 [0.80, 2.17]	0.28
Piperacetazine	4	49	48	1.68 [0.74, 3.80]	0.21
Prochlorperazine	4	92	91	1.16 [0.89, 1.51]	0.27
Promazine	3	116	108	1.07 [0.86, 1.35]	0.54
Quetiapine	4	543	549	1.12 [0.93, 1.36]	0.22
Reserpine	4	124	126	1.17 [0.74, 1.85]	0.50
Risperidone	1	12	15	0.63 [0.06, 6.09]	0.69
Sulpiride	3	92	98	1.07 [0.52, 2.17]	0.86
Thiopropazate	2	70	71	0.74 [0.44, 1.24]	0.26
Thioridazine	9	512	515	1.08 [0.91, 1.27]	0.39
Thiothixene	3	40	42	1.16 [0.64, 2.10]	0.62
Trifluoperazine	6	225	221	0.84 [0.48, 1.46]	0.54
Trifluperidol	3	55	56	3.00 [0.34, 26.19]	0.32
Triflupromazine	6	205	206	1.01 [0.87, 1.16]	0.93
Ziprasidone	1	154	152	1.17 [0.63, 2.19]	0.62
Zotepine	1	53	53	1.32 [0.83, 2.08]	0.24
Zuclopenthixol	1	44	50	1.45 [0.91, 2.31]	0.12

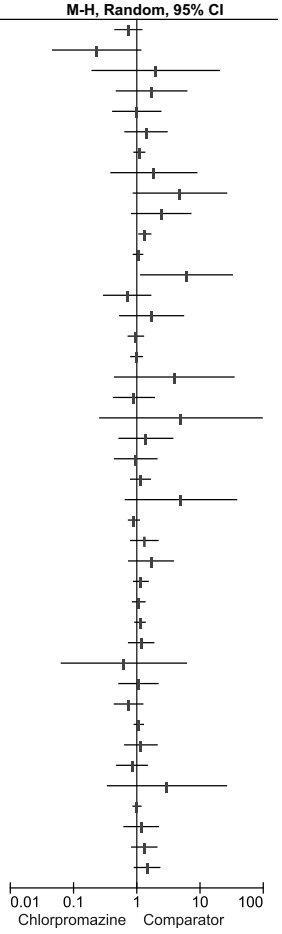

Fig. 4 All cause discontinuation of chlorpromazine versus all other antipsychotic drugs (effect sizes of the individual trials are shown in eFig. 4 in the Supplement). *N*=number, M-H=Maentel-Haenszel, CI=Confidence interval.

3.8. Publication bias

No single antipsychotic drug could be assessed for publication bias since all comparators had less than 10 included studies. For all drugs combined, the funnel-plot was symmetrical (Egger's regression test: intercept −0.3, 95% CI −0.8 to 0.1, *p*-value=0.16) (see eFig. 8 in the Supplement), and the trim-and-fill adjusted relative risk did not differ (RR 0.95, 95% CI 0.87-1.03).

4. Discussion

"Equal efficacy of all antipsychotic drugs" is one of the major dicta of psychopharmacology. It probably originated from an old narrative review from 1969 (Klein and Davis, 1969) on the mainly phenothiazine neuroleptics available at that time which has never been updated, let alone has this older literature on first-generation antipsychotics ever been systematically addressed. As this statement is so essential, we examined the origin of the dogma by a large meta-analysis based on 128 RCTs with 10667 participants that compared the benchmark antipsychotic chlorpromazine with 43 other antipsychotics, with an emphasis on first-generation antipsychotics on which the dictum was originally based. A few statistically significant differences in the primary outcome were found. Whether these findings allow us to confirm or refute the dogma of equal efficacy of all antipsychotic drugs needs to be discussed.

First, we address the eleven comparisons that resulted in significant differences in either response rates or mean values of rating scales. Trikalinos et al. presented an important benchmark according to which, as long as approximately less than 1000 participants have been included, the results of a meta-analysis in psychiatry are not robust; before this point, if new trials get published, effect sizes can still change considerably (Trikalinos et al., 2004). Only one of the eleven comparator antipsychotics (quetiapine) reached this threshold. Butaperazine, mepazine, oxypertine (all three less efficacious than chlorpromazine) and clomacran, levomepromazine and risperidone (more efficacious) had minimal sample sizes (ranging from 20 to 100 participants) indicating that the derived evidence is uncertain and allows no definite interpretation. Indications that butaperazine, mepazine and oxypertine may be less effective than other FGAs were reported as early as in the 1960s (Klein and Davis, 1969; Rajotte et al., 1965), whereas clomacran, which was marketed in the UK but not in other countries, was withdrawn after 60 months (1982) due to serious hepatotoxicity (Abraham and Davis, 2005).

The only reasonably sized comparisons were those with clozapine, olanzapine, quetiapine, reserpine and zotepine (824, 194, 1092, 436 and 218 participants respectively). The fact that clozapine, olanzapine and zotepine were more efficacious than chlorpromazine while quetiapine was less efficacious is in part consistent with a meta-analysis comparing second-generation and first-generation antipsychotics. In this systematic review the first three drugs were overall more efficacious than first-generation antipsychotics, while – for positive symptoms – quetiapine was less efficacious (Leucht et al., 2009). A recent network meta-analysis showed a similar efficacy ranking (Leucht et al., 2013). However, olanzapine's superiority was no longer significant when open studies were excluded. As for reserpine, its inferiority to chlorpromazine remained significant even in a sensitivity analysis when a Bonferroni correction was applied; the rest of the comparisons did not reach significance. Reserpine was officially introduced two years after chlorpromazine. Although it is sometimes mentioned as an option in therapy-refractory schizophrenia (Christison et al., 1991), its use declined shortly after its introduction.

Second, we need to discuss the 25 comparisons that demonstrated no significant differences. Here, the number of included studies and the sample sizes were also small, making the evidence base weak. The median sample size of 50 reflects the use of very small sample sizes in most of the trials. For example, a clinically meaningful (and realistic) responder difference of 10% (which would lead to 100 additional responders among 1000 treated), assuming the average response rate in our meta-analysis (47%), would require a total sample size of 390 which is not met by most comparisons (Team, 2012). This trend changed gradually over the years when researchers learned that considerable number of patients was needed for RCTs to detect statistically significant differences (Leon, 2008; Moher et al., 1996). Registrational studies nowadays usually recruit several hundred patients (Leucht et al., 2013). The number of schizophrenia trials also increased steadily over time, from about 20 per year in the 1950s and 1960s to an average of nearly 75 per year in the 1990s (Thornley and Adams, 1998), offering the opportunity to thoroughly examine the effects of various interventions. Moreover, this allowed for large total numbers of patients to be included in modern meta-analyses. Unfortunately, this was not the case in our meta-analysis. For the majority of the individual comparisons, our findings were based on few participants and low numbers of trials, making most results inconclusive.

Several other limitations should be taken into account. The meta-analysis was restricted to comparisons of chlorpromazine – which we used as a benchmark – with all other antipsychotics which were mainly first-generation. A recent Cochrane review that compared haloperidol with all other first-generation antipsychotics yielded similar results (Dold and Leucht, 2012). Since most of the included studies were carried out more than 30 years ago, a long time before the first CONSORT statement (Begg et al., 1996), the lack of modern standards and the considerable bias in all Cochrane risk of bias tool domains are not surprising. As it is frequently the case in schizophrenia RCTs (Thornley and Adams, 1998), few studies adequately reported randomization and allocation concealment methods; and many used completer case analyses (CC) instead of ITT, which is a concern although a recent analysis found no significant difference in the results from ITT and CC data (Bohnke and Lutz, 2012; Leucht et al., 2007b). Moreover, blinding procedures, outcomes and dropout reasons were inadequately reported. Our a priori defined response criterion (at least 50% in PANSS or BPRS) was indicated only by 3 studies (Kane et al., 2006; Lieberman et al., 2003; Peuskens and Link, 1997); consequently, in most cases we had to recur to authors' definitions of response. Nevertheless, Furukawa and Leucht showed that the use of different response criteria does not lead to markedly different results in meta-analyses as long as relative risks or odds ratios are used as measures of the effect size (Furukawa et al., 2011; Leucht et al., 2007a); similarly, the results of rating scales were inadequately reported. The studies varied substantially in design, patient populations dosing and other factors. Several older RCTs were so poorly reported that no outcome could be used, leading to exclusion from our analysis. Even though we tried to contact the first authors of all studies, given the age of most publications few responses were obtained. These methodological limitations support the notion that conclusive data do not exist.

We can, therefore, neither confirm nor conclusively refute the dogma of equal efficacy of chlorpromazine and all other antipsychotic drugs by this review which was mainly based on old studies. Thus, the “equal efficacy statement” was never evidence-based; it was rather derived impressionistically from narrative overviews instead from meta-analyses. The recent meta-analyses on second-generation antipsychotics were in a much better position to address the question of efficacy differences between drugs and they did find small, but quite consistent efficacy superiorities of some SGAs compared to FGAs and other SGAs (Davis et al., 2003; Leucht et al., 2013, 2009; Zhang et al., 2012) which have in part been confirmed by large effectiveness studies such as CATIE (Lieberman et al., 2005a; McEvoy et al., 2006; Stroup et al., 2006), EUFEST (Kahn et al., 2008) and CUtLASS (Lewis et al., 2006).

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Contributors

MTS, JMD and SL designed the study and wrote the protocol. MTS, HC and BH managed the literature searches and extracted data. MTS and SL undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Stefan Leucht has received honoraria for consulting/advisory boards from Alkermes, BristolMyersSquibb, EliLilly, Janssen, Johnson&Johnson, Medavante, Roche, lecture honoraria from AstraZeneca, BristolMyersSquibb, EliLilly, EssexPharma, Janssen, Johnson&Johnson, Lundbeck

Institute, Pfizer, SanofiAventis, and EliLilly has provided medication for a trial with SL as the primary investigator. The other authors have no conflict of interest to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2014.03.012.

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D. Publications
Online supplement

Appendix A. Supporting information

eInitial protocol. Meta-analysis of chlorpromazine in schizophrenia

eReferences for protocol

eTable 1. Description of included studies

eReferences for eTable

eFigure 1. Risk of bias summary

eFigure 2. Response ratio of chlorpromazine versus all other antipsychotic drugs in individual trials (forest plot)

eFigure 3. Mean overall efficacy of chlorpromazine versus all other antipsychotic drugs in individual trials (forest plot)

eFigure 4. All cause discontinuation of chlorpromazine versus all other antipsychotic drugs in individual trials (forest plot)

eFigure 5. Discontinuation due to inefficacy of chlorpromazine versus all other antipsychotic drugs in individual trials (forest plot)

eFigure 6. Discontinuation due to adverse effects of chlorpromazine versus all other antipsychotic drugs in individual trials (forest plot)

eFigure 7. Meta-regression analysis with chlorpromazine/clozapine dose ratio as a moderator

eFigure 8. Funnel plot of all trials for the outcome response to treatment

eSubgroup and meta-regression analyses. Methods and results

D. Publications
Online supplement

eInitial protocol: Meta-analysis of chlorpromazine in schizophrenia

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BACKGROUND

Schizophrenia is a usually chronic psychiatric disorder which afflicts approximately 1% of the population world-wide with little gender differences. The degree of suffering and disability of afflicted people is considerable. 80% - 90% do not have a job(Marwaha and Johnson 2004) and up to 10% commit suicide(Tsuang 1978, Tsuang and Woolson 1978).

Antipsychotic drugs are the mainstay of treatment of schizophrenia, but still one of the major questions of psychopharmacology remains unanswered: do antipsychotic drugs differ in efficacy? In 1969 Klein and Davis wrote an influential narrative review which found no efficacy differences between the predominantly phenothiazine antipsychotics available at that time(Klein and Davis 1969). Consequently, a dogma of equal efficacy has been codified in numerous textbooks and guidelines which make statements such as “comparable efficacy... among the different first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs)” (PORT Psychopharmacological Treatment Recommendations and Summary Statements)(Buchanan, Kreyenbuhl et al. 2010) or “with the possible exception of clozapine … antipsychotics have similar efficacy” (APA Practice Guidelines)(Lehman, Lieberman et al. 2004). However, a part from an update in 1989(Davis, Barter et al. 1989) using insufficient ‘vote-counting’ this question has never again been systematically addressed. The dogma has been challenged by meta-analyses which consistently found small, but robust efficacy superiorities of some SGAs(Davis, Chen et al. 2003, Leucht, Wahlbeck et al. 2003, Martin, Perez et al. 2006, Leucht, Corves et al. 2009, Rabinowitz, Levine et al. 2009, Hartling, Abou-Setta et al. 2012, Zhang, Gallego et al. 2012, Kishimoto, Agarwal et al. 2013). But what about first-generation antipsychotics? These are still the mainstay of treatment in low or middle-income countries(Chong, Tan et al. 2004, Karagianis, Novick et al. 2009) – i.e. the largest part of the world - and they still maintain a relatively high market share in industrialised countries such as the UK, US and Germany(Hamann, Ruppert et al. 2003, Sernyak and Rosenheck 2008, Koranek, Smith et al. 2012, Prah, Petersen et al. 2012). Meta-analyses(Leucht, Corves et al. 2009, Leucht, Cipriani et al. in press) and the effectiveness studies CATIE(Lieberman, Stroup et al. 2005) and CUtLASS(Jones, Barnes et al. 2006) have challenged the classification into ‘typical’ and ‘atypical’ antipsychotics and point out to the fact that older drugs should not be neglected.

Chlorpromazine, together with haloperidol and fluphenazine depot, is the only antipsychotic listed as an “essential drug” by the World Health Organisation. As it was the first developed antipsychotic drug, it has served as a benchmark for many other compounds. We, therefore, will conduct a systematic review comparing the efficacy of chlorpromazine with every other first-generation antipsychotic drug. If chlorpromazine is shown to be more or less effective than other conventional antipsychotics, the long-standing dogma of equal efficacy will have to be rejected.

OBJECTIVES

To compare chlorpromazine with all other first generation antipsychotics.

D. Publications
Online supplement

METHODS

Criteria for considering studies for this review

Types of participants

Participants with schizophrenia and other types of schizophrenia(-like) psychoses, irrespective of the diagnostic system applied. No restrictions concerning age, gender and comorbidities. If a study involved patients with other diagnoses, we include only those studies which have a sample of at least 75% participants suffering from a schizophrenic syndrome or, if this is not the case, only results regarding patients exclusively with schizophrenia will be reported.

Types of intervention

Any oral form at any dose of chlorpromazine will be included. We will exclude depot formulations. Injections (I.M.-I.V.) will be allowed for initial treatment, only if patients were transferred to oral medication within the first week.

Comparators

Any other first generation antipsychotic agent which is or was available in at least one country world wide.

Types of studies

We will include all relevant randomised trials. We will exclude quasi-randomised studies such as those using allocation by day of the week, date of birth, alternate allocation. When a trial is described as "double blind", but randomisation is implied, we will include the trial in a sensitivity analysis. If there is no substantive difference within primary outcomes when these "implied randomisation" studies are added, then we will include these in the final analysis. If there is a substantive difference, we will only analyse clearly randomised trials and describe the results of the sensitivity analysis in the text.

Outcome measures

(1) Global State defined as clinically important response to treatment (primary outcome)

(2) Global state and mental state-behaviour measured by the total score or. mean overall change in symptom rating scales, based on the following hierarchy: change in of the Positive and Negative Syndrome Scale(Kay, Fiszbein et al. 1987), change in Brief Psychiatric Rating Scale(Overall and Gorham 1962), values of these scales at study endpoint, and then, if any of the previous measures were not available, other scales for overall schizophrenic symptomatology as long as the instrument had been published in a peer-reviewed journal(Marshall, Lockwood et al. 2000).
(3) Premature discontinuation due to any cause, due to adverse effects and due to inefficacy defined as drop-outs.

Search strategy

The Cochrane Schizophrenia Group's Register will be searched up to August 2009 using the term "chlorpromazin*" (later versions of the register were not available to us). We will also search reference lists, previous published reviews and we will try to obtain information from authors and drug companies. No language or publication restriction will be applied(Gregoire, Derderian et al. 1995, Moher, Fortin et al. 1996, Egger, Zellweger-Zahner et al. 1997, Moher, Pham et al. 2000).

Study selection and data extraction

Two reviewers will independently review references and abstracts. If both reviewers agree that the trial doesn't meet eligibility criteria, we will exclude it. We will obtain the full text of all remaining articles and criteria to determine which, if any, to exclude at this stage.
Two reviewers will then independently read each article, evaluate the eligibility criteria and the completeness of the data abstraction, and confirm the quality rating. We will design and use a structured data abstraction form to ensure consistency of appraisal for each study. Information extracted will include study characteristics (such as lead author, publication year, risk of bias), participant characteristics (such as diagnostic criteria for schizophrenia, age), intervention details (such as dose ranges, mean doses of study drugs) and outcome measures (see above). Any disagreements will be solved via discussion with a third member of the reviewing team.

Length of follow up

We will use endpoint data from each study, irrespectively of its length.

Risk of bias

Independent assessment of risk of bias and quality of trials will be mad by using the criteria described in the Cochrane Collaboration Handbook(Higgins and Green 2011). If the raters disagree, the final rating will be made by consensus, with the involvement of another member of the review group. Authors of the studies will be contacted if inadequate details of randomisation and other characteristics of trials are provided. The level of risk of bias will be noted in both the text of the review and in the summary of findings.

STATISTICAL ANALYSIS

Dichotomous outcomes will be analysed on an intention-to-treat (ITT) basis: drop-outs will always be, provided it is possible, included in this analysis. When data on drop-outs are carried forward and included in the evaluation (Last Observation Carried Forward, LOCF), they will be analysed according to the primary studies; when dropouts are excluded from any assessment in the primary studies, we will assume that for each dichotomous outcome, the percentage of patients who responded/dropped out would be the same.

Mean overall efficacy refers to change or endpoint values of PANSS, BPRS or any other validated scale. Unreported standard deviations will either be obtained from the authors upon request, or calculated from other statistics, or will be derived from the average of the other studies(Furukawa, Barbui et al. 2006). We will employ a random-effects model for analyses(DerSimonian and Laird 1986). We understand that there is no closed argument for preference of fixed or random/effects model. The random-effects model is usually more conservative in terms of statistical significance, although as a disadvantage it puts added weight onto smaller studies which can either inflate or deflate the effect size. Therefore, we will examine in a secondary analysis whether using a fixed-model markedly change the results of the primary outcome.

Sensitivity and subgroup analyses

We will examine the subgroups of people with a first episode of schizophrenia and patients with treatment-resistant schizophrenia to see if their results for primary outcomes substantively differed from other "participant groups".

If inconsistency is high, this will be reported. Potential causes of high heterogeneity will be explored. We are aware that subgroup analyses are observational by nature and therefore consider the results to be exploratory and not explanatory.

D. Publications
Online supplement

POST- HOC CHANGES OF THE INITIAL PROTOCOL

1. We decided to exclude studies published only in Chinese to avoid a systematic bias as many of them do not use appropriate randomization procedures and do not report their methods.

2. We decided to also add and examine every comparisons of chlorpromazine to any second generation antipsychotic in order to undertake a more comprehensive and thoroughgoing review.

D. Publications
Online supplement

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D. Publications
Online supplement

ETABLE 1: DESCRIPTION OF INCLUDED STUDIES

STUDY	Antipsychotics and daily dose in mg, on flexible dosage mean value (range)	n	Duration in weeks	Mean duration of illness in years	Selected characteristics of patients
Alfredsson 1984(Alfredsson, Bjerkenstedt et al. 1984, Alfredsson, Harnryd et al. 1984, Harnryd, Bjerkenstedt et al. 1984, Harnryd, Bjerkenstedt et al. 1984, Alfredsson, Harnryd et al. 1985, Wiesel, Alfredsson et al. 1985, Wiesel, Bjerkenstedt et al. 1985, Wiesel 1986)	Chlorpromazine 400 Sulpiride 800	25 25	8	n.i.	Acute psychosis of schizophrenic type (RDC)
Amin 1997(Amin, Ban et al. 1977)	Chlorpromazine (400-3600) Benzquinamide (200-1800) [Benzquinamide plus group therapy]	6 6 [6]	10	n.i.	Chronic schizophrenic patients, partially responsive to previous treatment
Ananth 1977a(Ananth and Ban 1977)	Chlorpromazine (n.i.) Periciazine (n.i.) (flexible)	15 15	12	n.i.	Newly admitted patients with schizophrenia

Anumonye 1976(Anumonye, Onibuwe-Johnson et al. 1976)	Chlorpromazine (300-600) Pimozide (1-4)	12 12	4	n.i.	Chronic hospitalized patients with schizophrenia, only females, who had relapsed following the termination of chlorpromazine therapy
AstraZeneca 5077IL/0031(AstraZeneca 2005)	Chlorpromazine 1040 (225-1200) Quetiapine 571 (113-750)	132 135	10	n.i.	Schizophrenia (DSM-IV), treatment resistant
AstraZeneca 5077IL/0054(AstraZeneca 2000)	Chlorpromazine 900 Quetiapine 600	119 117	10	n.i.	Schizophrenia (DSM-IV), treatment resistant
AstraZeneca NCT00882518(AstraZeneca 2010, AstraZeneca 2012)	Chlorpromazine (300-600) Quetiapine (400-800)	192 196	6	n.i.	Schizophrenia (DSM-IV)
Baker 1958b(Baker and Thorpe 1958)	Chlorpromazine 116.6 (25-200) Levomepromazine 81.3 (25-200)	14 14	20	n.i.	Deteriorated patients with schizophrenia, only females
Balasubramanian 1991(Balasubramanian, Baloch et al. 1991)	Chlorpromazine (100-600) Zuclopenthixol (25-150)	44 50	10	n.i.	Acute functional psychosis (RDC)
Ban 1975(Lehmann and Ban 1970, Ban, Lehmann et al. 1975)	Chlorpromazine (200-800) Thiothixene (10-40) [Placebo]	10 10 [10]	12	n.i.	Acute (50%) and chronic (50%) schizophrenia

Barrett 1957(Barrett, Ellsworth et al. 1957)	Chlorpromazine 520 (200-1200) Reserpine 5.9 (4-8) [Chlorpromazine plus reserpine]	10 10 [10]	12 (cross-over trial with a total duration of 16 weeks)	n.i.	Chronic regressed schizophrenic patients
Bennett 1961(Bennett and Kooi 1961)	Chlorpromazine 1200 (200-1200) Prochlorperazine 131.3 (25-150) Trifluprомazine 300 (50-300) Perphenazine 86.4 (16-96) Mepazine 300 (50-300) [Phenobarbital]	5 5 5 5 5 [5]	12	n.i.	Chronic schizophrenia, all males (ill for more than 2 years, all but 2 patients)
Bishop 1963(Bishop, Gallant et al. 1963)	Chlorpromazine 680 (200-800) Benzquinamide 920 (200-1200) [Placebo]	10 10 [10]	10	n.i.	Chronic schizophrenia (length of hospitalisation: CPZ 12,2±5,9; Benzq. 10,5±6,3 years)

Bratfos 1979(Bratfos and Haug 1979)	Chlorpromazine (225-675) Sulpiride (600-1800)	39 32 (n analysed, n randomized is n.i.)	4 (acute psychosis); 8 (chronic psychosis)	n.i.	"Patients with either acute schizophrenia, reactive psychoses, or acute exacerbations of chronic psychoses and patients with paranoid psychoses where previously used antipsychotic medication was without effect"
Bressler 1971(Bressler and Friedel 1971)	Chlorpromazine 400 (100-800) Thiothixene 20 (10-60)	13 13	4	n.i.	Schizophrenia, various subtypes, all males
Case 1971(Case, Ryder et al. 1971)	Chlorpromazine 187.5 (<400) Clomacran 170 (<400)	24 25	8	6 9	Schizophrenia, all but 7 were diagnosed as suffering from either paranoid or undifferentiated schizophrenia
Casey 1960a(Casey, Bennet et al. 1960)	Chlorpromazine 400 Promazine 400 [Phenobarbital] [Placebo]	170 171 [173] [178] (n analysed, n randomized is n.i.)	12 (cross-over trial with a total duration of 24 weeks)	10	Schizophrenic reactions (81% chronic, 73% non-disturbed)

Chien 1968(Chien and Tsuang 1968)	Chlorpromazine 616.6 (300-800) Clomacran 308.3 (150-400)	21 20	12	n.i.	Chronic psychotic patients, most of them undifferentiated schizophrenics, all females (average length of hospital stay: 25 years)
Chiu 1976(Chiu, Burrows et al. 1976)	Chlorpromazine 300 Clozapine 300	31 33	6	n.i. (reported 6.4 weeks but probably refers to duration of present episode)	Acute schizophrenia of moderate to severe symptomatology
Chouinard 1976[a](Chouinard and Annable 1976, Chouinard, Annable et al. 1977, Chouinard, Annable et al. 1977)	Chlorpromazine 650 (100-900) Penfluridol 102 (40-120)	19 14	12	n.i.	Newly admitted patients with schizophrenia (criteria similar to those used by NIMH-PSC)
Chouinard 1982b(Chouinard and Annable 1982)	Chlorpromazine 960 (300-1500) Pimozide 37.8 (10-70)	20 20	4	n.i.	Newly admitted patients with schizophrenia (RDC), presenting 2 or more symptoms listed in NIMH-PSC for acute schizophrenia
Claghorn 1967b study n:2(Claghorn, Schoolar et al. 1967)	Chlorpromazine 1000 (200-1200) Clomacran 500 (100-600)	10 10	n.i.	n.i.	Chronic schizophrenic inmates of a prison mental hospital

Claghorn 1967b study n:3(Claghorn, Schoolar et al. 1967)	Chlorpromazine 1000 (200-1200) Clomacran 500 (100-600)	10 10	6-77 days	n.i.	Acute schizophrenic reactions
Claghorn 1970a(Claghorn and Schoolar 1970)	Chlorpromazine 800 (150-1200) Oxypertine 300 (60-480)	20 20	6	n.i.	Schizophrenia, all males
Claghorn 1979(Claghorn, Mathew et al. 1979)	Chlorpromazine 241.3 (<760) Penfluridol 8.4 (<22.9)	28 28	52	8 11	Chronic schizophrenia, duration of illness >1.5 years
Clark 1968a(Clark, Huber et al. 1968)	Chlorpromazine 663 (258-835) Trifluperidol 6.7 (5.1-8.3) [Placebo] [No-drug]	18 18 [18] [18]	14	13.9 15.9	Chronic schizophrenia, duration of illness >2 years, all females
Clark 1968b(Clark, Ray et al. 1968)	Chlorpromazine 842.3 (<1000) Butaperazine 81.1 (<100) [Placebo]	23 23 [23]	16	21.7 19.2	Chronic schizophrenia, all females

Clark 1971a(Clark, Huber et al. 1971)	Chlorpromazine 718 (200-1000) Fluphenazine 7.3 (2-10) Thioridazine 760 (200-1000) [Placebo]	23 20 22 [21]	4	n.i.	Acutely exacerbated chronic schizophrenia, presence of 2 or > more symptoms listed in NIMH-PSC)
Clark 1972(Serafetinides, Willis et al. 1971, Clark, Huber et al. 1972)	Chlorpromazine 816.7 (<1000) Loxapine 80.6 (<100) [Placebo]	19 18 [18]	12	n.i.	Chronic schizophrenia, duration of illness >2 years
Cole 1967 (=NIMH PRB 1967)(Goldberg, Mattsson et al. 1967, Goldberg, Schooler et al. 1967, National Institute of Mental Health Psychopharmacology Research Branch Collaborative Study 1967, Goldberg and Mattsson 1968, Schooler, Boothe et al. 1971, Schooler and Goldberg 1972)	Chlorpromazine 690 (>200) Fluphenazine 7.6 (>2) Acetophenazine 152 (>40)	160 163 164	5 (total duration 26, we assess the first 5 that we have data)	n.i.	Newly admitted patients with acute schizophrenia

Conley 1998(Conley, Tamminga et al. 1998)	Chlorpromazine 1200 Olanzapine 25	42 42	8	20.99 21.64	Schizophrenia (DSM-III-R), treatment resistant
Coons 1962(Coons, Boyd et al. 1962)	Chlorpromazine 150 Trifluoperazine 15 [Placebo]	32 28 [33]	6	n.i.	Schizophrenia, all females (we assessed only the subset of patients suffering from schizophrenia)
Cooper 2000a(Cooper, Tweed et al. 2000)	Chlorpromazine (300 or 600) Zotepine (150 or 300) [Placebo]	53 53 [53]	8	11.9 10.8	Schizophrenia (DSM-III-R), acute episode or an acute exacerbation of subchronic or chronic schizophrenia
Digiacomo 1977(DiGiacomo, Sandler et al. 1977)	Chlorpromazine 690 (100-1200) Lenperone 62 (10-140)	15 19	4	n.i.	Acute schizophrenia, all males
Dossenbach 2007(Dossenbach, Treuer et al. 2007)	Chlorpromazine 232 (200-800) Olanzapine (5-20)	12 27	6	10.2 9.5	Schizophrenia (DSM-IV)
Douglas 1969(Douglas and Hindley 1969)	Chlorpromazine 600 (100-1200) Mesoridazine 320.3 (100-1000)	32 32	12	n.i.	Functional psychiatric disability, chronic inpatients, continuously hospitalized for the last six months

Dreyfus 1985(Pichot and Dreyfus 1983, Dreyfus 1985)	Chlorpromazine 257.1 (200;300) Sulpiride 1028.6 (800;1200)	29 35	3	n.i.	Acute psychosis
Dube 1976(Dube and Kumar 1976)	Chlorpromazine 320 (200-800) Loxapine 34.3 (20-80)	26 26	12	n.i.	Functional psychoses
Engelhardt 1969a(Engelhardt, Freedman et al. 1960, Engelhardt, Rosen et al. 1963, Engelhardt, Freedman et al. 1964, Engelhardt, Rosen et al. 1967, Freedman, Cutler et al. 1967, Rosen, Engelhardt et al. 1968, Engelhardt, Margolis et al. 1969, Freedman, Cutler et al. 1970)	Chlorpromazine 200(50-800) Promazine 200 (50-800) [Placebo]	62 55 [56]	72 (the study lasted up to 8.5 years, we assessed the first 18 months that there were usable data)	n.i.	Chronic schizophrenia, duration of illness >1 years (fundamental Bleulerian criteria at intake or clinical diagnosis made during previous hospitalization)
Engelhardt 1969b(Engelhardt 1969)	Chlorpromazine (100-600) Clomacran (100-600)	22 22	8	n.i.	Acute and chronic schizophrenia

Fleming 1959(Fleming, Spencer et al. 1959)	Chlorpromazine 300 (75-300) Promazine 300 (75-300) [Placebo]	21 21 [21]	24	21	Chronic refractory schizophrenia, characterized by gross disorder of, and disconnection between, thought, affect and behaviour; institutionalized patients, all females
Freeman 1969(Freeman and Frederick 1969, Freeman, Oktem et al. 1969)	Chlorpromazine 662.5 (<1000) Mesoridazine 340 (<500)	25 25	8	n.i.	Schizophrenia, most of the patients chronics (average length of hospitalization: 9.5 years)
Freeman 1973(Freeman 1973)	Chlorpromazine 960 (150-1200) Mesoridazine 318 (50-400)	25 25	12	n.i.	Chronic schizophrenia, patients hospitalized >6 months, none was considered treatment refractory (average length of present hospitalization: 10.5 years)
Galbrecht 1968(Galbrecht and Klett 1968)	Chlorpromazine 750 (200-1600) Fluphenazine 8.4 (2.5-20) Thioridazine 700 (200-1600)	102 104 104	8	n.i.	Schizophrenia, newly admitted or readmitted patients, with a diagnosis of one of the schizophrenic reaction subtypes, hospitalized for a reason closely related to the schizophrenic illness, all males

Gallant 1963d(Gallant, Bishop et al. 1963)	Chlorpromazine (200-1200) Trifluperidol (1-6)	18 18	10	n.i.	Chronic schizophrenia (average length of hospitalization: 13 years)
Gallant 1967c(Pratt, Bishop et al. 1964, Gallant, Bishop et al. 1967)	Chlorpromazine (<800) Haloperidol (<16) Trifluperidol (<4)	19 19 20	4 (30 days)	n.i.	Acute schizophrenia, “first admissions or to have been admitted no more than twice previously with a history of excellent remission between acute schizophrenic episodes”
Gallant 1970a,c,d(Gallant and Bishop 1970)	Chlorpromazine (120-1350) Piperacetazine (20-360)	13 13	6	n.i.	Chronic schizophrenia, all males (average length of hospitalization: 17.5 years)
Gallant 1970b(Gallant and Bishop 1970)	Chlorpromazine (240-1170) Piperacetazine (40-800)	8 8	6	n.i.	Chronic schizophrenia, all females

Gardos 1974a(Gardos 1974)	Chlorpromazine (n.i.) Thiothixene (n.i.) (flexible) [Doctor's choice]	17 19 [17] (n analysed, n randomized is n.i.)	96 (2 years)	n.i.	Chronic schizophrenia
Gelenberg 1979(Gelenberg and Doller 1979)	Chlorpromazine 606 (<1800) Clozapine 279 (<900)	8 7	4 to 8 (the study lasted up to 8, usable data for the first 4 weeks)	n.i.	Schizophrenia (DSM-II)
Geller 2005(Schliefer, Bersudsky et al. 2003, Geller, Gorzaltsan et al. 2005, Belmaker 2009)	Chlorpromazine (n.i.) Clotiapine (n.i.) (flexible)	20 21 (n refers only to inpatients)	12 (cross-over trial with a total duration of 24 weeks)	n.i.	Severe chronic active schizophrenia, with history of non-response to at least 3 neuroleptics
Gendron 1973(Gendron, Zimmermann et al. 1973)	Chlorpromazine (200-800) Carperone (100-400)	15 15	4	n.i.	Schizophrenia, newly admitted patients

Gershon 1970a(Gershon, Hekimian et al. 1970, Hekimian, Gershon et al. 1970)	Chlorpromazine 1040 (600-1600) Butaperazine 58 (20-160)	10 10	4	n.i.	Acute schizophrenia, patients recently admitted
Goldberg 1964 (=NIMH-PSC 1964)(Cole, Goldberg et al. 1964, Goldberg, Klerman et al. 1965, Goldberg, Schooler et al. 1967, Goldberg and Mattsson 1968, Klerman, Goldberg et al. 1970, Gibbons, Lewine et al. 1985)	Chlorpromazine 654.8 (200-1600) Fluphenazine 6.4 (2-16) Thioridazine 700 (200-1600) [Placebo]	112 115 111 [125]	6	n.i.	Acute schizophrenia, patients recently admitted
Goldberg 1970a(Goldberg, Brooke et al. 1970)	Chlorpromazine 300 (150-450) Oxypertine 180 (90-270)	20 20	12	n.i.	Chronic schizophrenia, “the most withdrawn patients were selected for the trial”
Guirguis 1977(Guirguis, Voineskos et al. 1977)	Chlorpromazine (150-900) Clozapine (75-450)	28 22	7	8.4 8.1	Acute schizophrenia

Hamilton 1960(Hamilton, Smith et al. 1960)	Chlorpromazine 300 Thiopropazate 30 [Placebo]	18 18 [18]	8	n.i.	Chronic schizophrenia, hospital residents for a continuous period of not less than 2 years, “typical patients to be found in a refractory or semi-refractory ward”, overactive and agressive from time to time, all males (average length of hospitalization: 8.6 years)
Hanlon 1965(Hanlon, Michaux et al. 1965)	Chlorpromazine 395.6 (300-1200) Thioridazine 193.5 (150-440) Trifluprom azine 95.9 (75-200) Prochlorperazine 51.2 (37.5-150) Perphenazine 38.6 (24-144) Thiopropazate 20.8 (15-80) Trifluoperazine 11.5 (7.5-40) Fluphenazine 5.9 (3.75-20)	52 53 53 52 53 53 52 53	4 (30 days)	n.i.	Newly admitted patients, considered candidates for tranquilizing drug therapy; selection independent of diagnosis; inclusion of the more acutely disturbed patients; 84% (270/322) psychotic patients (of whom 232 patients with schizophrenia)

Heikkinnen 1993(Heikkinen, Outakoski et al. 1993)	Chlorpromazine 500 Molindone 100	21 24	8	n.i.	Acute schizophrenia, patients fulfill DSM-III-R criteria *available only a letter to editor
Hong 1997(Hong, Chen et al. 1997)	Chlorpromazine 1163 (200-1800) Clozapine 543 (100-900)	19 21	12	n.i.	“All hospitalized treatment refractory schizophrenics...” (DSM-IV)
Honigfeld 1984a(Shopsin, Klein et al. 1978, Shopsin, Klein et al. 1979, Honigfeld, Patin et al. 1984)	Chlorpromazine 1183 (<1800) Clozapine 608 (<900) [Placebo]	15 16 [8]	4	n.i.	Acute exacerbation of schizophrenia, “newly admitted, floridly ill individuals”
Honigfeld 1984b(Honigfeld, Patin et al. 1984, Claghorn, Honigfeld et al. 1987)	Chlorpromazine 795 (300-1800) Clozapine 417 (150-900)	76 75	4 to 8	n.i.	Schizophrenia (DSM-II), treatment resistant

Honigfeld 1984d(Ekblom and Haggstrom 1974, Fischer-Cornelssen, Ferner et al. 1974, Fischer-Cornelssen, Ferner et al. 1974, Niskanen, Achté et al. 1974, Dick, Remy et al. 1975, Vencovsky, Peterova et al. 1975, Fischer-Cornelssen and Ferner 1976, Honigfeld, Patin et al. 1984)	Chlorpromazine 360 (25-900) Clozapine 310 (50-1000)	113 110	5.7 (40 days)	n.i.	Schizophrenia, moderate to severe
Howanitz 1999(Howanitz, Pardo et al. 1999)	Chlorpromazine 600 Clozapine 300	18 24	12	40 38	Chronic geriatric schizophrenia or schizoaffective disorder (DSM-IV), "all patients were chronically ill and had failed conventional treatment regimens…"
Johnson 1970(Johnson 1970)	Chlorpromazine (3-96) Piperacetazine (15-60)	13 13	6	n.i.	Acute and chronic schizophrenia, all males

Kane 1988(Small, Milstein et al. 1987, Borison, Diamond et al. 1988, Conley, Schulz et al. 1988, Heh, Herrera et al. 1988, Herrera, Costa et al. 1988, Herrera, Sramek et al. 1988, Kane, Honigfeld et al. 1988, Kane, Honigfeld et al. 1988, Honigfeld and Patin 1989)	Chlorpromazine 1200 (<1800) Clozapine 600 (<900)	142 126	6	15.3	Schizophrenia (DSM-III), treatment resistant
Kane 2006(Kane, Khanna et al. 2006)	Chlorpromazine 743.6 (200-1200) Ziprasidone 153.8 (80-160)	154 152	12	11.5	Acute or subacute schizophrenia (DSM-III-R), treatment resistant
Kaneko 1969(Kaneko, Tanimukai et al. 1969)	Chlorpromazine (150-600) Clotiapine (60-240)	41 43	8	n.i.	Schizophrenia
Kingstone 1970(Kingstone, Kolivakis et al. 1970)	Chlorpromazine 435 (150-1800) Clopenthixol 122 (75-600)	21 20	3	3.1 2.4	Acute psychotic symptomatology; diagnosis for all, except one, patients was schizophrenic reactions

Kolivakis 1974(Kolivakis, Azim et al. 1974)	Chlorpromazine 216 (75-450) Pimozide 7 (2.5-21)	25 26	24	n.i.	Chronic schizophrenia, notable high level of emotional withdrawal; under the study protocol, only patients whose symptoms had been controlled with other neuroleptics were evaluated
Kostakoglu 2001(Eli-Lilly 2000, Kostakoglu, Alptekin et al. 2000)	Chlorpromazine 388 (200-800) Olanzapine (5-20)	10 20	6	9.4 10.1	Acute schizophrenia (DSM-IV)
Kramer 1975(Kramer, Roth et al. 1975)	Chlorpromazine 427 (50-1200) Metiapine 219 (25-600) [Butabarbital]	38 39 [13] (n analysed, n randomized is n.i.)	4	n.i.	Acute schizophrenia of recent onset or exacerbation
Kurland 1956(Kurland 1956)	Chlorpromazine (200-400) Reserpine (3-6)	200 200	12	n.i.	Schizophrenia, all females *available only an abstract

Kurland 1961(Kurland, Nilsson et al. 1959, Kurland and Sutherland 1960, Kurland, Hanlon et al. 1961, Kurland, Hanlon et al. 1961)	Chlorpromazine 401.4 (300-1200) Mepazine 135.5 (75-450) Perphenazine 30.8 (24-96) Prochlorperazine 45.4 (30-125) Promazine 438.9 (300-1600) Trifluprom azine 110.5 (75-300) [Phenobarbital] [Placebo]	33 34 36 32 32 36 [37] [37]	6	n.i.	Candidates for tranquilizing drug therapy; “patients were referred on the basis of such target symptoms as anxiety, agitation and restlessness, without reference to the usual nosologic considerations, the resulting population being predominantly schizophrenic in character”
Lal 2006(Lal, Thavundayil et al. 2006)	Chlorpromazine 764 (100-1000) Levomepromazine 799 (100-1000)	19 19	15 (30-week trial, we assess the second double-blind half)	19.3 18.7	Treatment-resistant schizophrenia (criteria for chronic schizophrenia based on DSM-III-R and for TRS on Kane et al.)

Lasky 1962(Lasky, Klett et al. 1962, Bruck 1968)	Chlorpromazine 746 (200-1600) Fluphenazine 10 (2.5-20) Reserpine 6 (1.5-12) Thioridazine 845 (200-1600) Ttriflupromazine 208 (50-400) Chlorprothixene 224 (50-400)	86 84 88 84 83 87	24	n.i.	Acute schizophrenia, all males
Leitch 1960(Leitch and Seager 1960)	Chlorpromazine 150 Promazine 150 Acetylpromazine 75 Methotrimeprazine 120	14 10 11 8 (n analysed, n randomized is n.i., only the sub-group with schizophrenia was selected)	"a minimum of 4 weeks", "an average of 9 weeks", "no strict rules"	n.i.	Patients "suitable for treatment with one of the newer phenothiazine tranquillizing drugs"; we assessed only the sub-group of patients with schizophrenia

Lemperiere 1962(Lempérière, Delay et al. 1962)	Chlorpromazine (<400) Haloperidol (<10) Prochlorpemazine (<120) Thioproperazine (<60)	22 24 20 17	8	n.i.	Paranoid schizophrenia, French classification, all females *data from Cochrane review, we could not retrieve the original publication
Leon 1974(Leon and Estrada 1974, Leon 1978, Leon 1979)	Chlorpromazine 600 Clozapine 600 (<1600)	25 25	6	n.i.	Schizophrenia (DSM-II)
Lieberman 2003b(Lieberman, Phillips et al. 2003)	Chlorpromazine 400 Clozapine 300	83 81	52	1.5	Treatment naïve, first-episode schizophrenia or schizophreniform disorderl (DSM-IV)
Lomas 1957(Lomas 1957)	Chlorpromazine 300 Mepazine 300	50 50	12	4.4	Schizophrenia, praphrenia or schizoaffective disorder where the affective disorder was not predominant
Loza 1999(Loza, El-Dosoky et al. 1999, Eli-Lilly 2001)	Chlorpromazine 465 (200-800) Olanzapine (5-20)	14 27	6	n.i.	Acute schizophrenia (DSM-IV)
McCreadie 1977(McCreadie and MacDonald 1977)	Chlorpromazine 600 Haloperidol 100	10 10	12	n.i.	Chronic, treatment-resistant schizophrenia, presence of one or more “Schneiderian” first rank symptoms, all males (average length of hospitalization: 20 years)

Mercer 1997(Mercer, Finlayson et al. 1997)	Chlorpromazine 500 (50-850) Risperidone 8 (4-16)	12 15	9	14.1 15.6	Schizophrenia (DSM-III-R and fulfilment of Feighner criteria); treatment resistance (scheme of May)
Mielke 1975(Mielke, Gallant et al. 1975)	Chlorpromazine (150-1050) Lenperone (25-175)	15 14	8	n.i.	Chronic schizophrenia (average length of hospitalization: 15.6 years)
Moore 1975(Moore 1975)	Chlorpromazine 430 (200-1200) Loxapine 36 (20-120)	29 29	6 (ranged from 2-34 weeks, we assess the results of initial 6 weeks)	n.i.	Acute schizophrenia or acute episodes of chronic schizophrenia
Neal 1969(Neal, Collis et al. 1969)	Chlorpromazine 300 (150-400) Oxypertine 120 (60-180)	20 20	12	16 14.2	Chronic schizophrenia, “patients failed to show any sustained improvement to other antipsychotics over the years”, all males
Nishizono 1994(Nishizono 1994)	Chlorpromazine (75-450) Haloperidol (4.5-21) Zotepine (75-450)	52 57 60	4	n.i.	Schizophrenia (ICD-10)

Overall 1966(Overall, Hollister et al. 1969)	Chlorpromazine 710 (300-1200) Clomacran 370 (150-600)	47 40 (n analysed, n randomized is n.i.)	6	n.i.	Patients with "schizophrenic reaction and who meritied treatment with some antipsychotic drug", all males
Payne 1960(Payne 1960)	Chlorpromazine (75-300) Trifluopromazine (75-300) [Placebo]	7 7 [7]	6	n.i.	Chronic schizophrenia, all males (average length of hospitalization: 12.7 years)
Pecknold 1982(Pecknold, McClure et al. 1982)	Chlorpromazine 909.9 (300-2100) Pimozide 66.9 (10-70)	10 10	4	n.i.	Acute schizophrenia
Peuskens 1997(Peuskens and Link 1997)	Chlorpromazine 384 (100-750) Quetiapine 407 (75-750)	100 101	6	n.i.	Acute exacerbation of chronic or subchronic schizophrenia, or schizophreniform disorder (DSM-III-R)

Platz 1967(Platz, Klett et al. 1967)	Chlorpromazine 980 (<1600) Trifluoperazine 21 (<32) Carphenazine 260 (<400)	108 108 108 (324 n randomized, we assumed the above allocation)	24	n.i.	Chronic schizophrenia, patients continuously hospitalized for three or more years, all males (median length of hospitalization: 9 years)
Potter 1989(Potter, Ko et al. 1989)	Chlorpromazine (100-600) Clozapine (50-600) [Chlorpromazine plus clozapine]	20 17 [20]	8	5 5.8	Schizophrenia (DSM-III and the Society of Neurology and Psychiatry of the Medical Association of China, 1985)
Psaras 1984(Psaras, Paterakis et al. 1984)	Chlorpromazine 600 Bromperidol 20	20 20	12	n.i.	Chronic schizophrenia, criteria of Feighner et al., (average length of hospitalization: Cpz 19.8, Bromp. 14.8 years)
Rasch 1966(Rasch 1966)	Chlorpromazine 280 (100-600) Periciazine 28 (10-60)	21 21 (n analysed, n randomized is n.i.)	12 (cross over trial with a total duration of 1 year)	30.5	Chronic schizophrenia, patients “had been hospitalized for long periods of time”, “so stable for a prolonged period on cpz-therapy (in a few patients on thioridazine) that variations…could be assessed”, all females

Reardon 1966(Reardon and Abrams 1966)	Chlorpromazine 600 Trifluoperazine 40 [Placebo]	11 11 [12]	8 (minimum 4 weeks, maximum 12 weeks)	n.i.	Acute paranoid schizophrenia, thinking and affect disturbance as described by Bleuler and presence of persecutory delusions and hallucinations the last ten days within 10 days prior to admission
Rickels 1978(Rickels, Byrdy et al. 1978)	Chlorpromazine 926 (400-1600) Thiothixene 44.3 (20-80)	40 39 (n analysed, n randomized is n.i.)	3-4 (Cpz 3.5, Thioth. 3.3)	n.i.	Acute schizophrenia, newly admitted patients
Rifkin 1984(Rifkin, Rieder et al. 1984)	Chlorpromazine 1288 (200-1500) Loxapine 128.6 (20-150)	33 31	4	3.3	Paranoid schizophrenia (RDC), patients recently hospitalized with prominent persecutory delusions or hallucinations
Rompel 1978(Rompel and Segal 1978)	Chlorpromazine (<300) Haloperidol (<30)	13 12	8	n.i.	Chronic schizophrenia, hospitalized for at least 5 years, firmly diagnosed (average length of hospitalization: Cpz 12.8, Hal. 10.9 years)

Schiele 1961(Schiele, Vestre et al. 1961)	Chlorpromazine 894 (200-1000) Thioridazine 958 (200-1000) Trifluoperazine 35 (10-50) [Placebo]	20 20 20 [20]	16 (total 38, we assess the first 16-week double-blind phase)	n.i.	Chronic schizophrenia, either withdrawn or subject to periodic disturbances, generally ineffective, hospitalized continuously for 10 years
Schiele 1968(Schiele 1968)	Chlorpromazine (100-1200) Clomacran (100-600)	14 15	12	n.i.	Chronic schizophrenia
Schiele 1975(Schiele 1975)	Chlorpromazine 1100 (200-1500) Loxapine 110 (20-150)	24 26	12	n.i.	Chronic schizophrenia, hospitalized on a long term basis
Serafetinides 1972 (study n :1)(Clark 1969, Clark 1969, Serafetinides Ea//Collins S//Clark 1972, Serafetinides Ea//Willis D//Clark 1972, Serafetinides 1973, Serafetinides 1973, Serafetinides Ea//Clark 1973, Serafetinides Ea//Willis 1973)	Chlorpromazine 830 (200-1000) Haloperidol 12.3 (3-15) Clopenthixol 205 (50-250) [Placebo]	14 14 15 [13]	12	17 13 15	Chronic schizophrenia, duration of illness 2 years or longer

Serafetinides 1972 (study n :2)(Clark 1970, Clark, Huber et al. 1970, Serafetinides, Willis et al. 1971, Serafetinides 1973, Serafetinides Ea//Clark 1973, Serafetinides Ea//Willis 1973)	Chlorpromazine 684 (200-1000) Molindone 68.2 (20-100) [Placebo]	15 15 [14]	12	n.i.	Chronic schizophrenia, duration of illness 2 years or longer
Shepherd 1956(Shepherd and Watt 1956)	Chlorpromazine 300 Reserpine 10 (initial 15, reduced to 10 or 5) [Placebo]	8 8 [8]	6 (total of 18 weeks, Latin square-3 phases, we assess the 2nd)	n.i.	Chronic schizophrenia, all females, “the most deteriorated and apathetic patients” (average length of hospitalization: 15.8 years)
Shopsin 1972(Gershon 1972, Shopsin, Pearson et al. 1972)	Chlorpromazine (300-1200) Loxapine (30-120)	15 15	3	n.i.	Acute schizophrenia, patients newly admitted and fulfilling minimal criteria under disturbance of affect and association according to Symptom Profile for Schizophrenia
Simon 1958(Simon, Wirt et al. 1958, Simon, Wirt et al. 1965)	Chlorpromazine 400 (200-1200) Reserpine 6 (2-16) [Clinical judgement] [Hospital routine]	20 20 [20] [20]	4 (30 days)	n.i.	Schizophrenic reaction, no previous treatment for schizophrenia

Simpson 1973b,c(Simpson 1973, Simpson, Haher et al. 1973)	Chlorpromazine (100-600) Metiapine (100-600)	5 5	8 (cross-over trial with a total duration of 28 weeks)	n.i.	Chronic schizophrenia, all males (average length of hospitalization: 16.2 years)
Singam 2011(Singam, Mamarde et al. 2011)	Chlorpromazine (100-2000) Risperidone (3-16)	50 50 (n analysed, n randomized per group n.i., total n randomized Is 142)	12	n.i.	Schizophrenia (ICD-10)
Singer 1974(Singer and Law 1974)	Chlorpromazine 196 (75-600) Clozapine 155 (50-300)	20 20	5.7 (40 days)	3.3 1.7	Acute schizophrenia
Small 1970(Small 1970)	Chlorpromazine (60-1200) Piperacetazine (20-160)	15 14	6	n.i.	Schizophrenia, acute and chronic

Sommerville 1960(Somerville, Cohen et al. 1960)	Chlorpromazine 472 (200-800) Thioridazine 472 (200-800) [Chlorpromazine placebo] [Thioridazine placebo]	15 15 [15] [15]	6 (43 days)	10	Schizophrenic or paraphrenic psychoses, all patients except “4 manic-depressives”; in long-stay wards, with poor prognosis, all females
Stabenau 1964(Stabenau and Grinols 1964)	Chlorpromazine 371.4 (100-1000) Thioridazine 431.1 (100-1000)	24 28	5-72 days (not defined by the trial protocol)	n.i.	Patients to whom “phenothiazine chemotherapy was indicaded. Criteria included uncontrolled agressive behavior, severe anxiety, hyperactivity, schizophrenic thought disorder, and delusional and hallucinatory states.” Patients were acutely ill and recently hospitalized; a large proportion was schizophrenic (72.5%) and a similar proportion was hospitalized fot the first time.
Steinbook 1973(Steinbook 1973)	Chlorpromazine (200-1500) Loxapine (20-150)	28 26	6	n.i.	Acute schizophrenia, patients newly admitted

Steinbook 1975(Steinbook, Goldstein et al. 1975)	Chlorpromazine 627 (150-900) Metiapine 287 (75-450)	30 30	6	n.i.	Acute schizophrenia, patients newly admitted
Talbot 1964(Talbot 1964)	Chlorpromazine 525 (300-600) Trifluoperazine 17.5 (10-20) [Chlorpromazine plus trifluoperazine]	25 25 [27]	32	n.i.	Chronic schizophrenia, the most severely ill, disturbed and regressed patients were included, all men
Tetreault 1969a(Tetreault 1969, Tetreault, Bordeleau et al. 1969)	Chlorpromazine 539.3 (300-600) Mesoridazine 269.6 (150-300) [Placebo]	15 15 [15]	12	n.i.	Chronic schizophrenia, all females (average length of hospitalization: 16.3 years)
Toru 1971(Toru, Shimazono et al. 1971, Toru, Shimazono et al. 1972)	Chlorpromazine 500 (150-600) Sulpiride 1050 (300-1200)	38 38	8	n.i.	Chronic schizophrenia, “patients were thought non-responsive to conventional psychotropic drugs”and “patients with acute schizophrenia were excluded”
Tuason 1984(Tuason, Escobar et al. 1984)	Chlorpromazine 630 (300-1500) Loxapine 68 (30-150)	34 34	4	n.i.	Paranoid schizophrenia (RDC), newly admitted patients

Umene 1972(Umene, Uriu et al. 1972)	Chlorpromazine (150-600) Pimozide (3-12)	46 46	8	n.i.	Chronic schizophrenia with acute exacerbation, duration of illness for most of the patients (74) >10 years
Van Praag 1975a(van Praag, Dols et al. 1975, van Praag and Korf 1975)	Chlorpromazine 400 (0-600) Oxypertine 225 (0-450)	19 21	3	n.i.	Acute psychotic disorder, “patients showed delusions and/or hallucinations”
Vyas 1980(Vyas and Kalla 1980)	Chlorpromazine 551 (300-900) Loxapine 51.7 (30-90)	15 15	24	n.i.	Chronic schizophrenia
Waldrop 1961(Waldrop, Robertson et al. 1961)	Chlorpromazine 740 (<800) Thioridazine 740 (<800)	78 78	13	n.i.	Chronic schizophrenia (at least 5 years), poor prognosis for early rehabilitation and discharge, majority of patients underactive and withdrawn, all female (average length of hospitalization: Cpz 12.1, Thior. 14.6 years)
Walsh 1959(Walsh, Walton et al. 1959)	Chlorpromazine 242.9 (75-300) Triflupromazine 197.7 (75-300) [Placebo]	22 22 [22]	8	n.i.	Chronic schizophrenia, all females (average length of hospitalization: Cpz 12.6, Trif. 13.4 years)

Wang 1982(Wang, Larson et al. 1982)	Chlorpromazine (375-444/day) Penfluridol (72-81/week)	20 21	12-20 (preceded by a 4-12-weeks of penfluridol titration)	n.i.	Chronic schizophrenia for at least 18 months prior to study, all males
Wilson 1961(Anon 1961, Wilson, McKay et al. 1961)	Chlorpromazine 300 (150-450) Trifluoperazine 42.5 (15-30) Prochlorperazine 60 (30-90) [Placebo]	2 2 2 [2]	2 (cross-over trial with a total duration of 8 weeks)	2.75	Paranoid schizophrenia, “intermediate-stay patients, i.e. those who had failed to respond satisfactorily to the initial 3 months intensive therapy following admission”, all females
Wilson 1982a(Wilson, Roberts et al. 1982)	Chlorpromazine 381 (95-950) Pimozide 7.3 (2-20)	22 21	52	14 13.5	Chronic schizophrenia (DSM-II) plus “demonstrated capability of responding to drug treatment”

1. Abbreviations: Cpz= Chlorpromazine, DSM= Diagnostic and Statistical Manual of Mental Disorders, ICD= International Classification of Diseases, NIMH-PRB= National Institute of Mental Health-Psychopharmacology Reasearch Branch, NIMH-PSC= National Institute of Mental Health-Psychopharmacology Service Center, RDC= Reasearch Diagnostic Criteria, TRS= Treatment Resistant Schizophrenia, n=number, n.i.= not indicated
2. If there were several publications of the same study, the study names refer to the publication that we considered to be the main one
3. [Drug groups or numbers in squared brackets were not used in the analysis]

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D. Publications
Online supplement

eSubgroup and meta-regression analyses

We applied subgroup analysis assuming a common among-study variance component across subgroups using Comprehensive Meta-analysis Version 2 to identify associations between potential subgroups and effect sizes and meta-regression analysis with residual maximum likelihood (REML) to estimate the additive (between-study) component of variance tau2 using STATA 12. The following a priori defined moderators were assessed: first-episode status, treatment resistance status, age and chlorpromazine dose.

The analyses were conducted on the primary outcome response to treatment only. Analyses were applied as long as at least 3 studies provided data for subgroup analysis and 5 for meta-regression analysis. It should be noted that the number of studies in most analyses was small. Moreover, not all studies provided data on each moderator. Thus, the statistical power to find significant differences was limited.

A. Subgroup analyses (assuming a common among-study variance component across subgroups, random effects model)

First episode versus treatment resistant versus neither first episode nor treatment resistant status

eTable A.1: Chlorpromazine versus clozapine

	Effect size (Response Ratio, M-H)				Test of null hypothesis (2-Tail)		Heterogeneity		
Groups	**Number of studies**	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**Z-Value**	**p-Value**	**Q-Value**	**df(Q)**	**p-Value**
First episode	1	0.961	0.701	1.318	-0.246	0.805			
Treatment-resistant	2	0.113	0.046	0.276	-4.780	0.00			
Not first episode or treatment resistant	5	0.730	0.573	1.929	-2.558	0.011			
Total between							**19.622**	**2**	***0.000***
Overall	8	0.510	0.249	1.045	-1.840	0.066			

M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval

eTable A.2: Chlorpromazine versus haloperidol

	Effect size (Response Ratio, M-H)				Test of null hypothesis (2-Tail)		Heterogeneity		
Groups	**Number of studies**	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**Z-Value**	**p-Value**	**Q-Value**	**df(Q)**	**p-Value**
Treatment-resistant	1	0.750	0.203	2.778	-0.431	0.667			
Not treatment resistant	4	0.727	0.403	1.309	-1.063	0.288			
Total between							0.002	1	0.966
Overall	5	0.731	0.427	1.250	-1.146	0.252			

M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval

eTable A.3: Chlorpromazine versus olanzapine

	Effect size (Response Ratio, M-H)				Test of null hypothesis (2-Tail)		Heterogeneity		
Groups	**Number of studies**	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**Z-Value**	**p-Value**	**Q-Value**	**df(Q)**	**p-Value**
Treatment-resistant	1	0.143	0.008	2.683	-1.300	0.193			
Not treatment resistant	3	0.204	0.060	0.700	-2.528	0.011			
Total between							0.048	1	0.826
Overall	4	0.193	0.062	0.602	-2.835	0.005			

M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval

eTable A.4: Chlorpromazine versus quetiapine

	Effect size (Response Ratio, M-H)				Test of null hypothesis (2-Tail)		Heterogeneity		
Groups	**Number of studies**	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**Z-Value**	**p-Value**	**Q-Value**	**df(Q)**	**p-Value**
Treatment-resistant	2	0.873	0.481	1.582	-0.449	0.654			
Not treatment resistant	2	0.963	0.621	1.492	-0.171	0.864			
Total between							0.068	1	0.795
Overall	4	0.930	0.653	1.323	-0.403	0.687			

M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval

eTable A.5: Chlorpromazine versus sulpiride

	Effect size (Response Ratio, M-H)				Test of null hypothesis (2-Tail)		Heterogeneity		
Groups	**Number of studies**	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**Z-Value**	**p-Value**	**Q-Value**	**df(Q)**	**p-Value**
Treatment-resistant	2	0.812	0.362	1.824	-0.503	0.615			
Not treatment resistant	1	0.615	0.175	2.161	-0.757	0.449			
Total between							0.133	1	0.716
Overall	3	0.749	0.379	1.478	-0.833	0.405			

M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval

eTable A.6: Chlorpromazine versus all other first generation antipsychotics

Effect size (Response Ratio, M-H)					Test of null hypothesis (2-Tail)		Heterogeneity		
Groups	**Number of studies**	**Point estimate**	**Lower limit of 95% CI**	**Upper limit of 95% CI**	**Z-Value**	**p-Value**	**Q-Value**	**df(Q)**	**p-Value**
First episode	1	0.961	0.429	2.151	-0.096	0.923			
Treatment resistant	12	0.756	0.541	1.057	-1.634	0.102			
Not first episode or treatment resistant	72	0.964	0.846	1.098	-0.555	0.579			
Total between							1.756	2	0.416
Overall	85	0.905	0.741	1.105	-0.980	0.327			

M-H=Maentel-Haenszel, 95% CI=95% Confidence Interval

B. Meta-regression analyses (mixed effects unrestricted maximum likelihood)

B.1. Age

eTable B.1.1: Chlorpromazine versus clozapine

	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI	t-test	p-Value
Slope	-0.219	-0.451	0.012	-2.63	0.058
Intercept	6.041	-1.031	13.113	2.37	0.077
Tau-squared	0.195				

95% CI=95% Confidence Interval

eTable B.1.2: Chlorpromazine versus loxapine

	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI	t-test	p-Value
Slope	-0.013	-0.088	0.032	-0.46	0.667
Intercept	0.346	-2.199	2.890	0.35	0.741
Tau-squared	0.054				

95% CI=95% Confidence Interval

eTable B.1.3: Chlorpromazine versus all other first generation antipsychotics

	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI	t-test	p-Value
Slope	0.008	-0.013	0.029	0.78	0.439
Intercept	-0.379	-1.113	0.355	-1.03	0.307
Tau-squared	0.03966				

95%CI=95% Confidence Interval

B.2. Chlorpromazine dose

eTable B.2.1: Chlorpromazine versus clozapine

	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI	t-test	p-Value
Slope	-0.002	-0.003	-0.001	-4.43	***0.004***
Intercept	0.573	-0.095	1.051	2.93	**0.026**
Tau-squared	0.006				

95% CI=95% Confidence Interval

eTable B.2.2: Chlorpromazine versus loxapine

	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI	t-test	p-Value
Slope	0.0002	-0.0012	0.0015	0.27	0.799
Intercept	- 0.1905	-1.2845	0.9036	-0.43	0.685
Tau-squared	0.126				

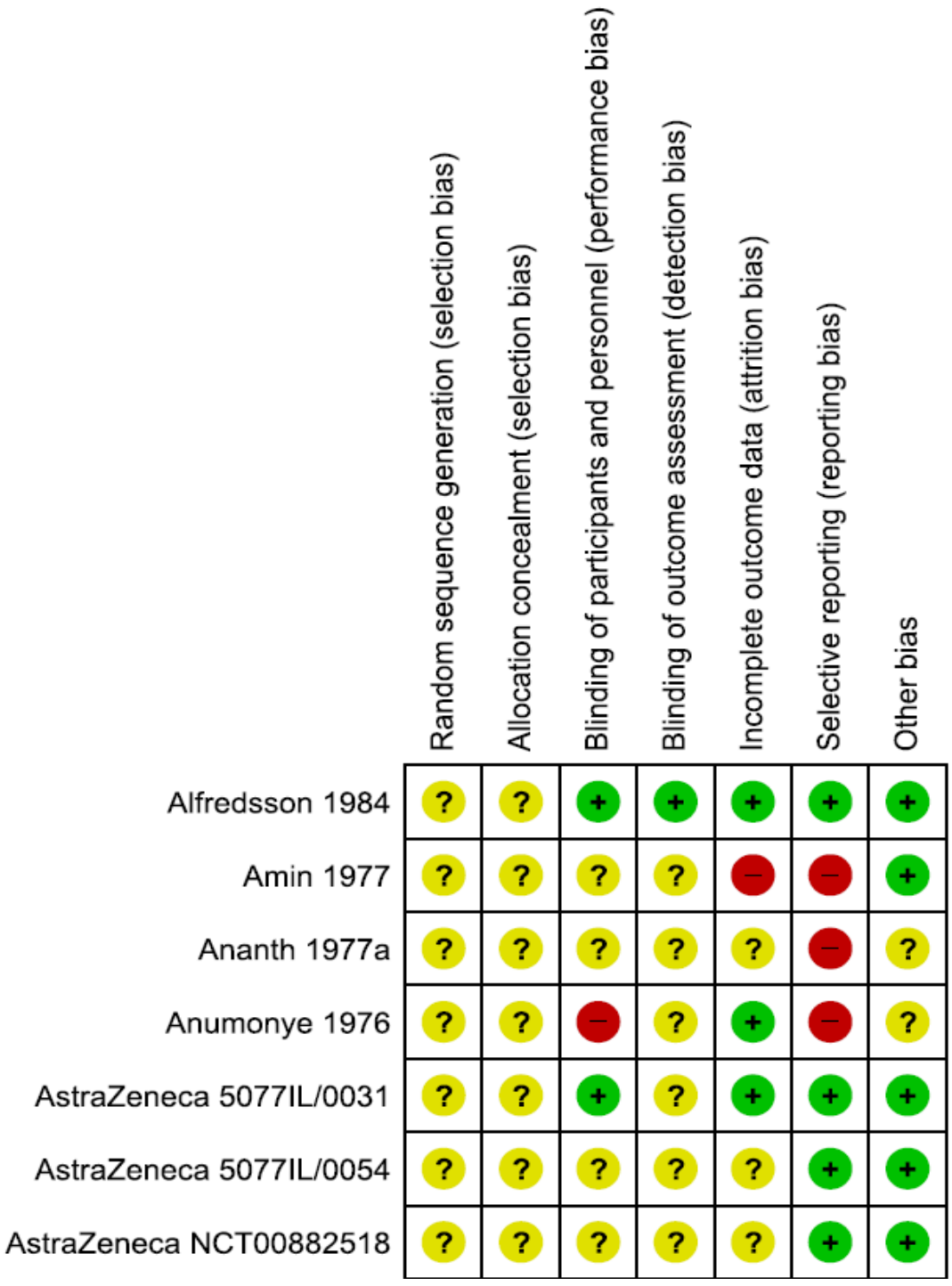
95% CI=95% Confidence Interval

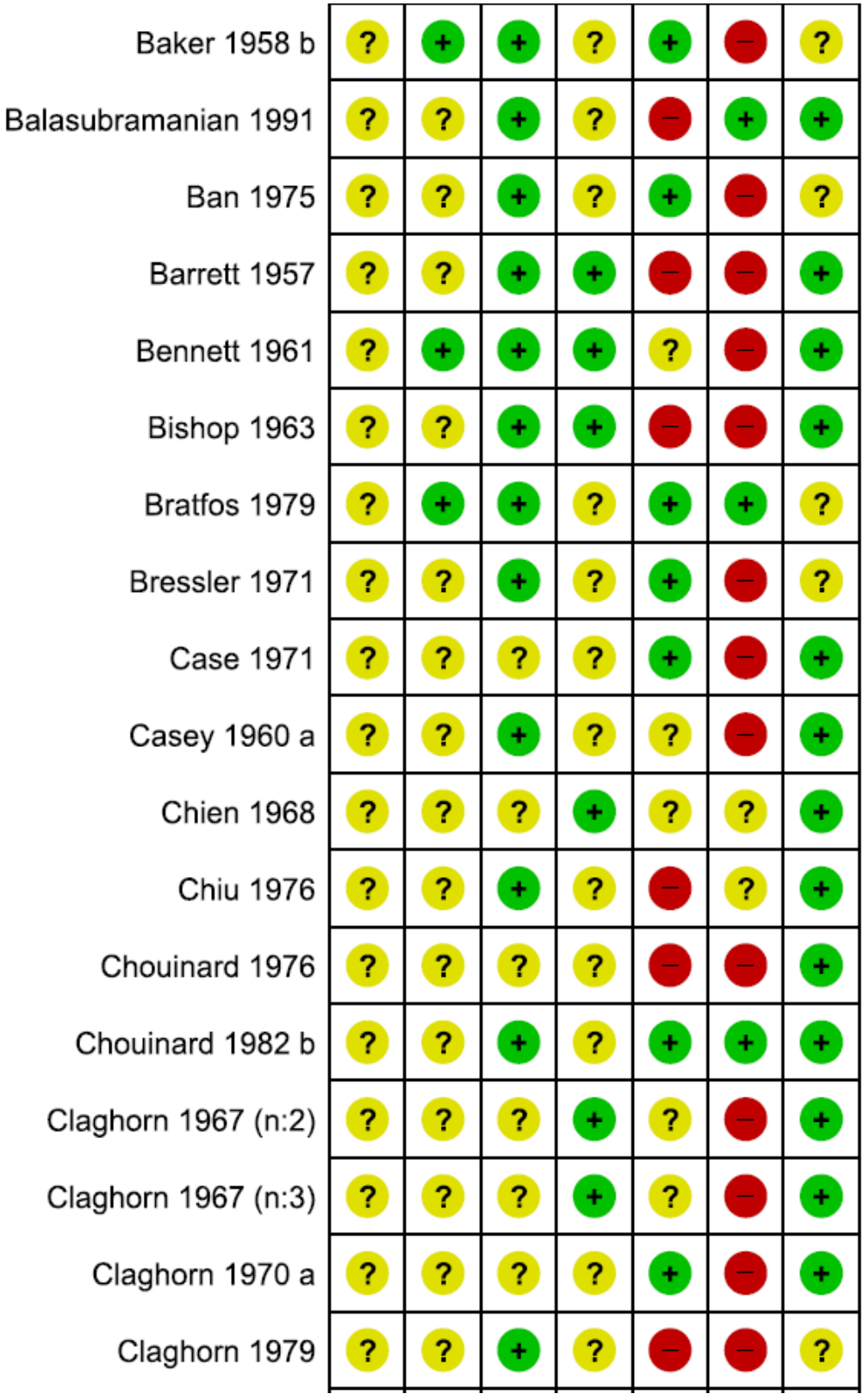
eTable B.2.3: Chlorpromazine versus all other first generation antipsychotics

	Point estimate	Lower limit of 95% CI	Upper limit of 95% CI	t-test	p-Value
Slope	-0.0004	-0.0008	-0.0001	-2.45	***0.017***
Intercept	0.1982	-0.0232	0.4196	1.78	0.079
Tau-squared	0.05107				

95%CI=95% Confidence Interval

eFigure 1: Risk of bias summary

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Bennett 1961
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Case 1971
Casey 1960 a
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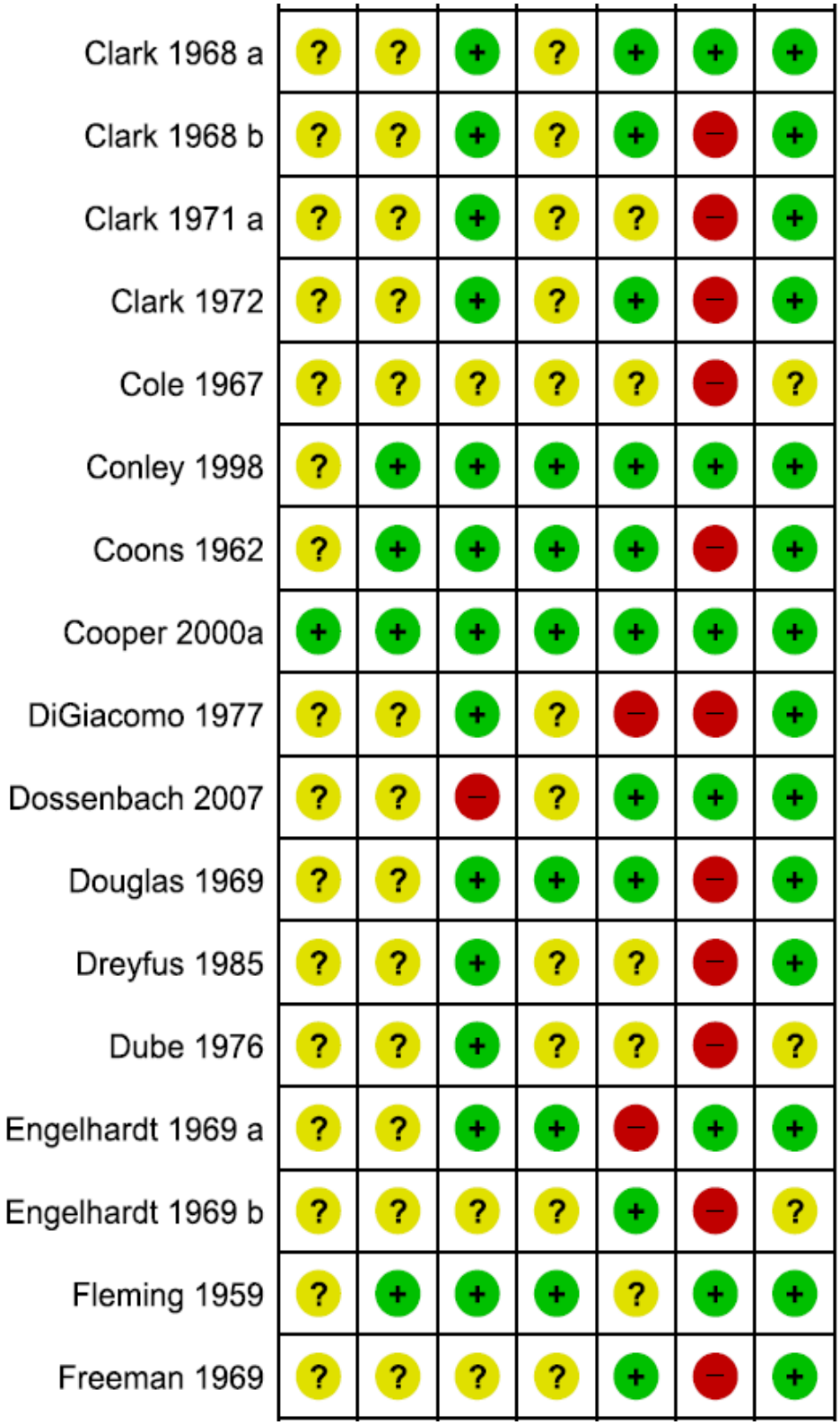
Claghorn 1967 (n:3)
Claghorn 1970 a
Claghorn 1979


Clark 1968 a
Clark 1968 b
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Cole 1967
Conley 1998
Coons 1962
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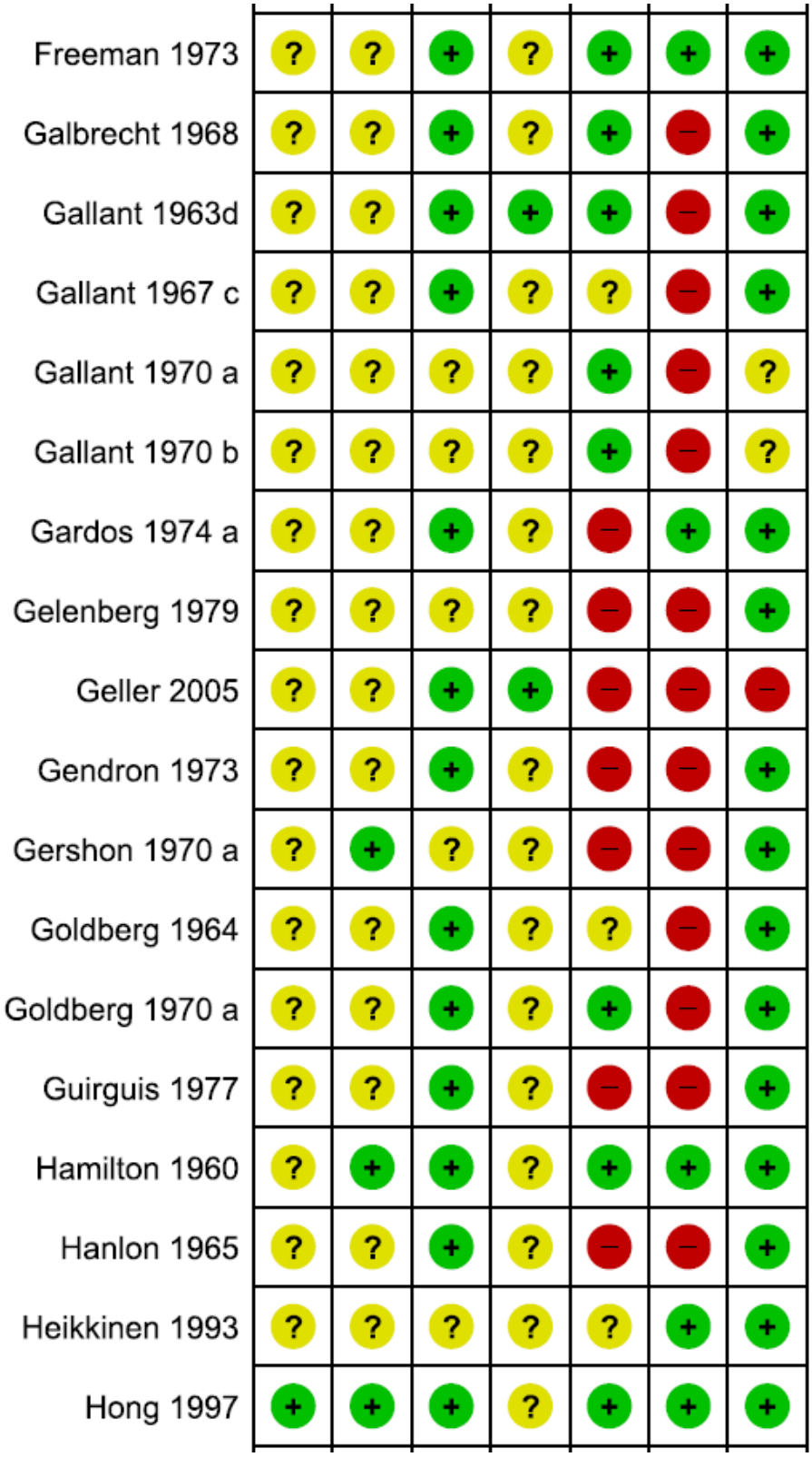
Fleming 1959
Freeman 1969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Goldberg 1964
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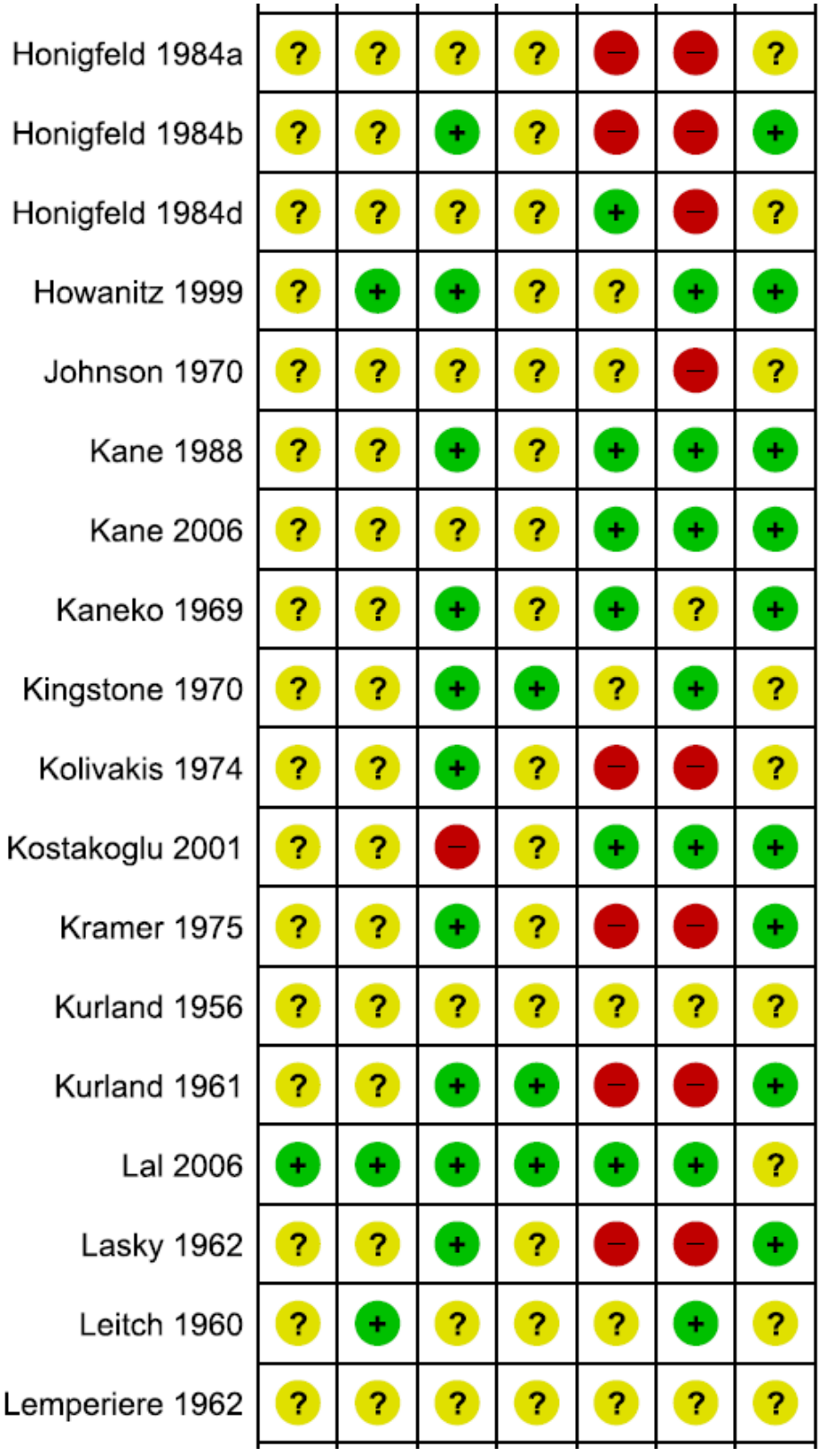
Guirguis 1977
Hamilton 1960
Hanlon 1965
Heikkinen 1993
Hong 1997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Honigfeld 1984d
Howanitz 1999
Johnson 1970
Kane 1988
Kane 2006
Kaneko 1969
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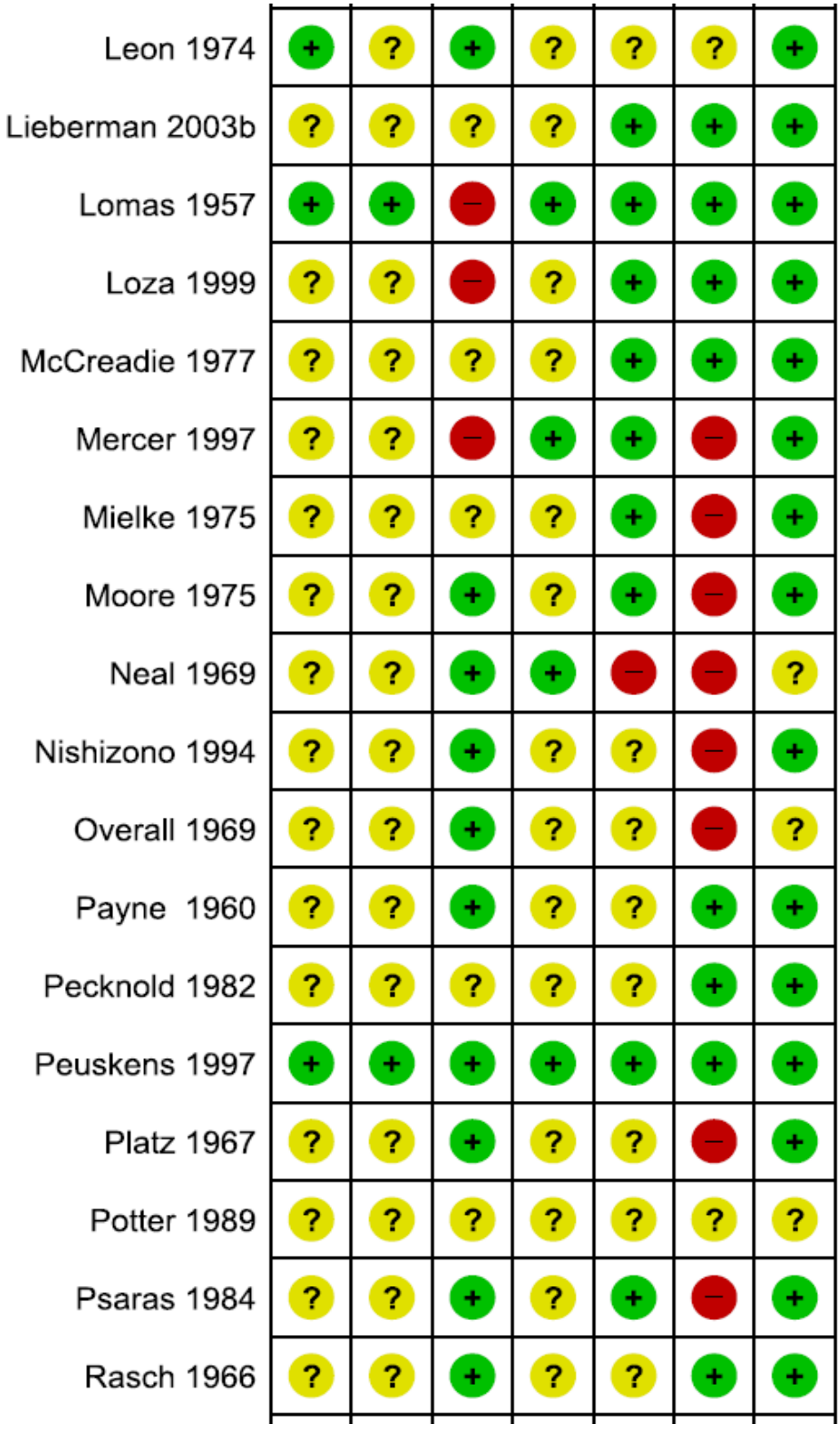
Lasky 1962
Leitch 1960
Lemperiere 1962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Lieberman 2003b
Lomas 1957
Loza 1999
McCreadie 1977
Mercer 1997
Mielke 1975
Moore 1975
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Payne 1960
Pecknold 1982
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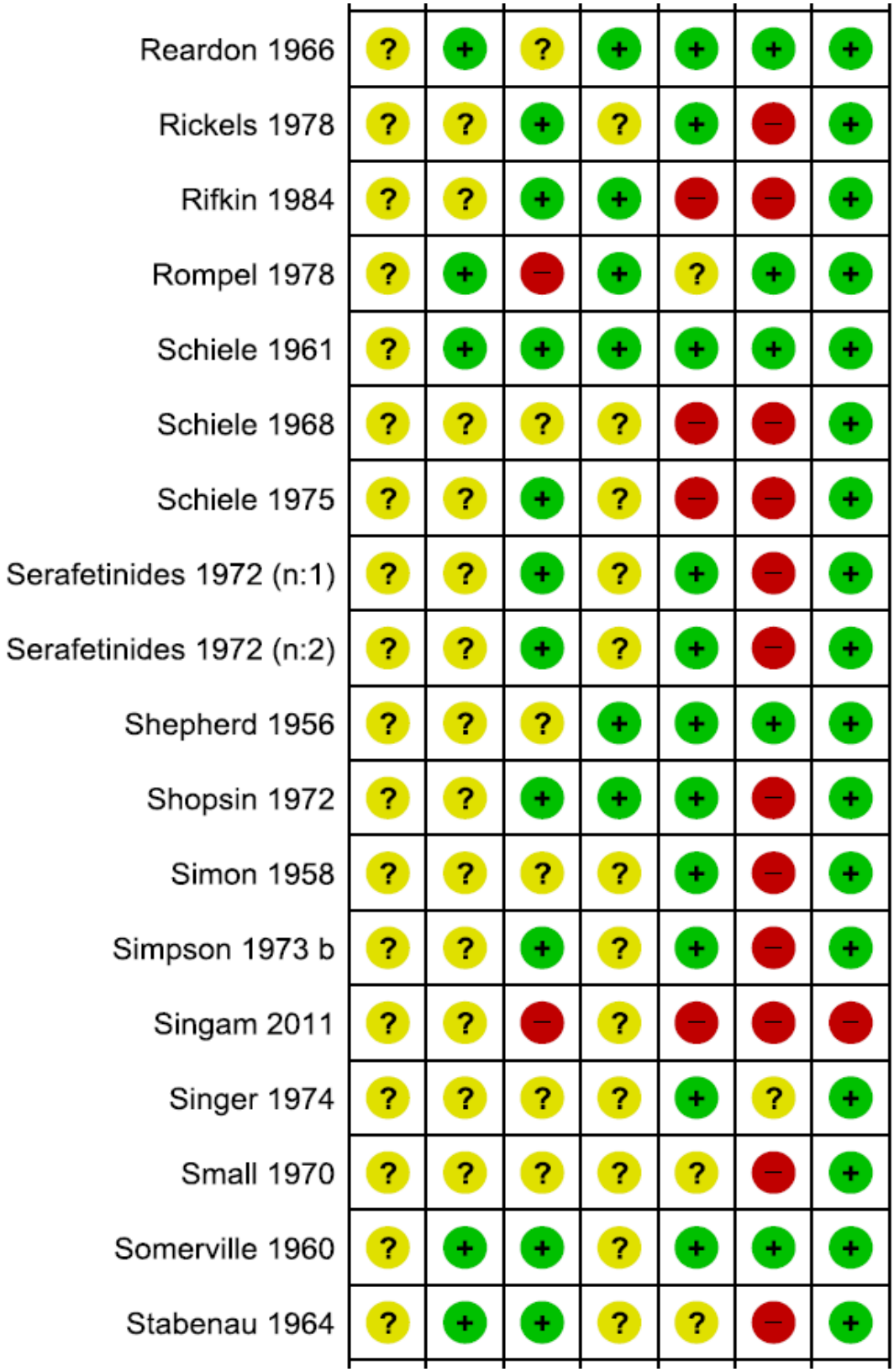
Platz 1967
Potter 1989
Psaras 1984
Rasch 1966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Rifkin 1984
Rompel 1978
Schiele 1961
Schiele 1968
Schiele 1975
Serafetinides 1972 (n:1)
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Simon 1958
Simpson 1973 b
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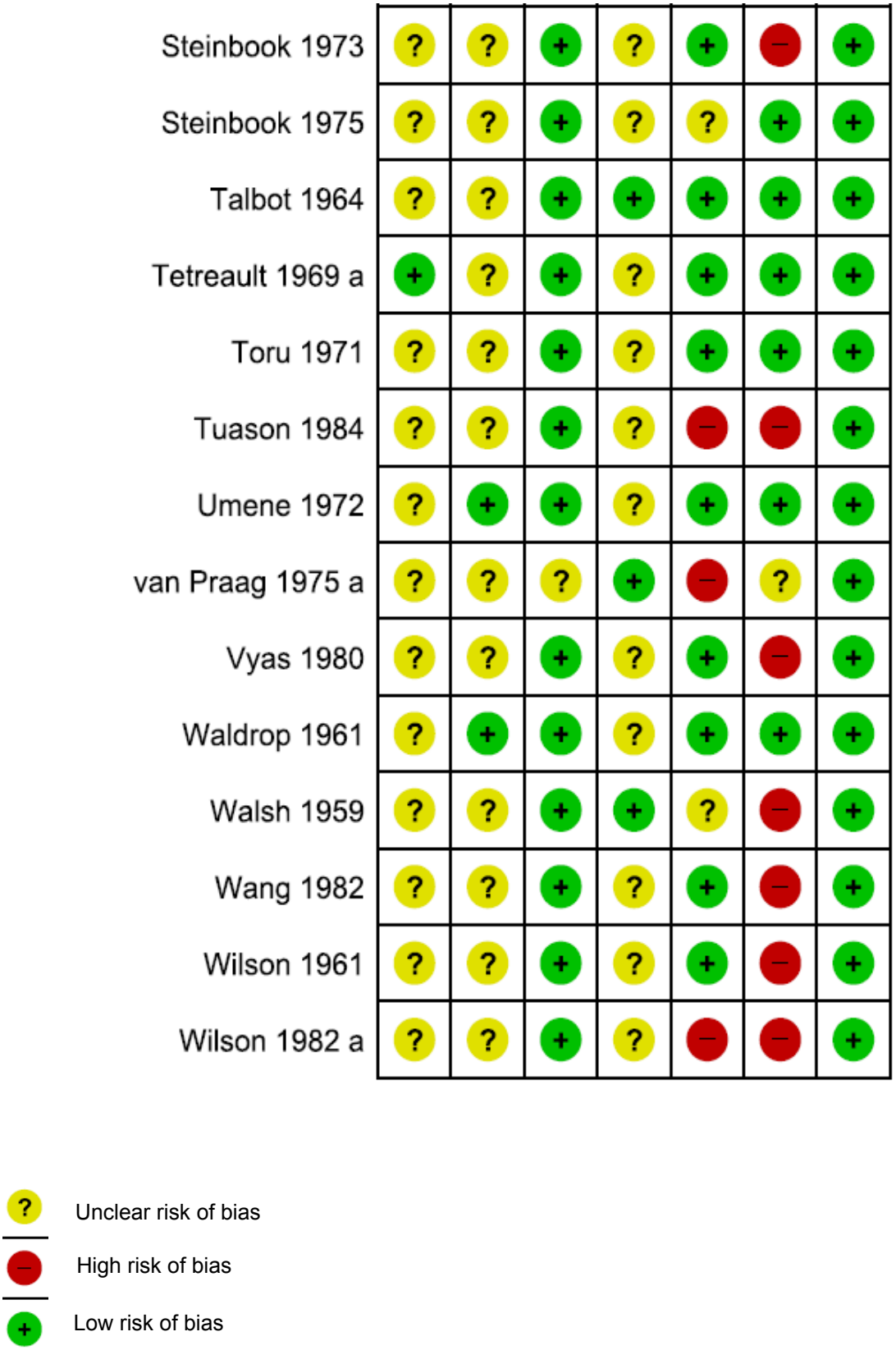
Small 1970
Somerville 1960
Stabenau 1964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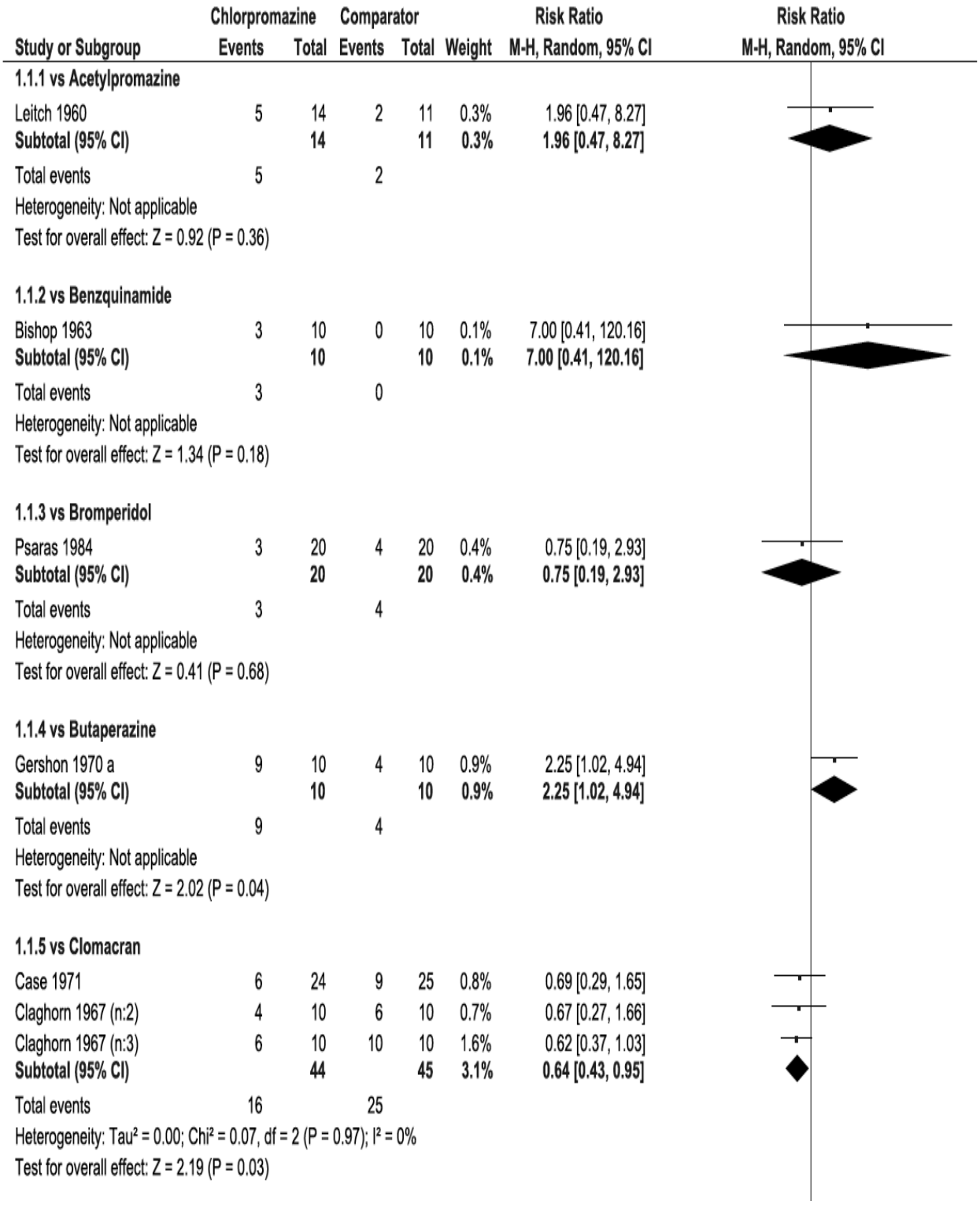
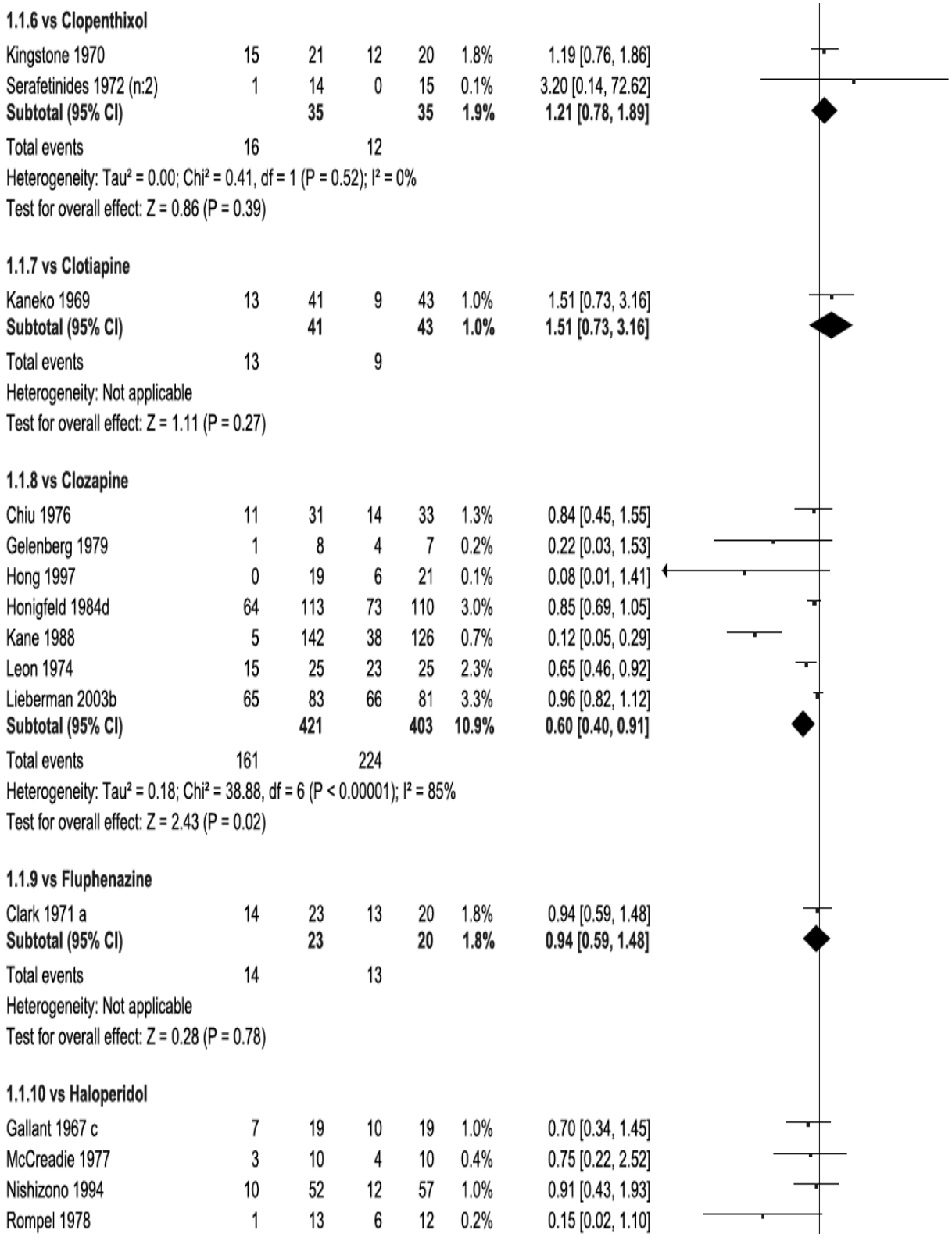
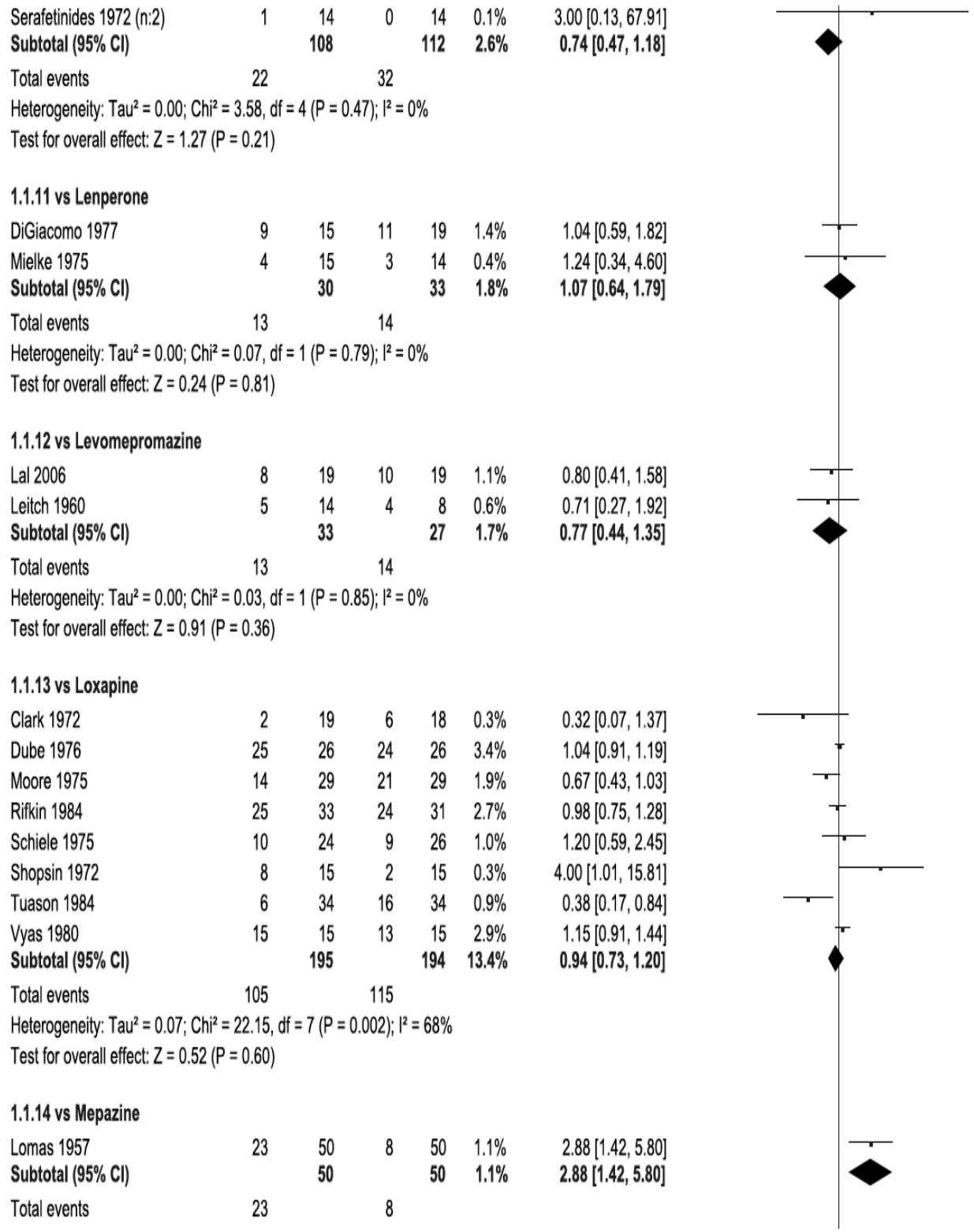
Steinbook 1975
Talbot 1964
Tetreault 1969 a
Toru 1971
Tuason 1984
Umene 1972
van Praag 1975 a
Vyas 1980
Waldrop 1961
Walsh 1959
Wang 1982
Wilson 1961
Wilson 1982 a
Unclear risk of bias
High risk of bias
Low risk of bias

eFigure 2: Response ratio of chlorpromazine versus all other antipsychotic drugs in individual trials




1.1.6 vs Clopenthixol
Kingstone 1970 15 21 12 20 1.8% 1.19 [0.76, 1.86]
Serafetinides 1972 (n:2) 1 14 0 15 0.1% 3.20 [0.14, 72.62]
Subtotal (95% CI) 35 35 1.9% 1.21 [0.78, 1.89]
Total events 16 12
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)
1.1.7 vs Clotiapine
Kaneko 1969 13 41 9 43 1.0% 1.51 [0.73, 3.16]
Subtotal (95% CI) 41 43 1.0% 1.51 [0.73, 3.16]
Total events 13 9
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)
1.1.8 vs Clozapine
Chiu 1976 11 31 14 33 1.3% 0.84 [0.45, 1.55]
Gelenberg 1979 1 8 4 7 0.2% 0.22 [0.03, 1.53]
Hong 1997 0 19 6 21 0.1% 0.08 [0.01, 1.41]
Honigfeld 1984d 64 113 73 110 3.0% 0.85 [0.69, 1.05]
Kane 1988 5 142 38 126 0.7% 0.12 [0.05, 0.29]
Leon 1974 15 25 23 25 2.3% 0.65 [0.46, 0.92]
Lieberman 2003b 65 83 66 81 3.3% 0.96 [0.82, 1.12]
Subtotal (95% CI) 421 403 10.9% 0.60 [0.40, 0.91]
Total events 161 224
Heterogeneity: Tau² = 0.18; Chi² = 38.88, df = 6 (P < 0.00001); I² = 85%
Test for overall effect: Z = 2.43 (P = 0.02)
1.1.9 vs Fluphenazine
Clark 1971 a 14 23 13 20 1.8% 0.94 [0.59, 1.48]
Subtotal (95% CI) 23 20 1.8% 0.94 [0.59, 1.48]
Total events 14 13
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
1.1.10 vs Haloperidol
Gallant 1967 c 7 19 10 19 1.0% 0.70 [0.34, 1.45]
McCreadie 1977 3 10 4 10 0.4% 0.75 [0.22, 2.52]
Nishizono 1994 10 52 12 57 1.0% 0.91 [0.43, 1.93]
Rompel 1978 1 13 6 12 0.2% 0.15 [0.02, 1.10]



Serafetinides 1972 (n:2)	1	14	0	14	0.1%	3.00 [0.13, 67.91]
Subtotal (95% CI)		**108**		**112**	**2.6%**	**0.74 [0.47, 1.18]**
Total events	22		32			
Heterogeneity: Tau² = 0.00; Chi² = 3.58, df = 4 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.27 (P = 0.21)						
1.1.11 vs Lenperone						
DiGiacomo 1977	9	15	11	19	1.4%	1.04 [0.59, 1.82]
Mielke 1975	4	15	3	14	0.4%	1.24 [0.34, 4.60]
Subtotal (95% CI)		**30**		**33**	**1.8%**	**1.07 [0.64, 1.79]**
Total events	13		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.1.12 vs Levomepromazine						
Lal 2006	8	19	10	19	1.1%	0.80 [0.41, 1.58]
Leitch 1960	5	14	4	8	0.6%	0.71 [0.27, 1.92]
Subtotal (95% CI)		**33**		**27**	**1.7%**	**0.77 [0.44, 1.35]**
Total events	13		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.1.13 vs Loxapine						
Clark 1972	2	19	6	18	0.3%	0.32 [0.07, 1.37]
Dube 1976	25	26	24	26	3.4%	1.04 [0.91, 1.19]
Moore 1975	14	29	21	29	1.9%	0.67 [0.43, 1.03]
Rifkin 1984	25	33	24	31	2.7%	0.98 [0.75, 1.28]
Schiele 1975	10	24	9	26	1.0%	1.20 [0.59, 2.45]
Shopsin 1972	8	15	2	15	0.3%	4.00 [1.01, 15.81]
Tuason 1984	6	34	16	34	0.9%	0.38 [0.17, 0.84]
Vyas 1980	15	15	13	15	2.9%	1.15 [0.91, 1.44]
Subtotal (95% CI)		**195**		**194**	**13.4%**	**0.94 [0.73, 1.20]**
Total events	105		115			
Heterogeneity: Tau² = 0.07; Chi² = 22.15, df = 7 (P = 0.002); I² = 68%						
Test for overall effect: Z = 0.52 (P = 0.60)						
1.1.14 vs Mepazine						
Lomas 1957	23	50	8	50	1.1%	2.88 [1.42, 5.80]
Subtotal (95% CI)		**50**		**50**	**1.1%**	**2.88 [1.42, 5.80]**
Total events	23		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.95 (P = 0.003)

1.1.15 vs Mesoridazine

Douglas 1969	9	32	8	32	0.8%	1.13 [0.50, 2.55]
Freeman 1969	12	25	15	25	1.6%	0.80 [0.48, 1.34]
Subtotal (95% CI)		**57**		**57**	**2.4%**	**0.88 [0.57, 1.37]**
Total events	21		23			

Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.56 (P = 0.58)

1.1.16 vs Metiapine

Kramer 1975	20	38	15	39	1.6%	1.37 [0.83, 2.25]
Steinbook 1975	21	30	21	30	2.4%	1.00 [0.72, 1.39]
Subtotal (95% CI)		**68**		**69**	**4.0%**	**1.11 [0.82, 1.50]**
Total events	41		36			

Heterogeneity: Tau² = 0.01; Chi² = 1.16, df = 1 (P = 0.28); I² = 14%
Test for overall effect: Z = 0.67 (P = 0.50)

1.1.17 vs Molindone

Serafetinides 1972 (n:2)	3	15	3	15	0.3%	1.00 [0.24, 4.18]
Subtotal (95% CI)		**15**		**15**	**0.3%**	**1.00 [0.24, 4.18]**
Total events	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

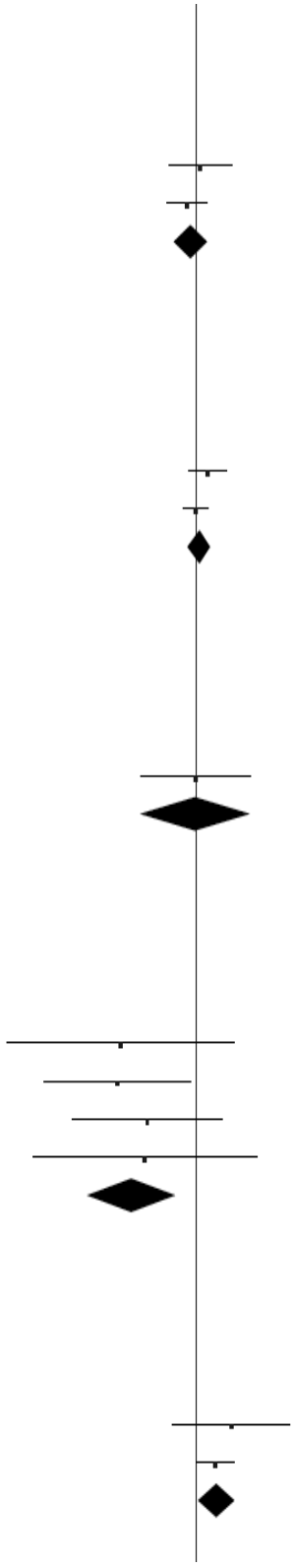
1.1.18 vs Olanzapine

Conley 1998	0	42	3	42	0.1%	0.14 [0.01, 2.68]
Dossenbach 2007	1	12	17	27	0.2%	0.13 [0.02, 0.88]
Kostakoglu 2001	1	10	7	20	0.2%	0.29 [0.04, 2.01]
Loza 1999	0	14	3	27	0.1%	0.27 [0.01, 4.83]
Subtotal (95% CI)		**78**		**116**	**0.5%**	**0.19 [0.06, 0.60]**
Total events	2		30			

Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 3 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)

1.1.19 vs Oxypertine

Neal 1969	5	20	2	20	0.3%	2.50 [0.55, 11.41]
van Praag 1975 a	15	19	10	21	1.6%	1.66 [1.00, 2.75]
Subtotal (95% CI)		**39**		**41**	**1.9%**	**1.73 [1.07, 2.79]**
Total events	20		12			



Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

1.1.20 vs Penfluridol

Claghorn 1979	25	28	23	28	3.0%	1.09 [0.88, 1.35]
Subtotal (95% CI)		**28**		**28**	**3.0%**	**1.09 [0.88, 1.35]**
Total events	25		23			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

1.1.21 vs Periciazine

Rasch 1966	2	21	0	21	0.1%	5.00 [0.25, 98.27]
Subtotal (95% CI)		**21**		**21**	**0.1%**	**5.00 [0.25, 98.27]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)

1.1.22 vs Pimozide

Anumonye 1976	10	12	10	12	2.2%	1.00 [0.70, 1.43]
Kolivakis 1974	8	25	11	26	1.0%	0.76 [0.37, 1.56]
Pecknold 1982	6	10	10	10	1.6%	0.62 [0.37, 1.03]
Umene 1972	9	46	6	46	0.7%	1.50 [0.58, 3.87]
Wilson 1982 a	0	22	0	21		Not estimable
Subtotal (95% CI)		**115**		**115**	**5.5%**	**0.87 [0.64, 1.19]**
Total events	33		37			

Heterogeneity: Tau² = 0.02; Chi² = 3.76, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 0.88 (P = 0.38)

1.1.23 vs Piperacetazine

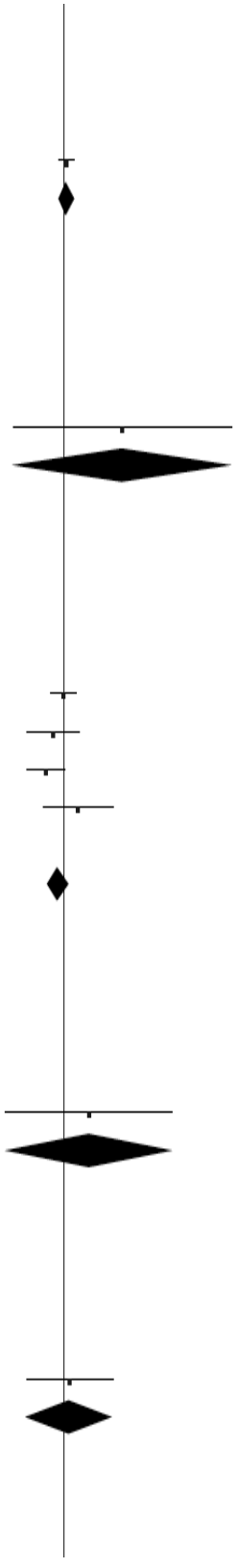
Gallant 1970 a	2	13	1	13	0.1%	2.00 [0.21, 19.44]
Subtotal (95% CI)		**13**		**13**	**0.1%**	**2.00 [0.21, 19.44]**
Total events	2		1			

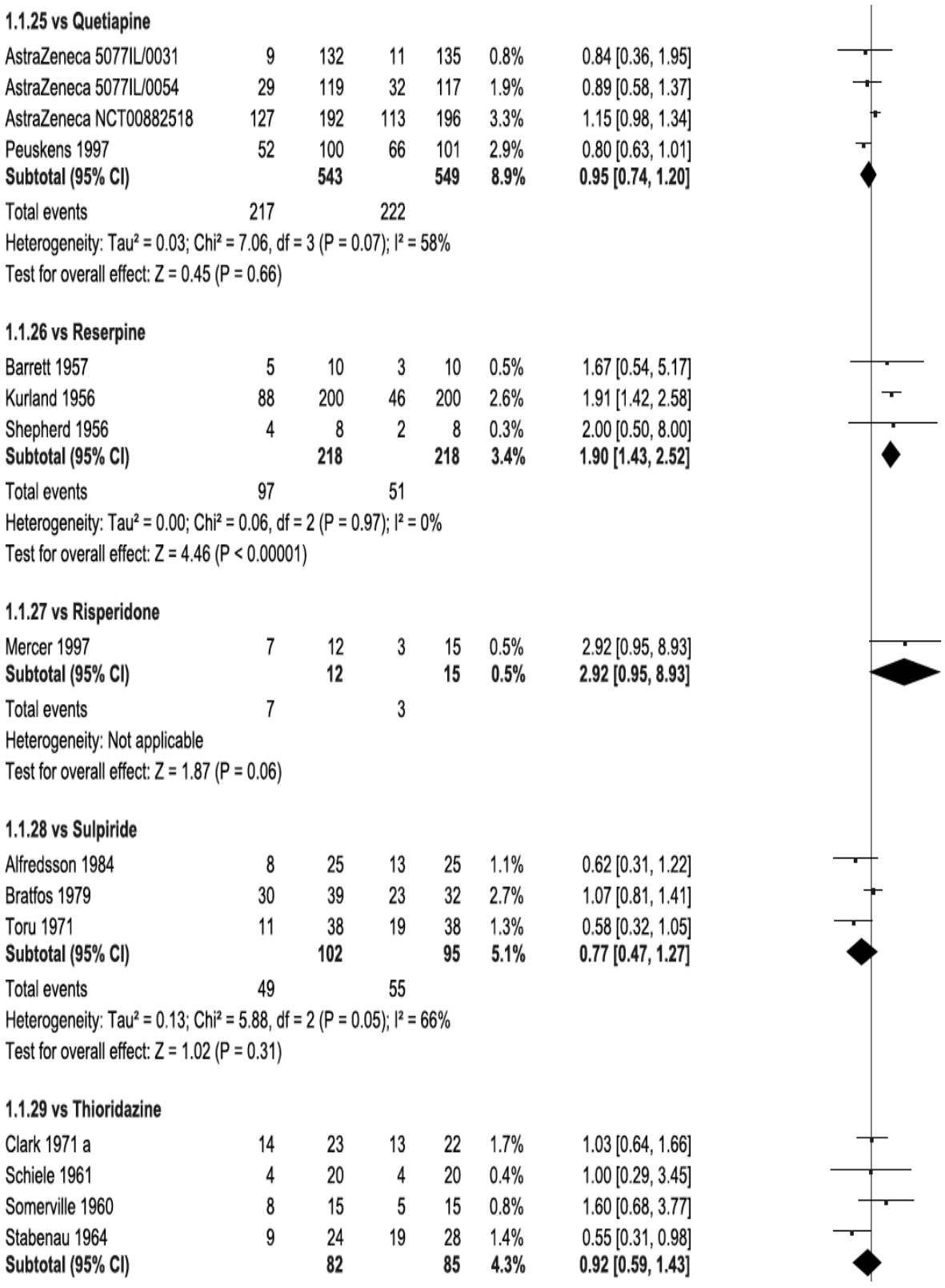
Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

1.1.24 vs Promazine

Leitch 1960	5	14	3	10	0.5%	1.19 [0.37, 3.87]
Subtotal (95% CI)		**14**		**10**	**0.5%**	**1.19 [0.37, 3.87]**
Total events	5		3			

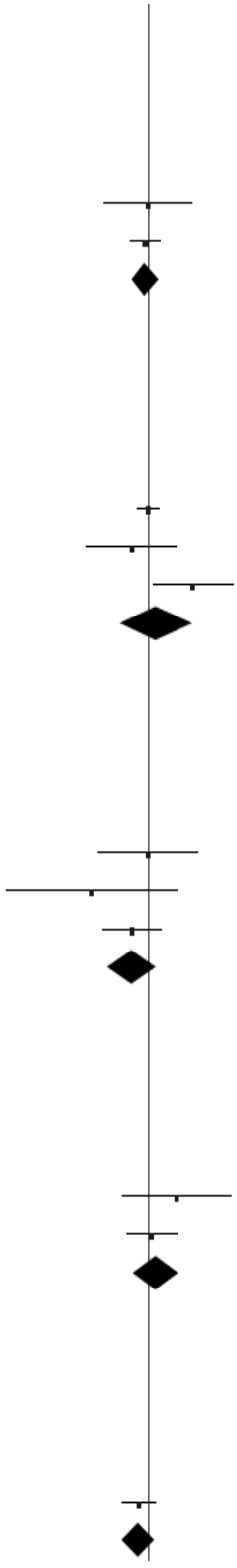
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)

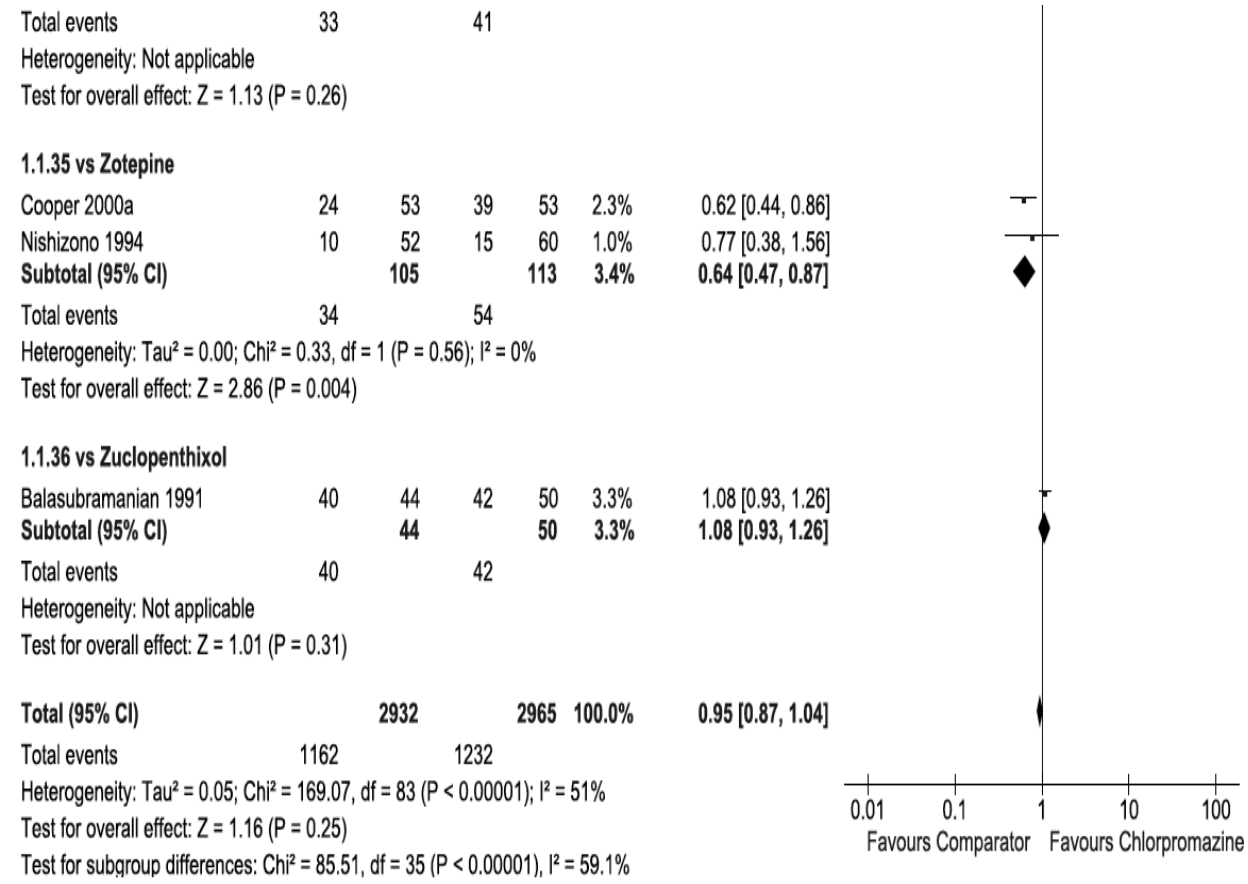




1.1.25 vs Quetiapine						
AstraZeneca 5077IL/0031	9	132	11	135	0.8%	0.84 [0.36, 1.95]
AstraZeneca 5077IL/0054	29	119	32	117	1.9%	0.89 [0.58, 1.37]
AstraZeneca NCT00882518	127	192	113	196	3.3%	1.15 [0.98, 1.34]
Peuskens 1997	52	100	66	101	2.9%	0.80 [0.63, 1.01]
Subtotal (95% CI)		**543**		**549**	**8.9%**	**0.95 [0.74, 1.20]**
Total events	217		222			
Heterogeneity: Tau² = 0.03; Chi² = 7.06, df = 3 (P = 0.07); I² = 58%						
Test for overall effect: Z = 0.45 (P = 0.66)						
1.1.26 vs Reserpine						
Barrett 1957	5	10	3	10	0.5%	1.67 [0.54, 5.17]
Kurland 1956	88	200	46	200	2.6%	1.91 [1.42, 2.58]
Shepherd 1956	4	8	2	8	0.3%	2.00 [0.50, 8.00]
Subtotal (95% CI)		**218**		**218**	**3.4%**	**1.90 [1.43, 2.52]**
Total events	97		51			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 4.46 (P < 0.00001)						
1.1.27 vs Risperidone						
Mercer 1997	7	12	3	15	0.5%	2.92 [0.95, 8.93]
Subtotal (95% CI)		**12**		**15**	**0.5%**	**2.92 [0.95, 8.93]**
Total events	7		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.87 (P = 0.06)						
1.1.28 vs Sulpiride						
Alfredsson 1984	8	25	13	25	1.1%	0.62 [0.31, 1.22]
Bratfos 1979	30	39	23	32	2.7%	1.07 [0.81, 1.41]
Toru 1971	11	38	19	38	1.3%	0.58 [0.32, 1.05]
Subtotal (95% CI)		**102**		**95**	**5.1%**	**0.77 [0.47, 1.27]**
Total events	49		55			
Heterogeneity: Tau² = 0.13; Chi² = 5.88, df = 2 (P = 0.05); I² = 66%						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.1.29 vs Thioridazine						
Clark 1971 a	14	23	13	22	1.7%	1.03 [0.64, 1.66]
Schiele 1961	4	20	4	20	0.4%	1.00 [0.29, 3.45]
Somerville 1960	8	15	5	15	0.8%	1.60 [0.68, 3.77]
Stabenau 1964	9	24	19	28	1.4%	0.55 [0.31, 0.98]
Subtotal (95% CI)		**82**		**85**	**4.3%**	**0.92 [0.59, 1.43]**

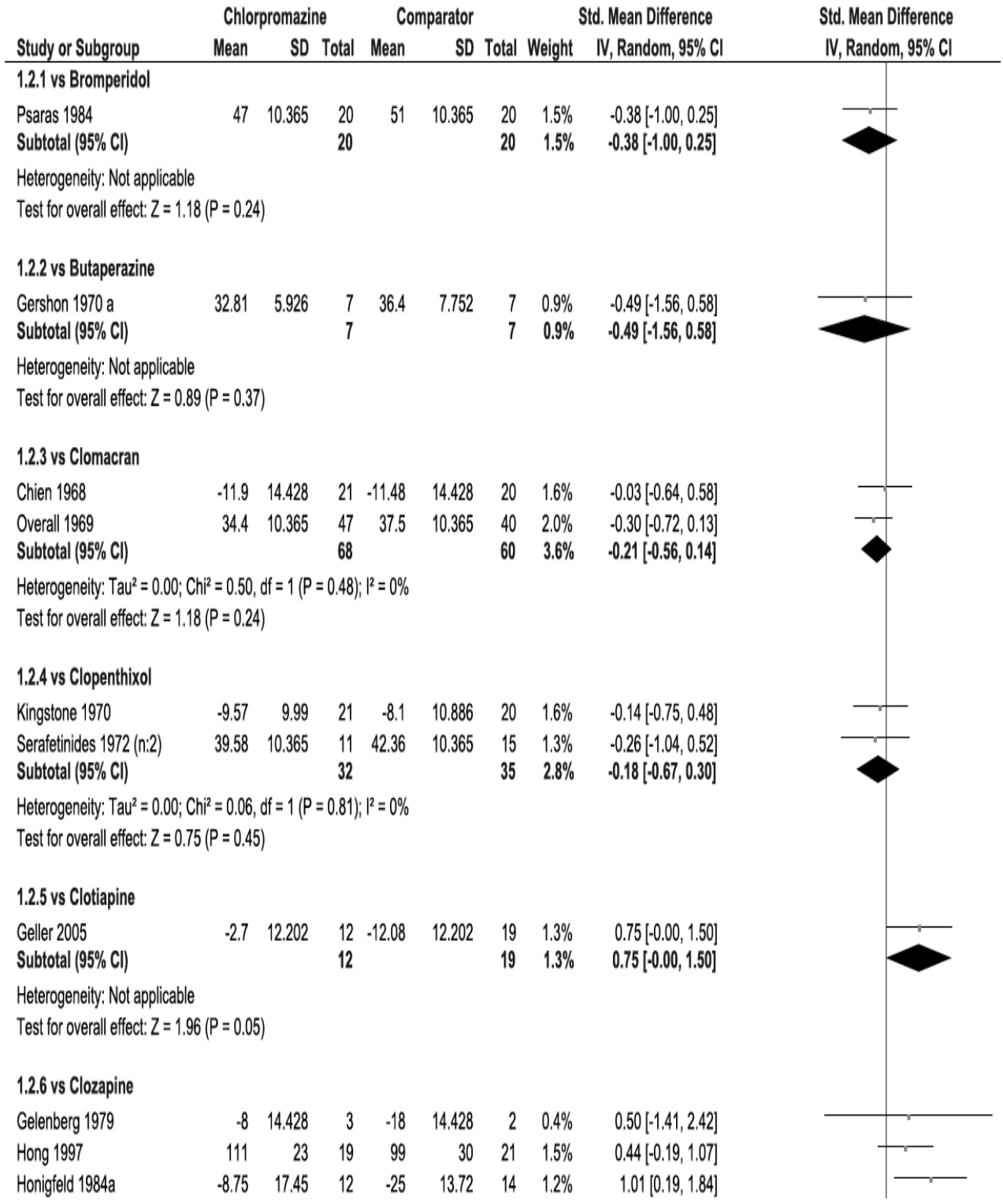
Total events	35		41			
Heterogeneity: Tau² = 0.08; Chi² = 4.82, df = 3 (P = 0.19); I² = 38%						
Test for overall effect: Z = 0.38 (P = 0.70)						
1.1.30 vs Thiothixene						
Ban 1975	4	10	4	10	0.5%	1.00 [0.34, 2.93]
Rickels 1978	23	40	24	39	2.2%	0.93 [0.65, 1.34]
Subtotal (95% CI)		**50**		**49**	**2.7%**	**0.94 [0.67, 1.33]**
Total events	27		28			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.1.31 vs Trifluoperazine						
Reardon 1966	10	11	10	11	2.7%	1.00 [0.77, 1.30]
Schiele 1961	4	20	6	20	0.5%	0.67 [0.22, 2.01]
Talbot 1964	12	25	4	25	0.6%	3.00 [1.12, 8.05]
Subtotal (95% CI)		**56**		**56**	**3.9%**	**1.24 [0.51, 3.03]**
Total events	26		20			
Heterogeneity: Tau² = 0.46; Chi² = 7.95, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 0.47 (P = 0.64)						
1.1.32 vs Trifluperidol						
Clark 1968 a	4	18	4	18	0.4%	1.00 [0.29, 3.39]
Gallant 1963d	1	18	4	18	0.2%	0.25 [0.03, 2.02]
Gallant 1967 c	7	19	11	20	1.0%	0.67 [0.33, 1.36]
Subtotal (95% CI)		**55**		**56**	**1.6%**	**0.68 [0.38, 1.23]**
Total events	12		19			
Heterogeneity: Tau² = 0.00; Chi² = 1.28, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 1.28 (P = 0.20)						
1.1.33 vs Triflupromazine						
Payne 1960	4	7	2	7	0.4%	2.00 [0.53, 7.60]
Walsh 1959	11	22	10	22	1.2%	1.10 [0.59, 2.04]
Subtotal (95% CI)		**29**		**29**	**1.6%**	**1.22 [0.70, 2.15]**
Total events	15		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.64, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.1.34 vs Ziprasidone						
Kane 2006	33	154	41	152	2.0%	0.79 [0.53, 1.18]
Subtotal (95% CI)		**154**		**152**	**2.0%**	**0.79 [0.53, 1.18]**





M-H= Maentel-Haenszel, CI= Confidence Interval, vs= versus

eFigure 3: Mean overall efficacy of chlorpromazine versus all other antipsychotic drugs in individual trials



Honigfeld 1984b	-13.94	14.24	63	-23.42	14.64	62	2.1%	0.65 [0.29, 1.01]
Howanitz 1999	77.23	18.16	11	74.48	17.2	21	1.3%	0.15 [-0.58, 0.88]
Kane 1988	56	12	139	45	13	126	2.4%	0.88 [0.63, 1.13]
Leon 1974	2.24	0.926	25	1.44	0.768	25	1.6%	0.93 [0.34, 1.51]
Lieberman 2003b	22.1	3.8	80	22.3	3.8	80	2.2%	-0.05 [-0.36, 0.26]
Potter 1989	25	8.9	20	29	12.3	17	1.5%	-0.37 [-1.02, 0.28]
Singer 1974	-25.1	4.25	19	-27.5	4.25	19	1.5%	0.55 [-0.10, 1.20]
Subtotal (95% CI)			**391**			**387**	**15.8%**	**0.47 [0.15, 0.78]**

Heterogeneity: Tau² = 0.16; Chi² = 32.74, df = 9 (P = 0.0001); I² = 73%

Test for overall effect: Z = 2.90 (P = 0.004)

1.2.8 vs Fluphenazine

Clark 1971 a	32.05	10.365	20	34.65	10.365	18	1.5%	-0.25 [-0.89, 0.39]
Subtotal (95% CI)			**20**			**18**	**1.5%**	**-0.25 [-0.89, 0.39]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.75 (P = 0.45)

1.2.9 vs Haloperidol

McCreadie 1977	27	9.6	8	15	5.6	10	0.9%	1.50 [0.42, 2.58]
Serafetinides 1972 (n:2)	39.58	10.365	11	42.51	10.365	14	1.2%	-0.27 [-1.07, 0.52]
Subtotal (95% CI)			**19**			**24**	**2.1%**	**0.57 [-1.16, 2.31]**

Heterogeneity: Tau² = 1.34; Chi² = 6.71, df = 1 (P = 0.010); I² = 85%

Test for overall effect: Z = 0.65 (P = 0.52)

1.2.10 vs Lenperone

DiGiacomo 1977	38	10.365	10	42	10.365	10	1.1%	-0.37 [-1.26, 0.52]
Subtotal (95% CI)			**10**			**10**	**1.1%**	**-0.37 [-1.26, 0.52]**

Heterogeneity: Not applicable

Test for overall effect: Z = 0.82 (P = 0.41)

1.2.11 vs Levomepromazine

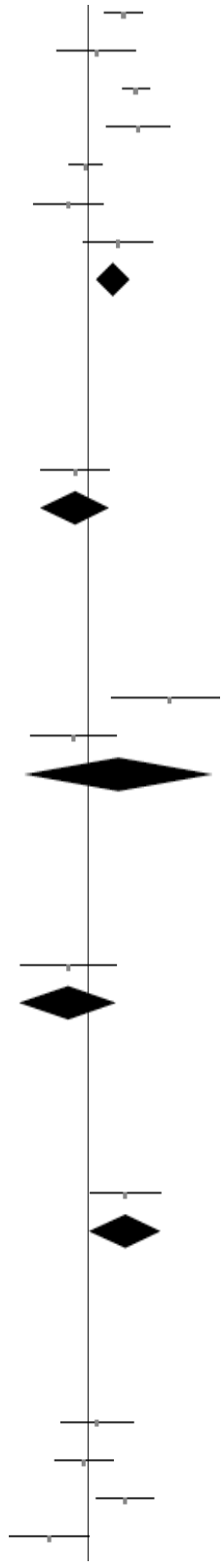
Lal 2006	97	24	19	81.1	21.2	19	1.5%	0.69 [0.03, 1.34]
Subtotal (95% CI)			**19**			**19**	**1.5%**	**0.69 [0.03, 1.34]**

Heterogeneity: Not applicable

Test for overall effect: Z = 2.05 (P = 0.04)

1.2.12 vs Loxapine

Clark 1972	41.305	10.365	17	39.63	10.365	17	1.5%	0.16 [-0.52, 0.83]
Dube 1976	18.907	10.365	26	19.783	10.365	26	1.7%	-0.08 [-0.63, 0.46]
Moore 1975	-17.78	14.428	29	-27.7	14.428	28	1.7%	0.68 [0.14, 1.21]
Shopsin 1972	3.3	1.42	15	4.5	1.74	15	1.3%	-0.74 [-1.48, 0.01]



Steinbook 1973	179.21	27.496	28	195.93	27.496	26	1.7%	-0.60 [-1.15, -0.05]
Vyas 1980	7	10.365	15	11	10.365	15	1.4%	-0.38 [-1.10, 0.35]
Subtotal (95% CI)			**130**			**127**	**9.3%**	**-0.14 [-0.58, 0.30]**

Heterogeneity: Tau² = 0.20; Chi² = 15.26, df = 5 (P = 0.009); I² = 67%

Test for overall effect: Z = 0.62 (P = 0.54)

1.2.13 vs Mesoridazine

Freeman 1969	39.5	10.365	25	40.5	10.365	25	1.7%	-0.09 [-0.65, 0.46]
Freeman 1973	-2.7	14.428	24	-5.2	14.428	25	1.7%	0.17 [-0.39, 0.73]
Tetreault 1969 a	41.2	9.14	15	42.5	9.14	15	1.4%	-0.14 [-0.86, 0.58]
Subtotal (95% CI)			**64**			**65**	**4.8%**	**-0.00 [-0.35, 0.34]**

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%

Test for overall effect: Z = 0.02 (P = 0.98)

1.2.14 vs Metiapine

Kramer 1975	36	10.365	38	36	10.365	39	1.9%	0.00 [-0.45, 0.45]
Steinbook 1975	45.29	17.174	30	42.75	17.174	30	1.8%	0.15 [-0.36, 0.65]
Subtotal (95% CI)			**68**			**69**	**3.7%**	**0.06 [-0.27, 0.40]**

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%

Test for overall effect: Z = 0.37 (P = 0.71)

1.2.15 vs Molindone

Heikkinen 1993	32.7	10.8	21	32.6	9.2	24	1.6%	0.01 [-0.58, 0.60]
Serafetinides 1972 (n:2)	33.84	10.365	14	35.71	10.365	15	1.3%	-0.18 [-0.91, 0.55]
Subtotal (95% CI)			**35**			**39**	**3.0%**	**-0.06 [-0.52, 0.39]**

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%

Test for overall effect: Z = 0.27 (P = 0.79)

1.2.16 vs Olanzapine

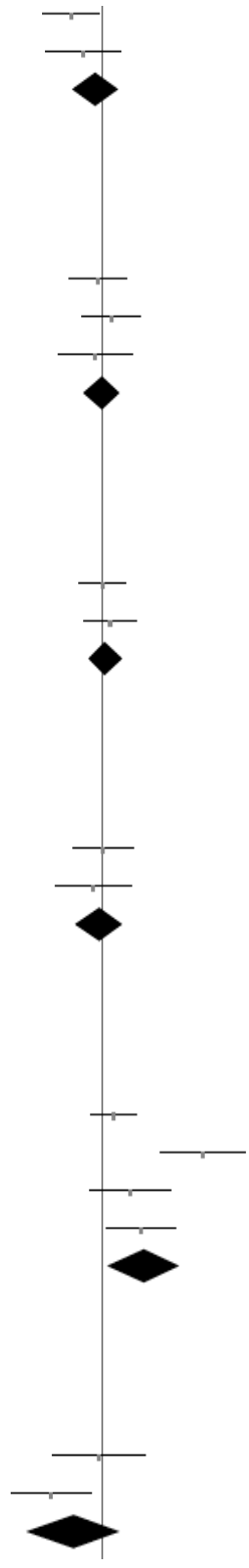
Conley 1998	56.9	11.7	39	54.1	14.1	42	2.0%	0.21 [-0.22, 0.65]
Dossenbach 2007	-29.8	18.6	12	-56.6	11	27	1.2%	1.92 [1.10, 2.73]
Kostakoglu 2001	-13.3	13.9	10	-24	21.7	20	1.3%	0.53 [-0.24, 1.31]
Loza 1999	-10.6	9.1	14	-23.4	20.1	27	1.5%	0.73 [0.06, 1.39]
Subtotal (95% CI)			**75**			**116**	**5.9%**	**0.80 [0.11, 1.49]**

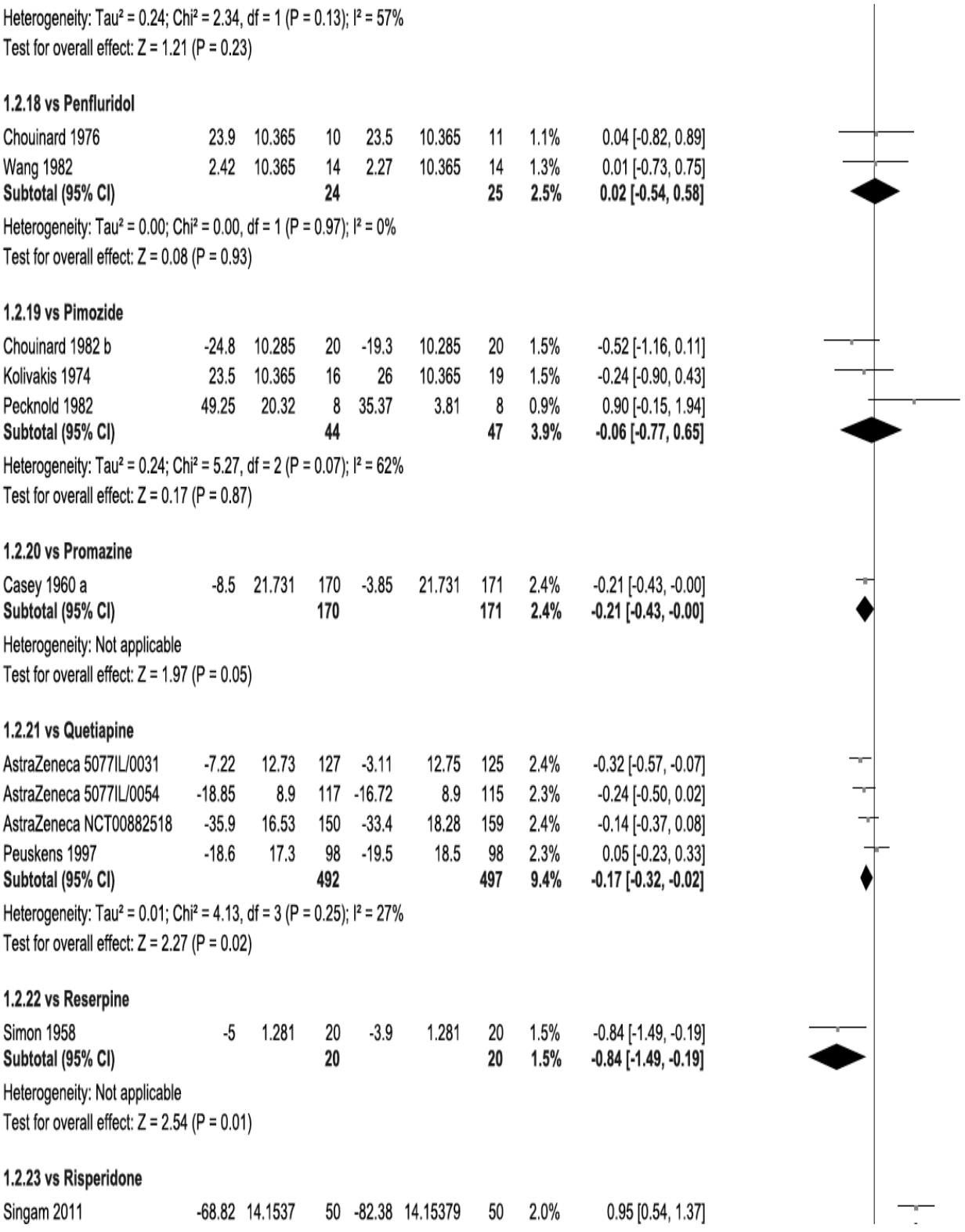
Heterogeneity: Tau² = 0.37; Chi² = 13.19, df = 3 (P = 0.004); I² = 77%

Test for overall effect: Z = 2.29 (P = 0.02)

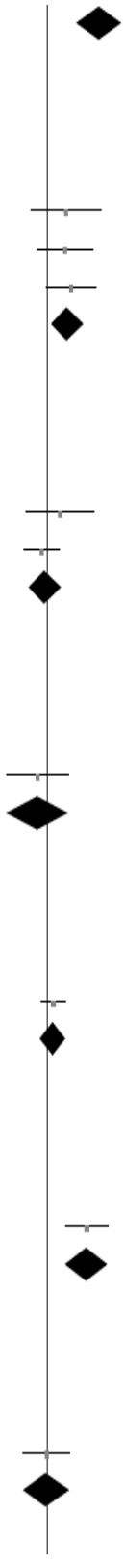
1.2.17 vs Oxypertine

Neal 1969	21.5	7.378	8	22	7.378	12	1.1%	-0.06 [-0.96, 0.83]
van Praag 1975 a	-8	3.859	15	-4.1	3.859	15	1.3%	-0.98 [-1.75, -0.22]
Subtotal (95% CI)			**23**			**27**	**2.4%**	**-0.55 [-1.45, 0.34]**




Heterogeneity: Tau² = 0.24; Chi² = 2.34, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 1.21 (P = 0.23)
1.2.18 vs Penfluridol
Chouinard 1976 23.9 10.365 10 23.5 10.365 11 1.1% 0.04 [-0.82, 0.89]
Wang 1982 2.42 10.365 14 2.27 10.365 14 1.3% 0.01 [-0.73, 0.75]
Subtotal (95% CI) 24 25 2.5% 0.02 [-0.54, 0.58]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.93)
1.2.19 vs Pimozide
Chouinard 1982 b -24.8 10.285 20 -19.3 10.285 20 1.5% -0.52 [-1.16, 0.11]
Kolivakis 1974 23.5 10.365 16 26 10.365 19 1.5% -0.24 [-0.90, 0.43]
Pecknold 1982 49.25 20.32 8 35.37 3.81 8 0.9% 0.90 [-0.15, 1.94]
Subtotal (95% CI) 44 47 3.9% -0.06 [-0.77, 0.65]
Heterogeneity: Tau² = 0.24; Chi² = 5.27, df = 2 (P = 0.07); I² = 62%
Test for overall effect: Z = 0.17 (P = 0.87)
1.2.20 vs Promazine
Casey 1960 a -8.5 21.731 170 -3.85 21.731 171 2.4% -0.21 [-0.43, -0.00]
Subtotal (95% CI) 170 171 2.4% -0.21 [-0.43, -0.00]
Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)
1.2.21 vs Quetiapine
AstraZeneca 5077IL/0031 -7.22 12.73 127 -3.11 12.75 125 2.4% -0.32 [-0.57, -0.07]
AstraZeneca 5077IL/0054 -18.85 8.9 117 -16.72 8.9 115 2.3% -0.24 [-0.50, 0.02]
AstraZeneca NCT00882518 -35.9 16.53 150 -33.4 18.28 159 2.4% -0.14 [-0.37, 0.08]
Peuskens 1997 -18.6 17.3 98 -19.5 18.5 98 2.3% 0.05 [-0.23, 0.33]
Subtotal (95% CI) 492 497 9.4% -0.17 [-0.32, -0.02]
Heterogeneity: Tau² = 0.01; Chi² = 4.13, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 2.27 (P = 0.02)
1.2.22 vs Reserpine
Simon 1958 -5 1.281 20 -3.9 1.281 20 1.5% -0.84 [-1.49, -0.19]
Subtotal (95% CI) 20 20 1.5% -0.84 [-1.49, -0.19]
Heterogeneity: Not applicable
Test for overall effect: Z = 2.54 (P = 0.01)
1.2.23 vs Risperidone
Singam 2011 -68.82 14.1537 50 -82.38 14.15379 50 2.0% 0.95 [0.54, 1.37]

Subtotal (95% CI)			**50**			**50**	**2.0%**	**0.95 [0.54, 1.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.50 (P < 0.00001)								
1.2.24 vs Sulpiride								
Alfredsson 1984	1.2	0.8	18	0.95	0.654	19	1.5%	0.34 [-0.31, 0.99]
Dreyfus 1985	47.4	10.365	27	44	10.365	32	1.8%	0.32 [-0.19, 0.84]
Toru 1971	-5.27	5.28	37	-7.8	6.29	38	1.9%	0.43 [-0.03, 0.89]
Subtotal (95% CI)			**82**			**89**	**5.2%**	**0.37 [0.07, 0.68]**
Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%								
Test for overall effect: Z = 2.41 (P = 0.02)								
1.2.25 vs Thioridazine								
Clark 1971 a	32.05	10.365	20	29.63	10.365	19	1.5%	0.23 [-0.40, 0.86]
Waldrop 1961	-4.58	15.34	71	-3.06	10.95	71	2.2%	-0.11 [-0.44, 0.22]
Subtotal (95% CI)			**91**			**90**	**3.7%**	**-0.04 [-0.33, 0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%								
Test for overall effect: Z = 0.27 (P = 0.79)								
1.2.26 vs Thiothixene								
Rickels 1978	162	27.496	23	167	27.496	24	1.7%	-0.18 [-0.75, 0.39]
Subtotal (95% CI)			**23**			**24**	**1.7%**	**-0.18 [-0.75, 0.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.2.27 vs Ziprasidone								
Kane 2006	-13	14.1537	154	-14.5	14.1537	152	2.4%	0.11 [-0.12, 0.33]
Subtotal (95% CI)			**154**			**152**	**2.4%**	**0.11 [-0.12, 0.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.92 (P = 0.36)								
1.2.28 vs Zotepine								
Cooper 2000a	-4.3	19.1	52	-16.8	14.9	53	2.1%	0.73 [0.33, 1.12]
Subtotal (95% CI)			**52**			**53**	**2.1%**	**0.73 [0.33, 1.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.60 (P = 0.0003)								
1.2.29 vs Zuclopenthixol								
Balasubramanian 1991	12.9	9.3	38	13.1	11.7	45	2.0%	-0.02 [-0.45, 0.41]
Subtotal (95% CI)			**38**			**45**	**2.0%**	**-0.02 [-0.45, 0.41]**
Heterogeneity: Not applicable								



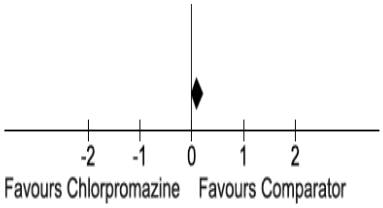
Test for overall effect: Z = 0.08 (P = 0.93)

Total (95% CI)	**2233**	**2305**	**100.0%**	**0.11 [-0.01, 0.23]**

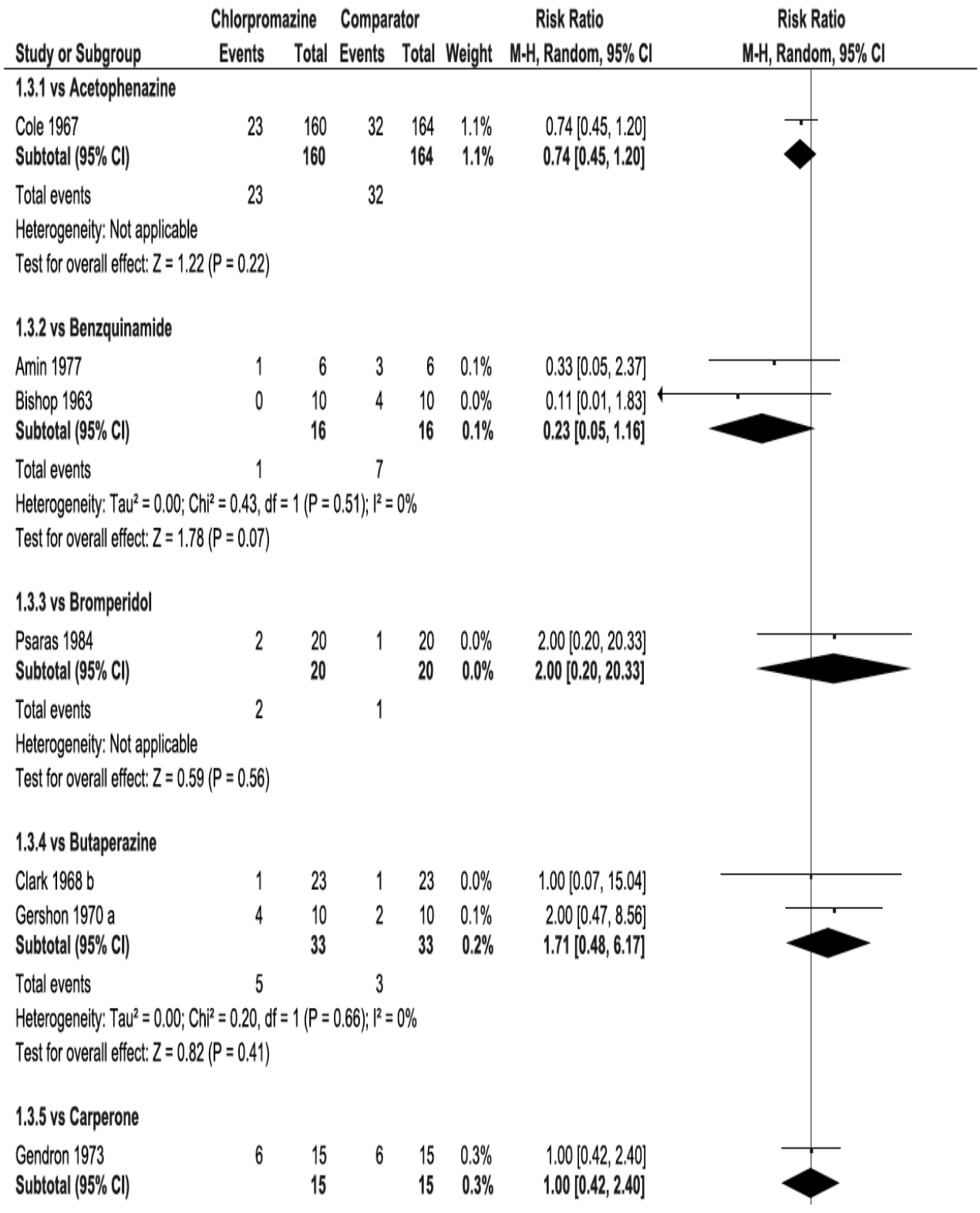
Heterogeneity: Tau² = 0.15; Chi² = 216.44, df = 61 (P < 0.00001); I² = 72%

Test for overall effect: Z = 1.77 (P = 0.08)

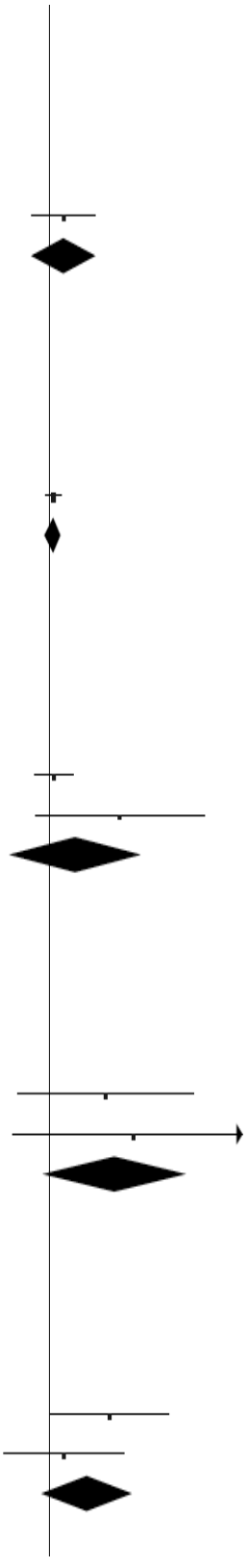
Test for subgroup differences: Chi² = 84.99, df = 27 (P < 0.00001), I² = 68.2%



eFigure 4: All cause discontinuation of chlorpromazine versus all other antipsychotic drugs in individual **trials**



Total events	6		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.3.6 vs Carphenazine						
Platz 1967	14	108	10	108	0.4%	1.40 [0.65, 3.01]
Subtotal (95% CI)		**108**		**108**	**0.4%**	**1.40 [0.65, 3.01]**
Total events	14		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.3.7 vs Chlorprothixene						
Lasky 1962	63	86	58	87	6.8%	1.10 [0.90, 1.34]
Subtotal (95% CI)		**86**		**87**	**6.8%**	**1.10 [0.90, 1.34]**
Total events	63		58			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.94 (P = 0.35)						
1.3.8 vs Clomacran						
Case 1971	15	24	14	25	1.2%	1.12 [0.70, 1.78]
Schiele 1968	5	14	1	15	0.1%	5.36 [0.71, 40.37]
Subtotal (95% CI)		**38**		**40**	**1.3%**	**1.86 [0.39, 8.89]**
Total events	20		15			
Heterogeneity: $Tau^2 = 0.89$; $Chi^2 = 2.59$, df = 1 (P = 0.11); $I^2 = 61\%$						
Test for overall effect: Z = 0.78 (P = 0.44)						
1.3.9 vs Clopenthixol						
Kingstone 1970	4	21	1	20	0.1%	3.81 [0.46, 31.23]
Serafetinides 1972 (n:2)	3	14	0	15	0.0%	7.47 [0.42, 132.78]
Subtotal (95% CI)		**35**		**35**	**0.1%**	**4.82 [0.88, 26.32]**
Total events	7		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$						
Test for overall effect: Z = 1.81 (P = 0.07)						
1.3.10 vs Clotiapine						
Geller 2005	8	20	2	21	0.1%	4.20 [1.01, 17.43]
Kaneko 1969	4	41	3	43	0.1%	1.40 [0.33, 5.87]
Subtotal (95% CI)		**61**		**64**	**0.3%**	**2.43 [0.83, 7.16]**
Total events	12		5			



Heterogeneity: Tau² = 0.08; Chi² = 1.14, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 1.61 (P = 0.11)

1.3.11 vs Clozapine

Chiu 1976	17	31	11	33	0.8%	1.65 [0.92, 2.93]
Gelenberg 1979	5	8	4	7	0.4%	1.09 [0.47, 2.52]
Guirguis 1977	9	28	6	22	0.3%	1.18 [0.49, 2.81]
Hong 1997	2	19	2	21	0.1%	1.11 [0.17, 7.09]
Honigfeld 1984a	11	15	6	16	0.5%	1.96 [0.97, 3.95]
Honigfeld 1984b	36	76	27	75	1.8%	1.32 [0.90, 1.93]
Honigfeld 1984d	11	113	11	110	0.4%	0.97 [0.44, 2.15]
Kane 1988	18	142	15	126	0.6%	1.06 [0.56, 2.02]
Lieberman 2003b	21	83	13	81	0.7%	1.58 [0.85, 2.93]
Singer 1974	1	20	1	20	0.0%	1.00 [0.07, 14.90]
Subtotal (95% CI)		**535**		**511**	**5.6%**	**1.34 [1.08, 1.67]**
Total events	131		96			

Heterogeneity: Tau² = 0.00; Chi² = 3.41, df = 9 (P = 0.95); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)

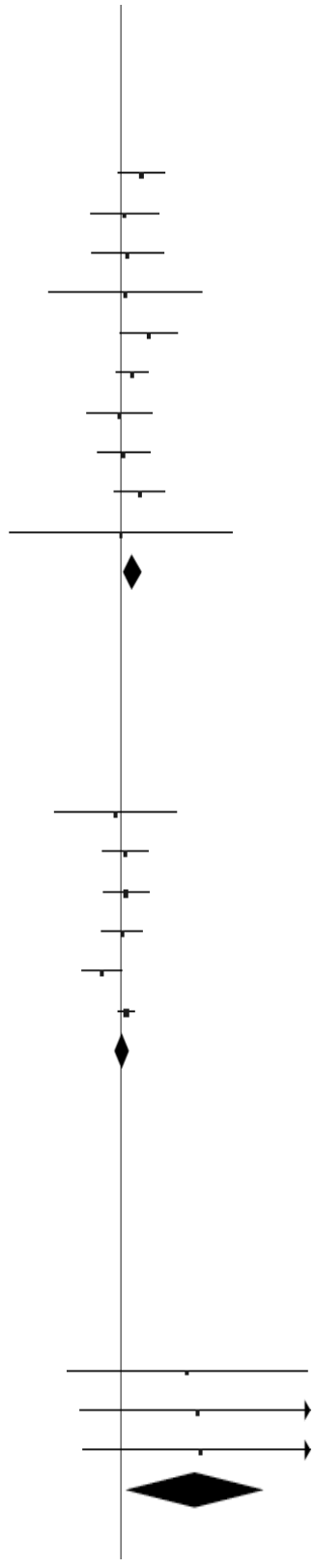
1.3.12 vs Fluphenazine

Clark 1971 a	3	23	3	20	0.1%	0.87 [0.20, 3.83]
Cole 1967	23	160	21	163	0.9%	1.12 [0.64, 1.93]
Galbrecht 1968	21	102	19	104	0.8%	1.13 [0.65, 1.97]
Goldberg 1964	24	112	24	115	1.0%	1.03 [0.62, 1.70]
Hanlon 1965	16	52	26	53	1.1%	0.63 [0.38, 1.03]
Lasky 1962	63	86	54	84	6.2%	1.14 [0.93, 1.40]
Subtotal (95% CI)		**535**		**539**	**10.2%**	**1.05 [0.88, 1.24]**
Total events	150		147			

Heterogeneity: Tau² = 0.00; Chi² = 5.16, df = 5 (P = 0.40); I² = 3%
Test for overall effect: Z = 0.52 (P = 0.60)

1.3.13 vs Haloperidol

Gallant 1967 c	0	19	0	19		Not estimable
Lemperiere 1962	0	22	0	24		Not estimable
McCreadie 1977	2	10	0	10	0.0%	5.00 [0.27, 92.62]
Rompel 1978	3	13	0	12	0.0%	6.50 [0.37, 114.12]
Serafetinides 1972 (n:2)	3	14	0	14	0.0%	7.00 [0.39, 124.14]
Subtotal (95% CI)		**78**		**79**	**0.1%**	**6.12 [1.16, 32.38]**
Total events	8		0			



Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.13 (P = 0.03)

1.3.14 vs Lenperone

DiGiacomo 1977	5	15	9	19	0.4%	0.70 [0.30, 1.66]
Mielke 1975	0	15	0	14		Not estimable
Subtotal (95% CI)		**30**		**33**	**0.4%**	**0.70 [0.30, 1.66]**
Total events	5		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)

1.3.15 vs Levomepromazine

Baker 1958 b	2	14	2	14	0.1%	1.00 [0.16, 6.14]
Lal 2006	5	19	2	19	0.1%	2.50 [0.55, 11.33]
Subtotal (95% CI)		**33**		**33**	**0.2%**	**1.72 [0.54, 5.49]**
Total events	7		4			

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

1.3.16 vs Loxapine

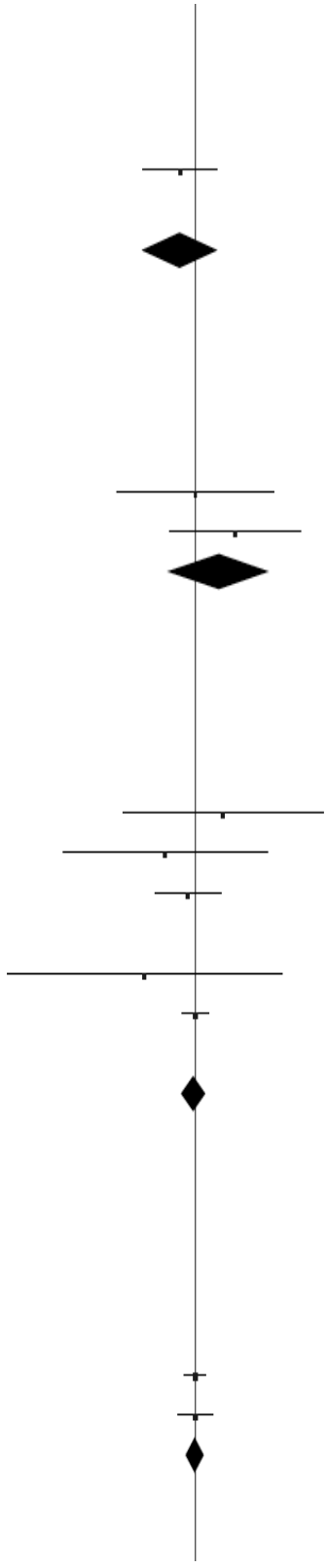
Clark 1972	2	19	1	18	0.0%	1.89 [0.19, 19.13]
Moore 1975	1	29	2	29	0.0%	0.50 [0.05, 5.21]
Rifkin 1984	9	33	10	31	0.5%	0.85 [0.40, 1.80]
Shopsin 1972	0	15	0	15		Not estimable
Steinbook 1973	0	28	1	26	0.0%	0.31 [0.01, 7.30]
Tuason 1984	24	34	24	34	2.8%	1.00 [0.74, 1.36]
Vyas 1980	0	15	0	15		Not estimable
Subtotal (95% CI)		**173**		**168**	**3.3%**	**0.97 [0.73, 1.28]**
Total events	36		38			

Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 4 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

1.3.17 vs Mepazine

Bennett 1961	0	5	0	5		Not estimable
Kurland 1961	26	33	27	34	4.3%	0.99 [0.78, 1.27]
Lomas 1957	24	50	24	50	1.6%	1.00 [0.66, 1.50]
Subtotal (95% CI)		**88**		**89**	**5.9%**	**0.99 [0.81, 1.23]**
Total events	50		51			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%



Test for overall effect: Z = 0.05 (P = 0.96)

1.3.18 vs Mesoridazine

Douglas 1969	2	32	0	32	0.0%	5.00 [0.25, 100.20]
Freeman 1969	0	25	0	25		Not estimable
Freeman 1973	1	25	0	25	0.0%	3.00 [0.13, 70.30]
Tetreault 1969 a	0	15	0	15		Not estimable
Subtotal (95% CI)		**97**		**97**	**0.1%**	**3.92 [0.45, 34.46]**
Total events	3		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 1.23 (P = 0.22)

1.3.19 vs Metiapine

Simpson 1973 b	0	5	0	5		Not estimable
Steinbook 1975	9	30	10	30	0.5%	0.90 [0.43, 1.90]
Subtotal (95% CI)		**35**		**35**	**0.5%**	**0.90 [0.43, 1.90]**
Total events	9		10			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.28 (P = 0.78)

1.3.20 vs Molindone

Serafetinides 1972 (n:2)	2	15	0	15	0.0%	5.00 [0.26, 96.13]
Subtotal (95% CI)		**15**		**15**	**0.0%**	**5.00 [0.26, 96.13]**
Total events	2		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.07 (P = 0.29)

1.3.21 vs Olanzapine

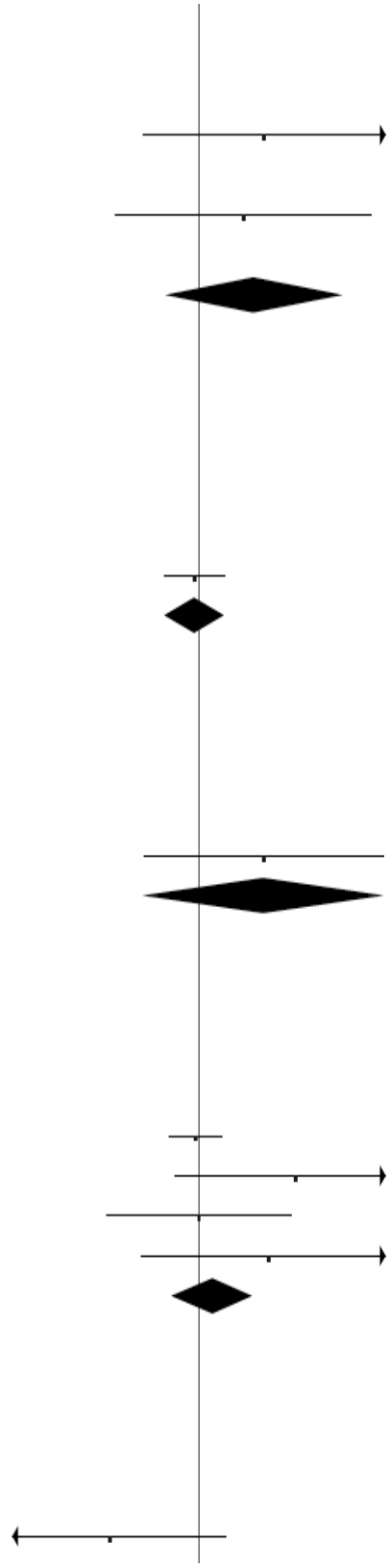
Conley 1998	12	42	13	42	0.6%	0.92 [0.48, 1.78]
Dossenbach 2007	2	12	0	27	0.0%	10.77 [0.56, 208.71]
Kostakoglu 2001	1	10	2	20	0.1%	1.00 [0.10, 9.75]
Loza 1999	1	14	0	27	0.0%	5.60 [0.24, 129.20]
Subtotal (95% CI)		**78**		**116**	**0.7%**	**1.39 [0.52, 3.71]**
Total events	16		15			

Heterogeneity: Tau² = 0.27; Chi² = 3.75, df = 3 (P = 0.29); I² = 20%

Test for overall effect: Z = 0.66 (P = 0.51)

1.3.22 vs Oxypertine

Claghorn 1970 a	0	20	4	20	0.0%	0.11 [0.01, 1.94]



Goldberg 1970 a	2	20	2	20	0.1%	1.00 [0.16, 6.42]
Neal 1969	12	20	8	20	0.6%	1.50 [0.79, 2.86]
van Praag 1975 a	4	19	6	21	0.2%	0.74 [0.24, 2.22]
Subtotal (95% CI)		**79**		**81**	**0.9%**	**0.97 [0.45, 2.09]**
Total events	18		20			

Heterogeneity: Tau² = 0.20; Chi² = 4.43, df = 3 (P = 0.22); I² = 32%

Test for overall effect: Z = 0.09 (P = 0.93)

1.3.23 vs Penfluridol

Chouinard 1976	9	19	3	14	0.2%	2.21 [0.73, 6.70]
Claghorn 1979	18	28	17	28	1.6%	1.06 [0.71, 1.59]
Wang 1982	5	20	5	21	0.2%	1.05 [0.36, 3.09]
Subtotal (95% CI)		**67**		**63**	**2.0%**	**1.14 [0.80, 1.64]**
Total events	32		25			

Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 2 (P = 0.44); I² = 0%

Test for overall effect: Z = 0.73 (P = 0.47)

1.3.24 vs Periciazine

Ananth 1977a	5	15	1	15	0.1%	5.00 [0.66, 37.85]
Subtotal (95% CI)		**15**		**15**	**0.1%**	**5.00 [0.66, 37.85]**
Total events	5		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.56 (P = 0.12)

1.3.25 vs Perphenazine

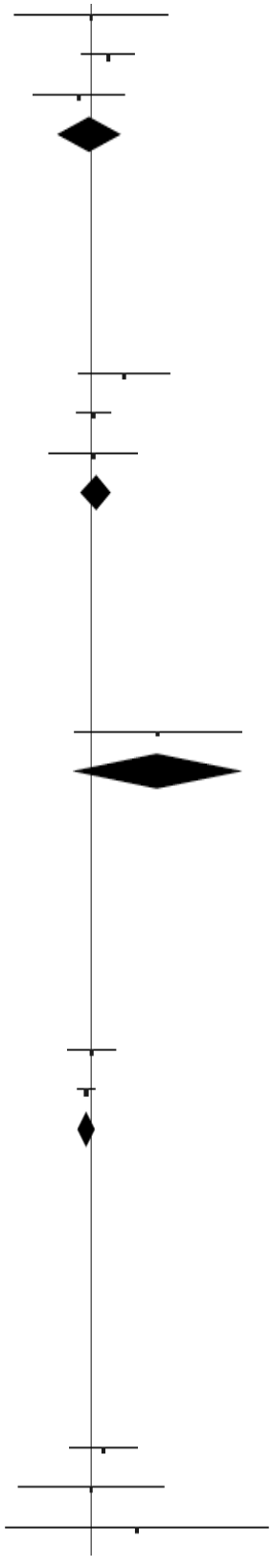
Bennett 1961	0	5	0	5		Not estimable
Hanlon 1965	16	52	16	53	0.8%	1.02 [0.57, 1.82]
Kurland 1961	26	33	32	36	5.8%	0.89 [0.72, 1.09]
Subtotal (95% CI)		**90**		**94**	**6.6%**	**0.90 [0.74, 1.10]**
Total events	42		48			

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%

Test for overall effect: Z = 1.03 (P = 0.30)

1.3.26 vs Pimozide

Anumonye 1976	0	12	0	12		Not estimable
Chouinard 1982 b	0	20	0	20		Not estimable
Kolivakis 1974	9	25	7	26	0.4%	1.34 [0.59, 3.04]
Pecknold 1982	2	10	2	10	0.1%	1.00 [0.17, 5.77]
Umene 1972	1	46	0	46	0.0%	3.00 [0.13, 71.78]



Wilson 1982 a	11	22	8	21	0.6%	1.31 [0.66, 2.61]
Subtotal (95% CI)		**135**		**135**	**1.0%**	**1.32 [0.80, 2.17]**
Total events	23		17			

Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 3 (P = 0.95); I² = 0%

Test for overall effect: Z = 1.09 (P = 0.28)

1.3.27 vs Piperacetazine

Gallant 1970 a	0	13	0	13		Not estimable
Gallant 1970 b	0	8	0	8		Not estimable
Johnson 1970	0	13	0	13		Not estimable
Small 1970	9	15	5	14	0.4%	1.68 [0.74, 3.80]
Subtotal (95% CI)		**49**		**48**	**0.4%**	**1.68 [0.74, 3.80]**
Total events	9		5			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.25 (P = 0.21)

1.3.28 vs Prochlorperazine

Bennett 1961	0	5	0	5		Not estimable
Hanlon 1965	16	52	13	52	0.7%	1.23 [0.66, 2.29]
Kurland 1961	26	33	22	32	3.0%	1.15 [0.85, 1.54]
Wilson 1961	0	2	0	2		Not estimable
Subtotal (95% CI)		**92**		**91**	**3.7%**	**1.16 [0.89, 1.51]**
Total events	42		35			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 1.10 (P = 0.27)

1.3.29 vs Promazine

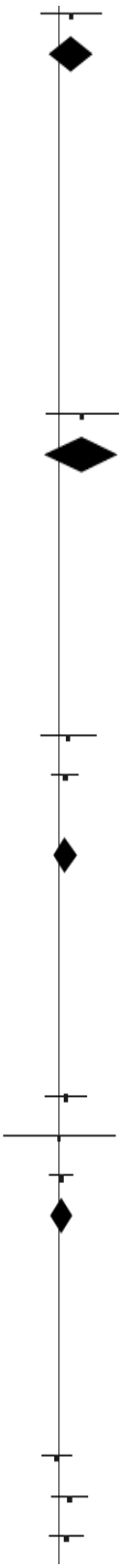
Engelhardt 1969 a	25	62	19	55	1.2%	1.17 [0.73, 1.87]
Fleming 1959	4	21	4	21	0.2%	1.00 [0.29, 3.48]
Kurland 1961	26	33	24	32	3.6%	1.05 [0.80, 1.37]
Subtotal (95% CI)		**116**		**108**	**5.0%**	**1.07 [0.86, 1.35]**
Total events	55		47			

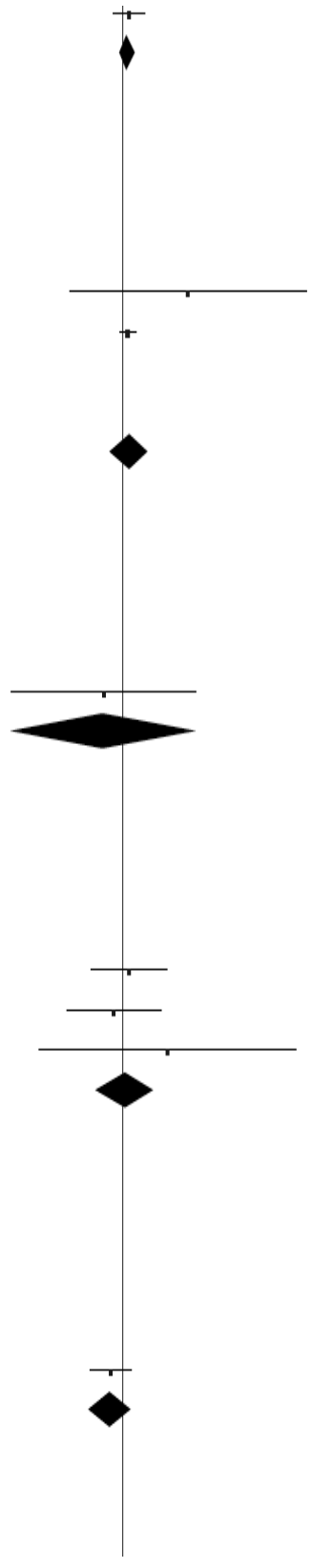
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 2 (P = 0.91); I² = 0%

Test for overall effect: Z = 0.62 (P = 0.54)

1.3.30 vs Quetiapine

AstraZeneca 5077IL/0031	43	132	46	135	2.3%	0.96 [0.68, 1.34]
AstraZeneca 5077IL/0054	40	119	31	117	1.7%	1.27 [0.86, 1.88]
AstraZeneca NCT00882518	44	192	38	196	1.7%	1.18 [0.80, 1.74]





Peuskens 1997	36	100	31	101	1.7%	1.17 [0.79, 1.74]
Subtotal (95% CI)		**543**		**549**	**7.4%**	**1.12 [0.93, 1.36]**
Total events	163		146			

Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 3 (P = 0.72); I² = 0%

Test for overall effect: Z = 1.22 (P = 0.22)

1.3.31 vs Reserpine

Barrett 1957	2	10	0	10	0.0%	5.00 [0.27, 92.62]
Lasky 1962	63	86	57	88	6.5%	1.13 [0.93, 1.38]
Shepherd 1956	0	8	0	8		Not estimable
Simon 1958	0	20	0	20		Not estimable
Subtotal (95% CI)		**124**		**126**	**6.5%**	**1.17 [0.74, 1.85]**
Total events	65		57			

Heterogeneity: Tau² = 0.05; Chi² = 1.04, df = 1 (P = 0.31); I² = 4%

Test for overall effect: Z = 0.68 (P = 0.50)

1.3.32 vs Risperidone

Mercer 1997	1	12	2	15	0.1%	0.63 [0.06, 6.09]
Subtotal (95% CI)		**12**		**15**	**0.1%**	**0.63 [0.06, 6.09]**
Total events	1		2			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

1.3.33 vs Sulpiride

Alfredsson 1984	7	25	6	25	0.3%	1.17 [0.46, 2.98]
Dreyfus 1985	4	29	6	35	0.2%	0.80 [0.25, 2.58]
Toru 1971	1	38	0	38	0.0%	3.00 [0.13, 71.40]
Subtotal (95% CI)		**92**		**98**	**0.5%**	**1.07 [0.52, 2.17]**
Total events	12		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.67, df = 2 (P = 0.72); I² = 0%

Test for overall effect: Z = 0.17 (P = 0.86)

1.3.34 vs Thiopropazate

Hamilton 1960	0	18	0	18		Not estimable
Hanlon 1965	16	52	22	53	1.0%	0.74 [0.44, 1.24]
Subtotal (95% CI)		**70**		**71**	**1.0%**	**0.74 [0.44, 1.24]**
Total events	16		22			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.13 (P = 0.26)

1.3.35 vs Thioridazine

Clark 1971 a	3	23	3	22	0.1%	0.96 [0.22, 4.24]
Galbrecht 1968	21	102	16	104	0.7%	1.34 [0.74, 2.41]
Goldberg 1964	24	112	20	111	0.9%	1.19 [0.70, 2.02]
Hanlon 1965	16	52	22	53	1.0%	0.74 [0.44, 1.24]
Lasky 1962	63	86	54	84	6.2%	1.14 [0.93, 1.40]
Schiele 1961	0	20	1	20	0.0%	0.33 [0.01, 7.72]
Somerville 1960	0	15	0	15		Not estimable
Stabenau 1964	3	24	9	28	0.2%	0.39 [0.12, 1.28]
Waldrop 1961	7	78	7	78	0.3%	1.00 [0.37, 2.72]
Subtotal (95% CI)		**512**		**515**	**9.5%**	**1.08 [0.91, 1.27]**
Total events	137		132			

Heterogeneity: Tau² = 0.00; Chi² = 6.54, df = 7 (P = 0.48); I² = 0%

Test for overall effect: Z = 0.87 (P = 0.39)

1.3.36 vs Thiothixene

Ban 1975	4	10	5	10	0.3%	0.80 [0.30, 2.13]
Bressler 1971	0	13	0	13		Not estimable
Gardos 1974 a	9	17	7	19	0.5%	1.44 [0.69, 3.01]
Subtotal (95% CI)		**40**		**42**	**0.7%**	**1.16 [0.64, 2.10]**
Total events	13		12			

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%

Test for overall effect: Z = 0.50 (P = 0.62)

1.3.37 vs Trifluoperazine

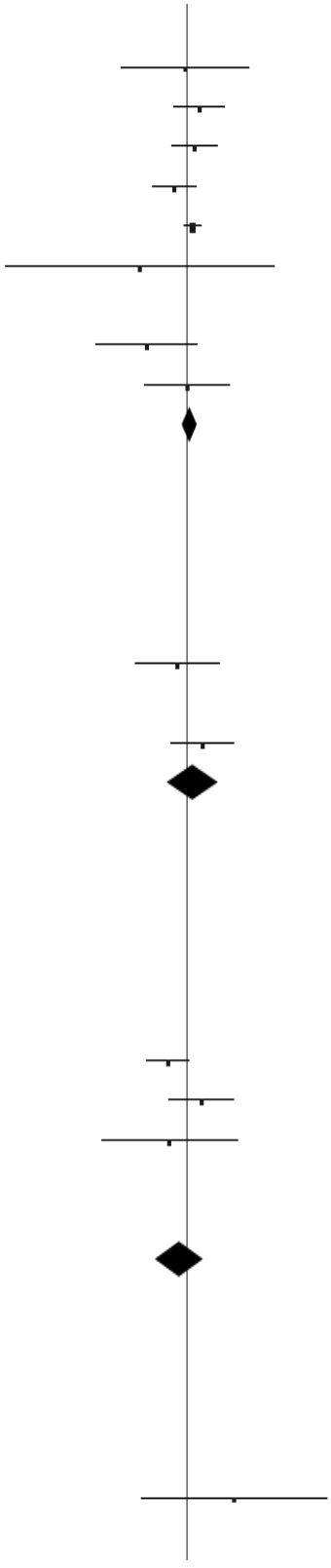
Coons 1962	0	32	0	28		Not estimable
Hanlon 1965	16	52	25	52	1.1%	0.64 [0.39, 1.05]
Platz 1967	14	108	10	108	0.4%	1.40 [0.65, 3.01]
Reardon 1966	2	11	3	11	0.1%	0.67 [0.14, 3.24]
Schiele 1961	0	20	0	20		Not estimable
Wilson 1961	0	2	0	2		Not estimable
Subtotal (95% CI)		**225**		**221**	**1.6%**	**0.84 [0.48, 1.46]**
Total events	32		38			

Heterogeneity: Tau² = 0.08; Chi² = 2.95, df = 2 (P = 0.23); I² = 32%

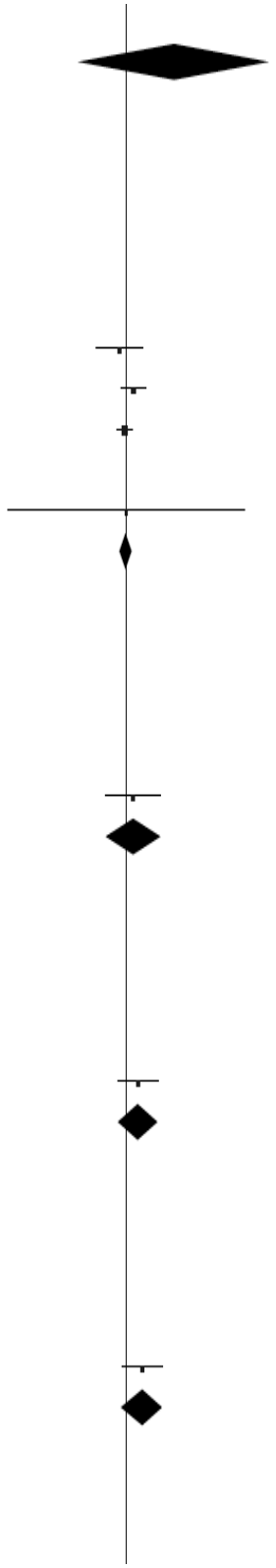
Test for overall effect: Z = 0.61 (P = 0.54)

1.3.38 vs Trifluperidol

Clark 1968 a	3	18	1	18	0.1%	3.00 [0.34, 26.19]
Gallant 1963d	0	18	0	18		Not estimable



Gallant 1967 c	0	19	0	20		Not estimable
Subtotal (95% CI)		**55**		**56**	**0.1%**	**3.00 [0.34, 26.19]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.3.39 vs Triflupromazine						
Bennett 1961	0	5	0	5		Not estimable
Hanlon 1965	16	52	19	53	0.9%	0.86 [0.50, 1.48]
Kurland 1961	26	33	24	36	3.1%	1.18 [0.88, 1.58]
Lasky 1962	63	86	63	83	8.4%	0.97 [0.81, 1.15]
Payne 1960	0	7	0	7		Not estimable
Walsh 1959	1	22	1	22	0.0%	1.00 [0.07, 15.00]
Subtotal (95% CI)		**205**		**206**	**12.4%**	**1.01 [0.87, 1.16]**
Total events	106		107			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.75$, df = 3 (P = 0.63); $I^2 = 0\%$						
Test for overall effect: Z = 0.09 (P = 0.93)						
1.3.40 vs Ziprasidone						
Kane 2006	19	154	16	152	0.7%	1.17 [0.63, 2.19]
Subtotal (95% CI)		**154**		**152**	**0.7%**	**1.17 [0.63, 2.19]**
Total events	19		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
1.3.41 vs Zotepine						
Cooper 2000a	25	53	19	53	1.2%	1.32 [0.83, 2.08]
Subtotal (95% CI)		**53**		**53**	**1.2%**	**1.32 [0.83, 2.08]**
Total events	25		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
1.3.42 vs Zuclopenthixol						
Balasubramanian 1991	23	44	18	50	1.2%	1.45 [0.91, 2.31]
Subtotal (95% CI)		**44**		**50**	**1.2%**	**1.45 [0.91, 2.31]**
Total events	23		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						

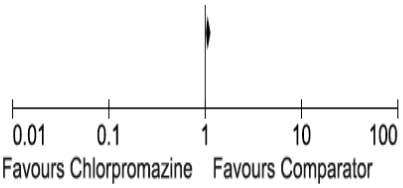


Total (95% CI)		**5041**	**5086**	**100.0%**	**1.08 [1.02, 1.13]**
Total events	1411		1288		

Heterogeneity: Tau² = 0.00; Chi² = 82.70, df = 103 (P = 0.93); I² = 0%

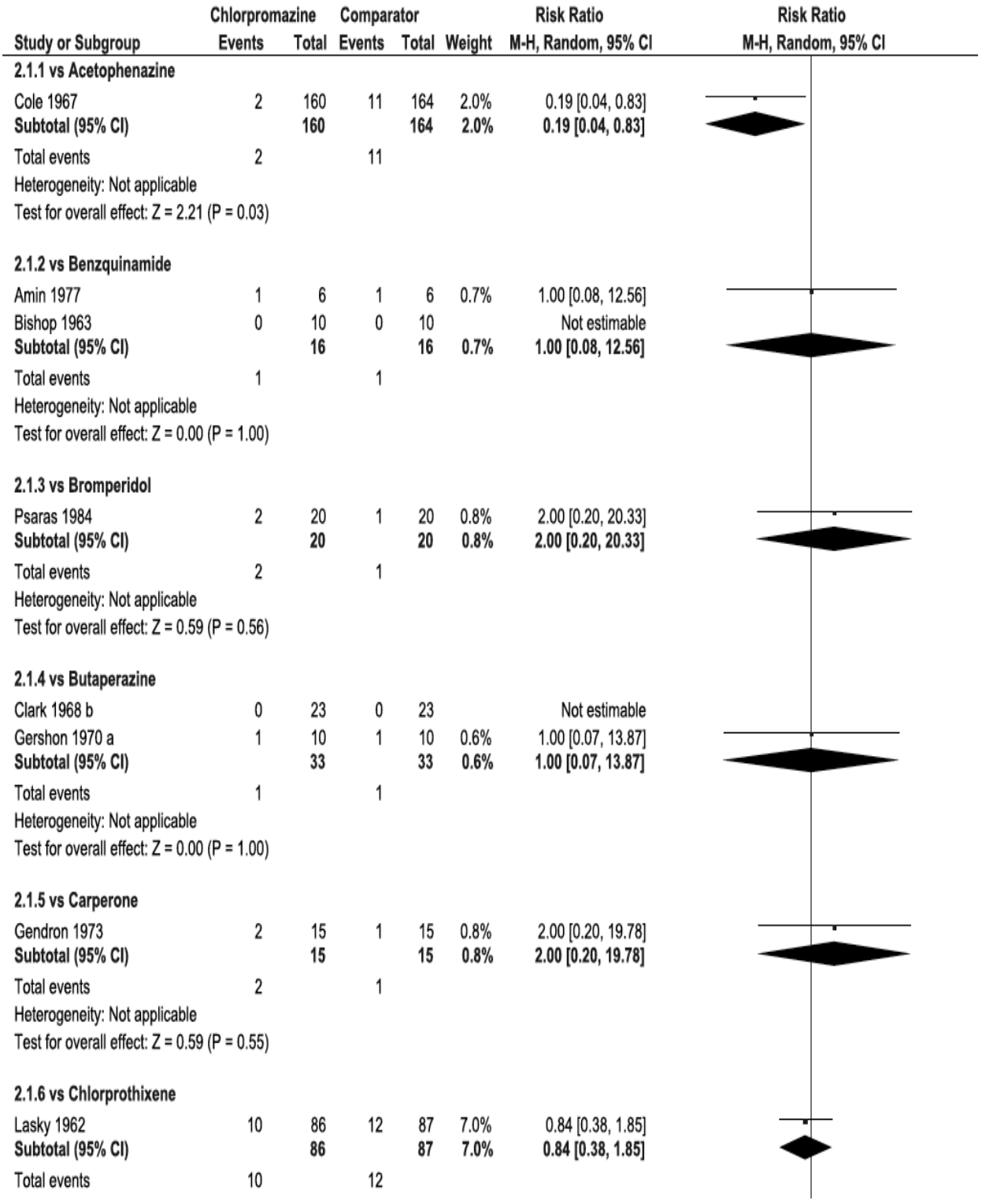
Test for overall effect: Z = 2.87 (P = 0.004)

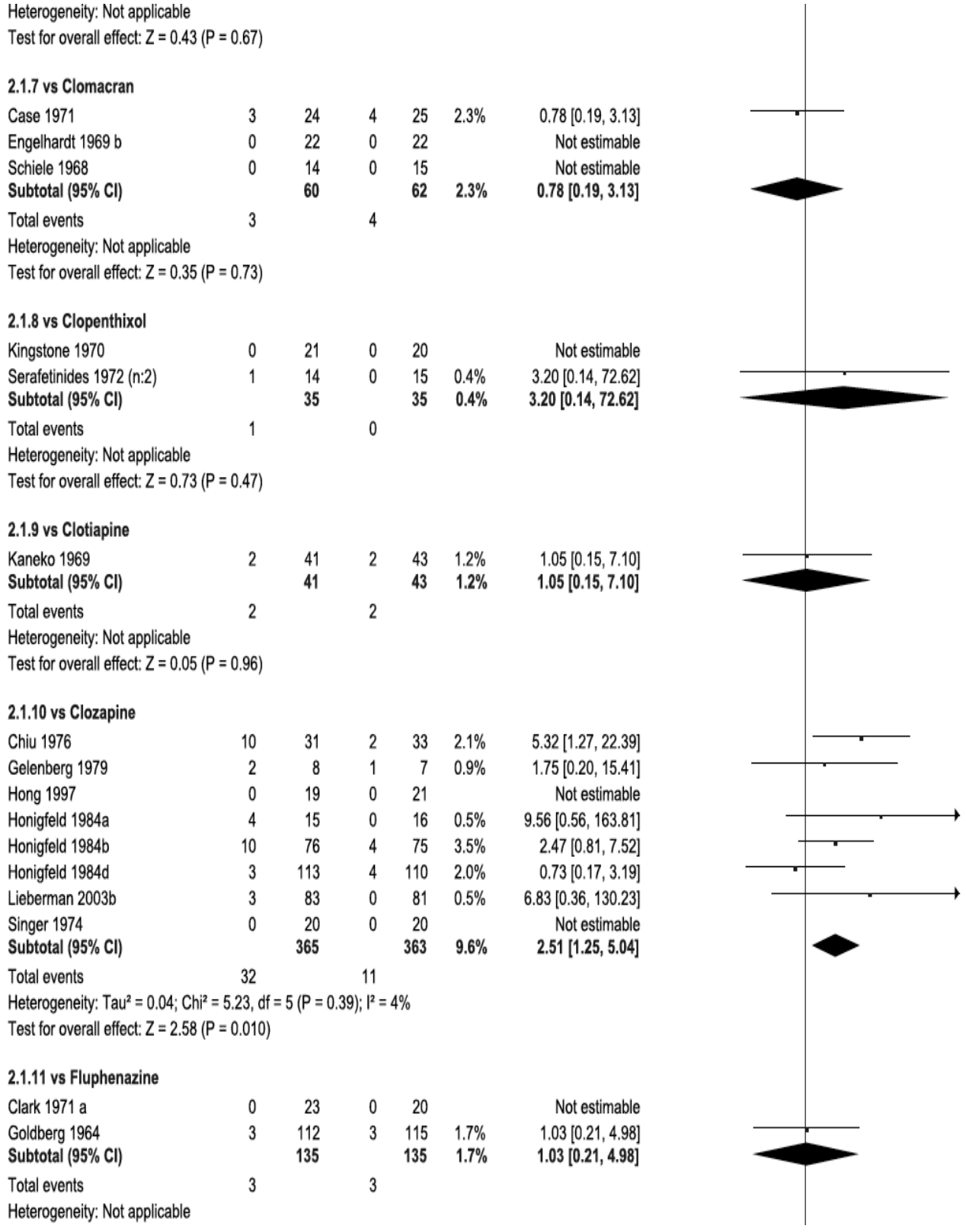
Test for subgroup differences: Chi² = 41.71, df = 41 (P = 0.44), I² = 1.7%



M-H= Maentel-Haenszel, CI= Confidence Interval, vs= versus

eFigure 5: Discontinuation due to inefficacy of chlorpromazine versus all other antipsychotic drugs in individual trials





Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)

2.1.7 vs Clomacran

Case 1971	3	24	4	25	2.3%	0.78 [0.19, 3.13]
Engelhardt 1969 b	0	22	0	22		Not estimable
Schiele 1968	0	14	0	15		Not estimable
Subtotal (95% CI)		**60**		**62**	**2.3%**	**0.78 [0.19, 3.13]**
Total events	3		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.73)

2.1.8 vs Clopenthixol

Kingstone 1970	0	21	0	20		Not estimable
Serafetinides 1972 (n:2)	1	14	0	15	0.4%	3.20 [0.14, 72.62]
Subtotal (95% CI)		**35**		**35**	**0.4%**	**3.20 [0.14, 72.62]**
Total events	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)

2.1.9 vs Clotiapine

Kaneko 1969	2	41	2	43	1.2%	1.05 [0.15, 7.10]
Subtotal (95% CI)		**41**		**43**	**1.2%**	**1.05 [0.15, 7.10]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.05 (P = 0.96)

2.1.10 vs Clozapine

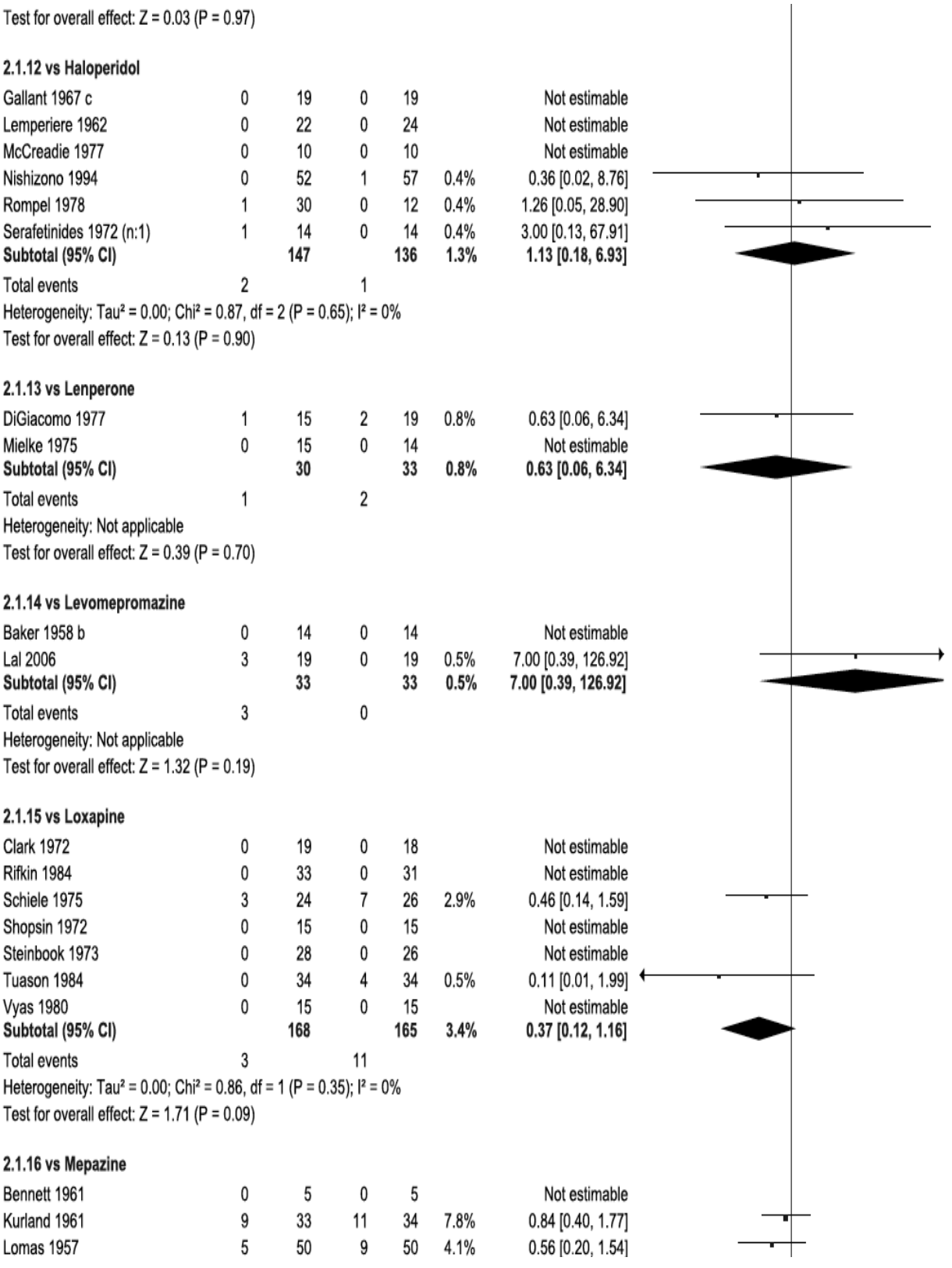
Chiu 1976	10	31	2	33	2.1%	5.32 [1.27, 22.39]
Gelenberg 1979	2	8	1	7	0.9%	1.75 [0.20, 15.41]
Hong 1997	0	19	0	21		Not estimable
Honigfeld 1984a	4	15	0	16	0.5%	9.56 [0.56, 163.81]
Honigfeld 1984b	10	76	4	75	3.5%	2.47 [0.81, 7.52]
Honigfeld 1984d	3	113	4	110	2.0%	0.73 [0.17, 3.19]
Lieberman 2003b	3	83	0	81	0.5%	6.83 [0.36, 130.23]
Singer 1974	0	20	0	20		Not estimable
Subtotal (95% CI)		**365**		**363**	**9.6%**	**2.51 [1.25, 5.04]**
Total events	32		11			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.23$, df = 5 (P = 0.39); $I^2 = 4\%$
Test for overall effect: Z = 2.58 (P = 0.010)

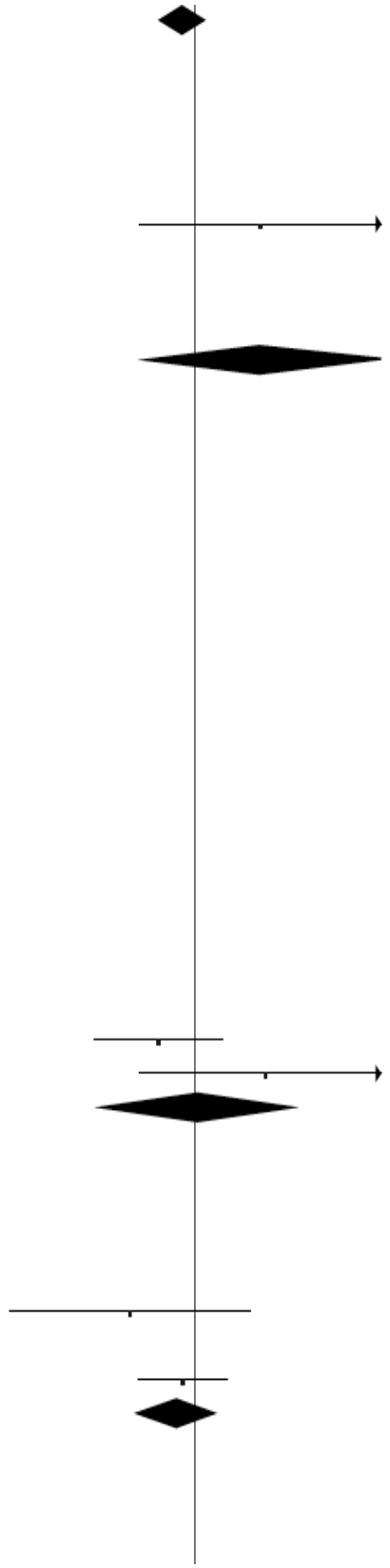
2.1.11 vs Fluphenazine

Clark 1971 a	0	23	0	20		Not estimable
Goldberg 1964	3	112	3	115	1.7%	1.03 [0.21, 4.98]
Subtotal (95% CI)		**135**		**135**	**1.7%**	**1.03 [0.21, 4.98]**
Total events	3		3			

Heterogeneity: Not applicable


Test for overall effect: Z = 0.03 (P = 0.97)
2.1.12 vs Haloperidol
Gallant 1967 c 0 19 0 19 Not estimable
Lemperiere 1962 0 22 0 24 Not estimable
McCreadie 1977 0 10 0 10 Not estimable
Nishizono 1994 0 52 1 57 0.4% 0.36 [0.02, 8.76]
Rompel 1978 1 30 0 12 0.4% 1.26 [0.05, 28.90]
Serafetinides 1972 (n:1) 1 14 0 14 0.4% 3.00 [0.13, 67.91]
Subtotal (95% CI) 147 136 1.3% 1.13 [0.18, 6.93]
Total events 2 1
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
2.1.13 vs Lenperone
DiGiacomo 1977 1 15 2 19 0.8% 0.63 [0.06, 6.34]
Mielke 1975 0 15 0 14 Not estimable
Subtotal (95% CI) 30 33 0.8% 0.63 [0.06, 6.34]
Total events 1 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)
2.1.14 vs Levomepromazine
Baker 1958 b 0 14 0 14 Not estimable
Lal 2006 3 19 0 19 0.5% 7.00 [0.39, 126.92]
Subtotal (95% CI) 33 33 0.5% 7.00 [0.39, 126.92]
Total events 3 0
Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
2.1.15 vs Loxapine
Clark 1972 0 19 0 18 Not estimable
Rifkin 1984 0 33 0 31 Not estimable
Schiele 1975 3 24 7 26 2.9% 0.46 [0.14, 1.59]
Shopsin 1972 0 15 0 15 Not estimable
Steinbook 1973 0 28 0 26 Not estimable
Tuason 1984 0 34 4 34 0.5% 0.11 [0.01, 1.99]
Vyas 1980 0 15 0 15 Not estimable
Subtotal (95% CI) 168 165 3.4% 0.37 [0.12, 1.16]
Total events 3 11
Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 1 (P = 0.35); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)
2.1.16 vs Mepazine
Bennett 1961 0 5 0 5 Not estimable
Kurland 1961 9 33 11 34 7.8% 0.84 [0.40, 1.77]
Lomas 1957 5 50 9 50 4.1% 0.56 [0.20, 1.54]

Subtotal (95% CI)		**88**		**89**	**12.0%**	**0.73 [0.40, 1.33]**
Total events	14		20			
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
2.1.17 vs Mesoridazine						
Douglas 1969	2	32	0	32	0.5%	5.00 [0.25, 100.20]
Freeman 1969	0	25	0	25		Not estimable
Freeman 1973	0	25	0	25		Not estimable
Tetreault 1969 a	0	15	0	15		Not estimable
Subtotal (95% CI)		**97**		**97**	**0.5%**	**5.00 [0.25, 100.20]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
2.1.18 vs Metiapine						
Simpson 1973 b	0	5	0	0		Not estimable
Subtotal (95% CI)		**5**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.1.19 vs Molindone						
Serafetinides 1972 (n:2)	0	15	0	15		Not estimable
Subtotal (95% CI)		**15**		**15**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.1.20 vs Olanzapine						
Conley 1998	2	42	5	42	1.7%	0.40 [0.08, 1.95]
Kostakoglu 2001	1	10	0	20	0.4%	5.73 [0.25, 129.23]
Subtotal (95% CI)		**52**		**62**	**2.2%**	**1.07 [0.09, 13.27]**
Total events	3		5			
Heterogeneity: Tau² = 1.97; Chi² = 2.24, df = 1 (P = 0.13); I² = 55%						
Test for overall effect: Z = 0.05 (P = 0.96)						
2.1.21 vs Oxypertine						
Claghorn 1970 a	0	20	2	20	0.5%	0.20 [0.01, 3.92]
Goldberg 1970 a	0	20	0	20		Not estimable
van Praag 1975 a	4	19	6	21	3.6%	0.74 [0.24, 2.22]
Subtotal (95% CI)		**59**		**61**	**4.1%**	**0.63 [0.22, 1.77]**
Total events	4		8			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.88 (P = 0.38)						



2.1.22 vs Penfluridol

Chouinard 1976	1	19	0	14	0.4%	2.25 [0.10, 51.46]
Wang 1982	2	20	2	21	1.3%	1.05 [0.16, 6.76]
Subtotal (95% CI)		**39**		**35**	**1.7%**	**1.28 [0.26, 6.35]**
Total events	3		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%

Test for overall effect: Z = 0.30 (P = 0.76)

2.1.23 vs Perphenazine

Bennett 1961	0	5	0	5		Not estimable
Subtotal (95% CI)		**5**		**5**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable

2.1.24 vs Pimozide

Anumonye 1976	0	12	0	12		Not estimable
Chouinard 1982 b	0	20	0	20		Not estimable
Kolivakis 1974	4	25	4	26	2.7%	1.04 [0.29, 3.71]
Pecknold 1982	1	10	2	10	0.9%	0.50 [0.05, 4.67]
Umene 1972	0	46	0	46		Not estimable
Wilson 1982 a	2	22	2	21	1.3%	0.95 [0.15, 6.17]
Subtotal (95% CI)		**135**		**135**	**4.8%**	**0.89 [0.34, 2.31]**
Total events	7		8			

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 2 (P = 0.85); I² = 0%

Test for overall effect: Z = 0.24 (P = 0.81)

2.1.25 vs Piperacetazine

Gallant 1970 a	0	13	0	13		Not estimable
Gallant 1970 b	0	8	0	8		Not estimable
Johnson 1970	0	13	0	13		Not estimable
Small 1970	4	15	4	14	3.1%	0.93 [0.29, 3.03]
Subtotal (95% CI)		**49**		**48**	**3.1%**	**0.93 [0.29, 3.03]**
Total events	4		4			

Heterogeneity: Not applicable

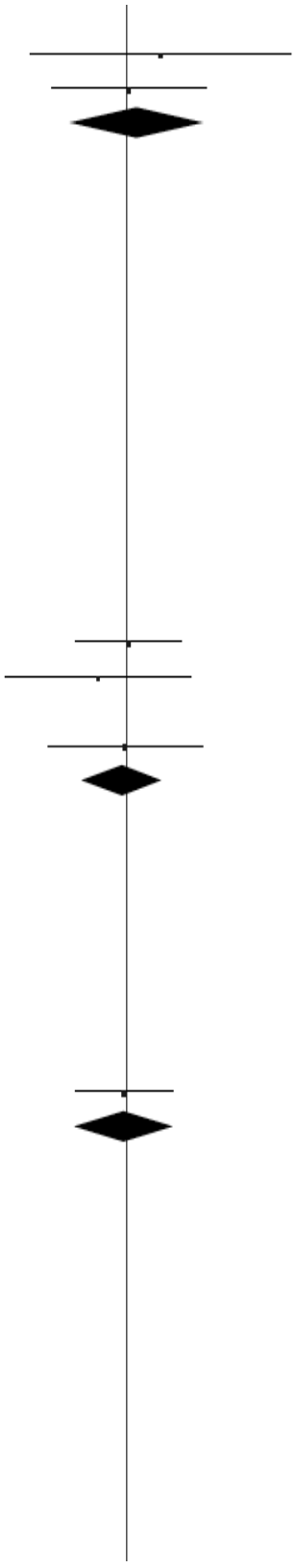
Test for overall effect: Z = 0.11 (P = 0.91)

2.1.26 vs Prochlorperazine

Bennett 1961	0	5	0	5		Not estimable
Wilson 1961	0	2	0	2		Not estimable
Subtotal (95% CI)		**7**		**7**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable



2.1.27 vs Promazine

Fleming 1959	1	21	1	21	0.6%	1.00 [0.07, 14.95]
Subtotal (95% CI)		**21**		**21**	**0.6%**	**1.00 [0.07, 14.95]**
Total events	1		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.00 (P = 1.00)

2.1.28 vs Propericiazine

Ananth 1977a	5	15	1	15	1.1%	5.00 [0.66, 37.85]
Subtotal (95% CI)		**15**		**15**	**1.1%**	**5.00 [0.66, 37.85]**
Total events	5		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.56 (P = 0.12)

2.1.29 vs Quetiapine

AstraZeneca NCT00882518	9	192	12	196	6.1%	0.77 [0.33, 1.78]
Peuskens 1997	15	100	17	101	10.5%	0.89 [0.47, 1.68]
Subtotal (95% CI)		**292**		**297**	**16.5%**	**0.84 [0.51, 1.40]**
Total events	24		29			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0\%$

Test for overall effect: Z = 0.66 (P = 0.51)

2.1.30 vs Reserpine

Barrett 1957	0	10	0	0		Not estimable
Shepherd 1956	0	8	0	8		Not estimable
Simon 1958	0	20	0	20		Not estimable
Subtotal (95% CI)		**38**		**28**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable

2.1.31 vs Risperidone

Mercer 1997	0	12	0	15		Not estimable
Singam 2011	18	50	6	50	6.1%	3.00 [1.30, 6.93]
Subtotal (95% CI)		**62**		**65**	**6.1%**	**3.00 [1.30, 6.93]**
Total events	18		6			

Heterogeneity: Not applicable

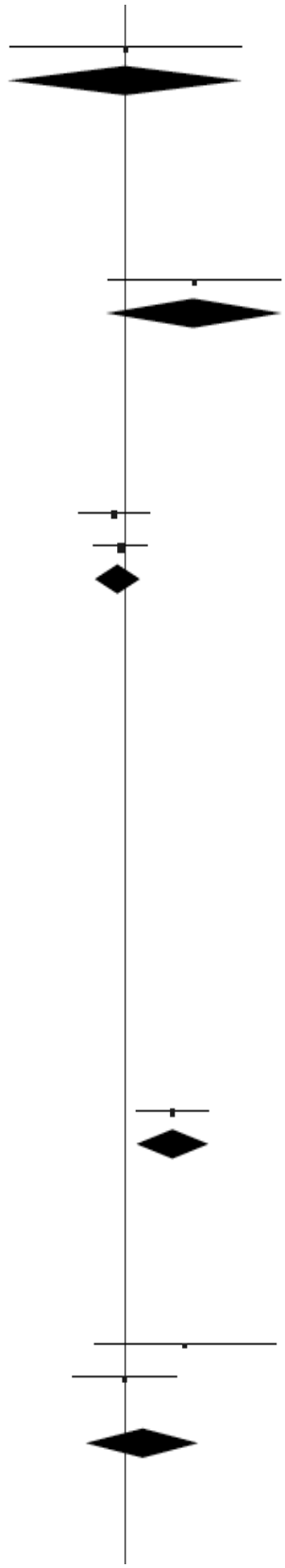
Test for overall effect: Z = 2.57 (P = 0.01)

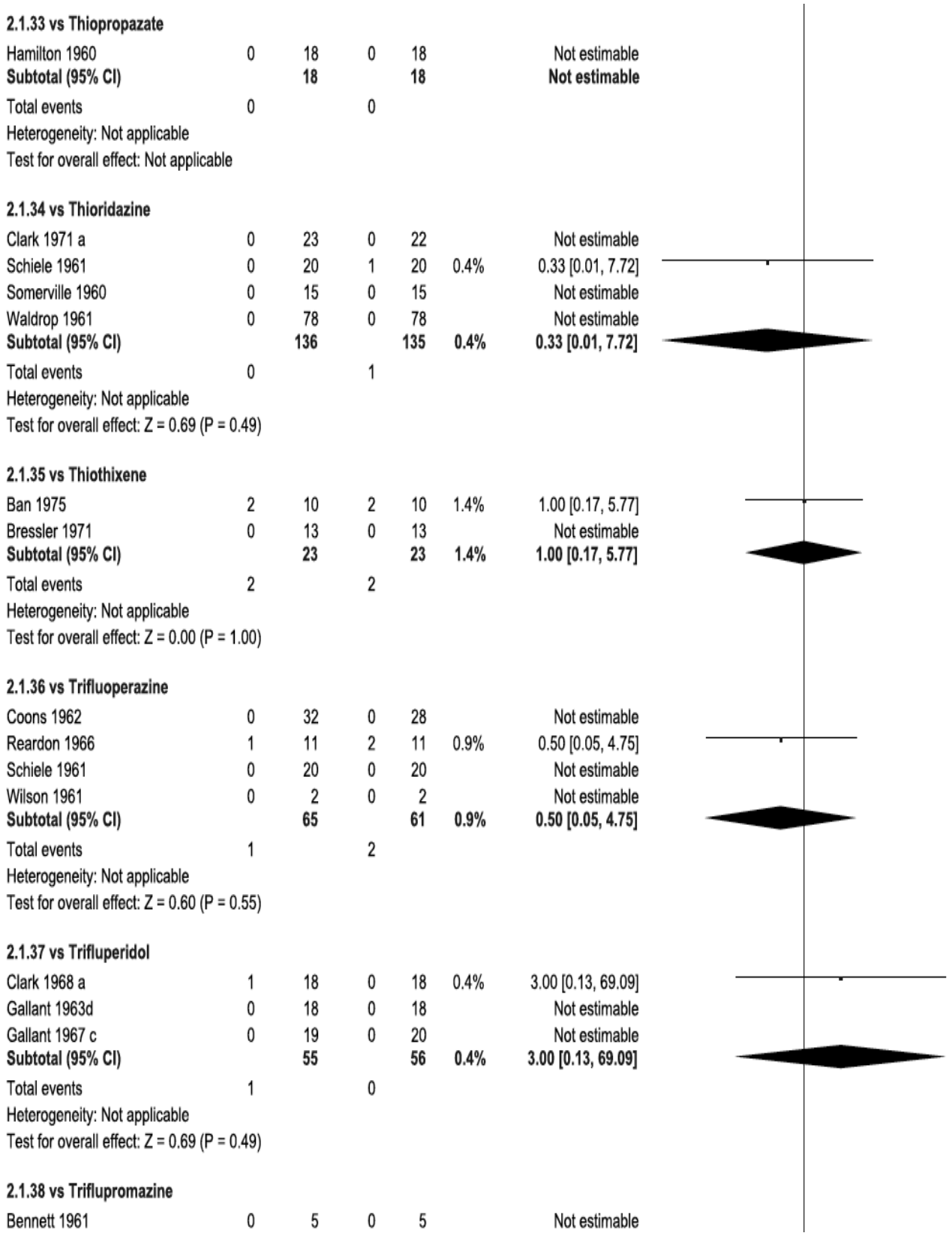
2.1.32 vs Sulpiride

Alfredsson 1984	4	25	1	25	1.0%	4.00 [0.48, 33.33]
Dreyfus 1985	4	29	5	35	2.9%	0.97 [0.29, 3.27]
Toru 1971	0	38	0	38		Not estimable
Subtotal (95% CI)		**92**		**98**	**3.9%**	**1.50 [0.41, 5.54]**
Total events	8		6			

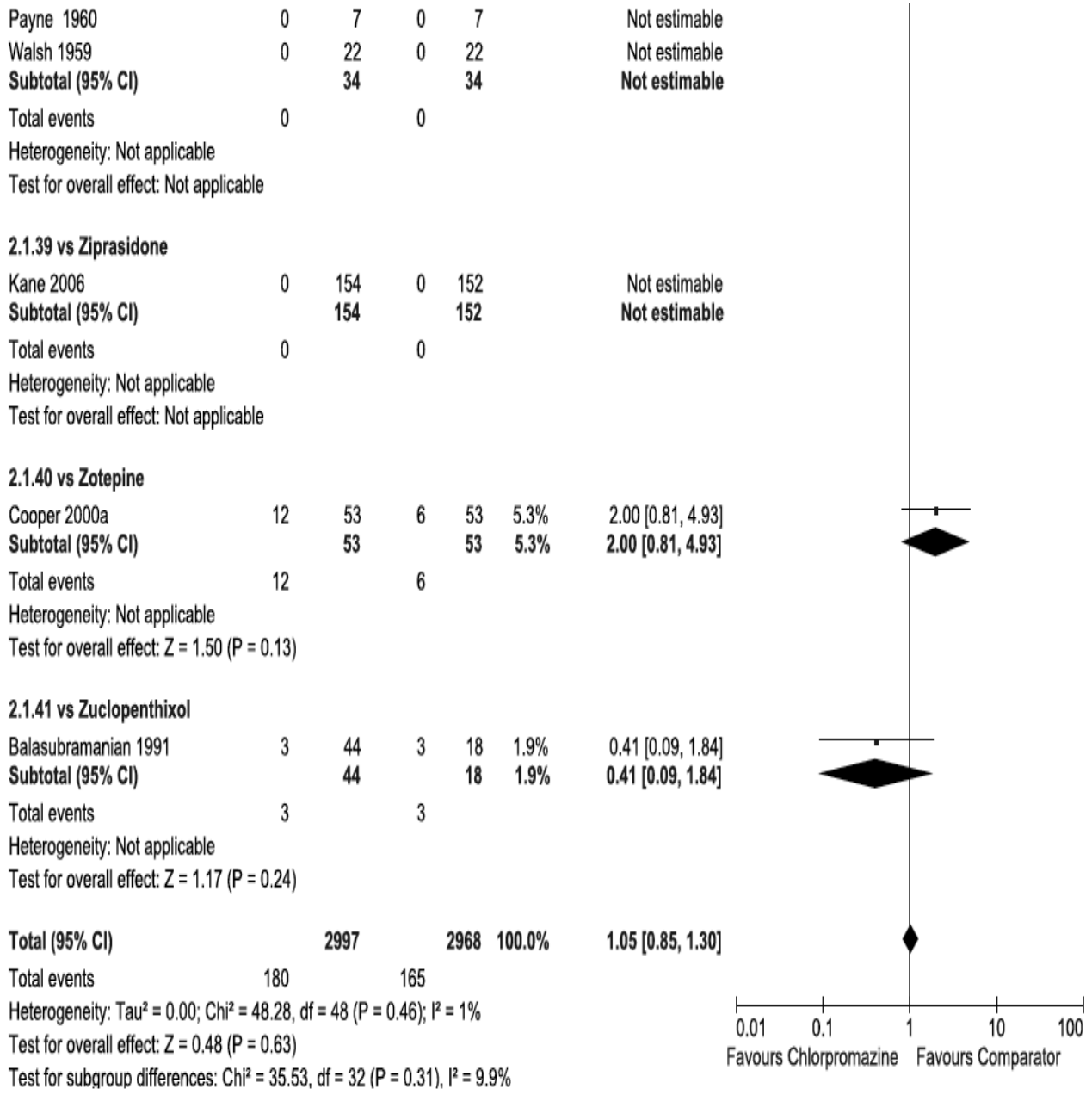
Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 1.33$, df = 1 (P = 0.25); $I^2 = 25\%$

Test for overall effect: Z = 0.61 (P = 0.54)



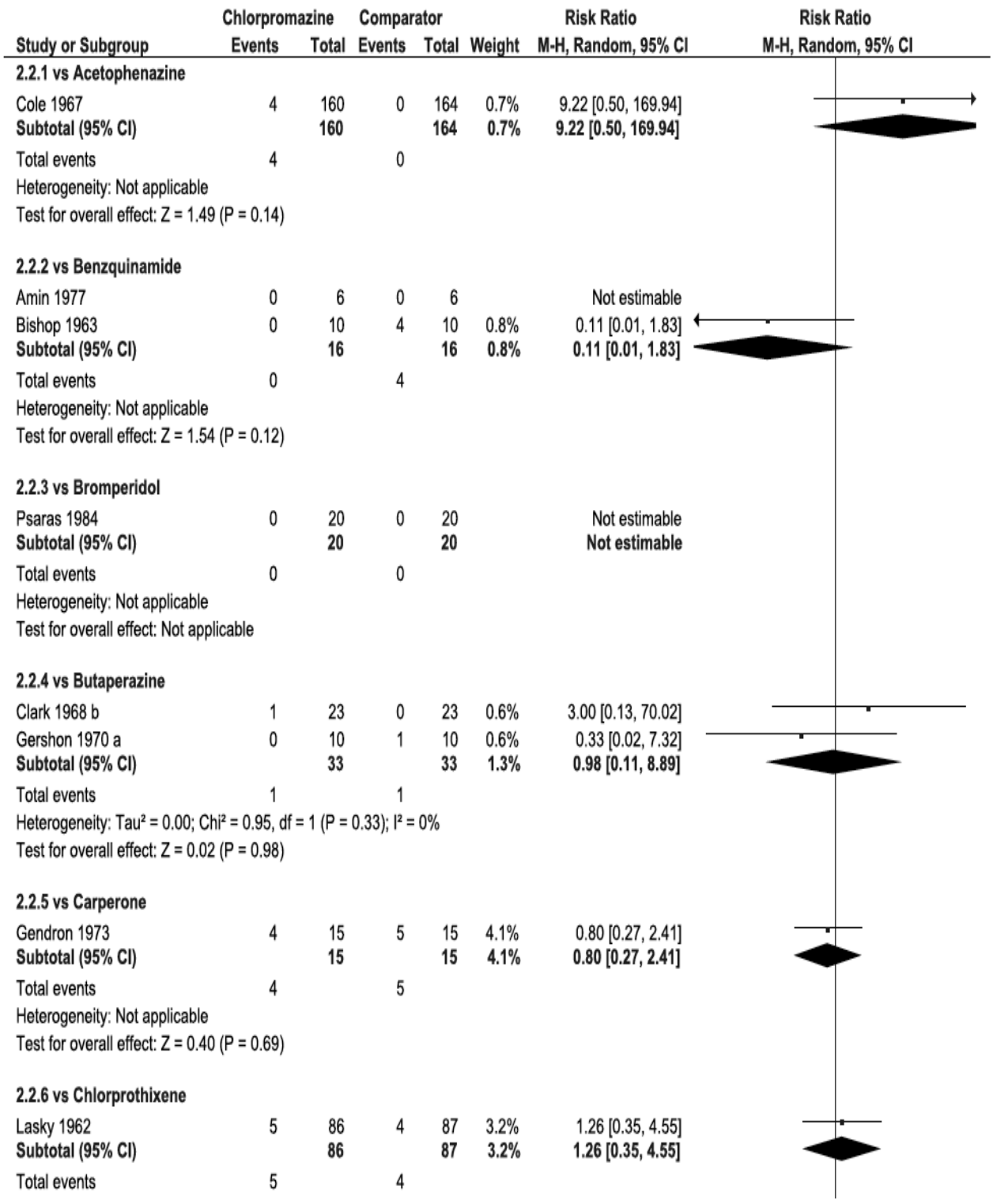


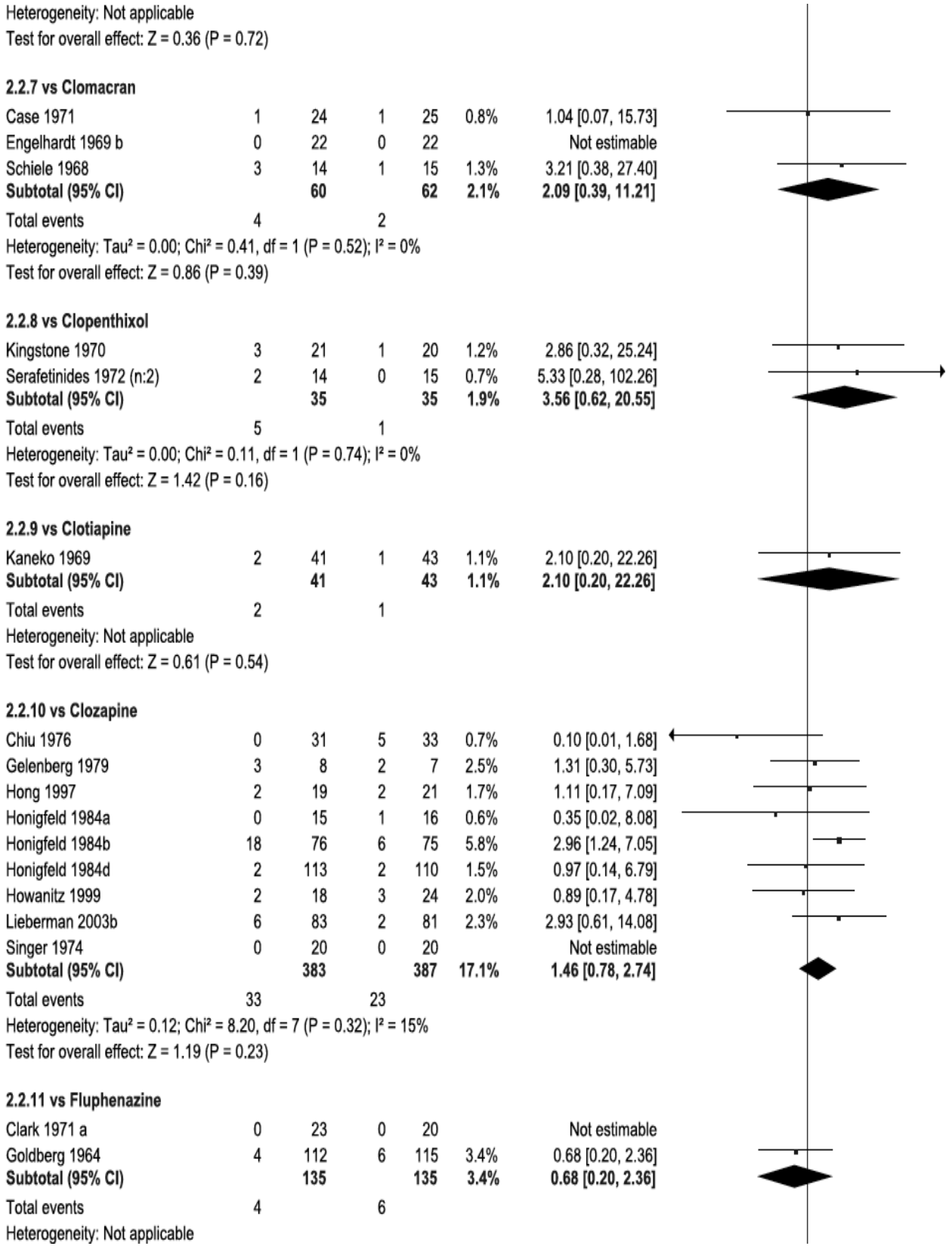
2.1.33 vs Thiopropazate						
Hamilton 1960	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.1.34 vs Thioridazine						
Clark 1971 a	0	23	0	22		Not estimable
Schiele 1961	0	20	1	20	0.4%	0.33 [0.01, 7.72]
Somerville 1960	0	15	0	15		Not estimable
Waldrop 1961	0	78	0	78		Not estimable
Subtotal (95% CI)		**136**		**135**	**0.4%**	**0.33 [0.01, 7.72]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
2.1.35 vs Thiothixene						
Ban 1975	2	10	2	10	1.4%	1.00 [0.17, 5.77]
Bressler 1971	0	13	0	13		Not estimable
Subtotal (95% CI)		**23**		**23**	**1.4%**	**1.00 [0.17, 5.77]**
Total events	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.1.36 vs Trifluoperazine						
Coons 1962	0	32	0	28		Not estimable
Reardon 1966	1	11	2	11	0.9%	0.50 [0.05, 4.75]
Schiele 1961	0	20	0	20		Not estimable
Wilson 1961	0	2	0	2		Not estimable
Subtotal (95% CI)		**65**		**61**	**0.9%**	**0.50 [0.05, 4.75]**
Total events	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.1.37 vs Trifluperidol						
Clark 1968 a	1	18	0	18	0.4%	3.00 [0.13, 69.09]
Gallant 1963d	0	18	0	18		Not estimable
Gallant 1967 c	0	19	0	20		Not estimable
Subtotal (95% CI)		**55**		**56**	**0.4%**	**3.00 [0.13, 69.09]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
2.1.38 vs Triflupromazine						
Bennett 1961	0	5	0	5		Not estimable



M-H= Maentel-Haenszel, CI= Confidence Interval, vs= versus

eFigure 6: Discontinuation due to adverse effects of chlorpromazine versus all other antipsychotic drugs in individual trials





Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

2.2.7 vs Clomacran

Case 1971	1	24	1	25	0.8%	1.04 [0.07, 15.73]
Engelhardt 1969 b	0	22	0	22		Not estimable
Schiele 1968	3	14	1	15	1.3%	3.21 [0.38, 27.40]
Subtotal (95% CI)		**60**		**62**	**2.1%**	**2.09 [0.39, 11.21]**
Total events	4		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)

2.2.8 vs Clopenthixol

Kingstone 1970	3	21	1	20	1.2%	2.86 [0.32, 25.24]
Serafetinides 1972 (n:2)	2	14	0	15	0.7%	5.33 [0.28, 102.26]
Subtotal (95% CI)		**35**		**35**	**1.9%**	**3.56 [0.62, 20.55]**
Total events	5		1			

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

2.2.9 vs Clotiapine

Kaneko 1969	2	41	1	43	1.1%	2.10 [0.20, 22.26]
Subtotal (95% CI)		**41**		**43**	**1.1%**	**2.10 [0.20, 22.26]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.61 (P = 0.54)

2.2.10 vs Clozapine

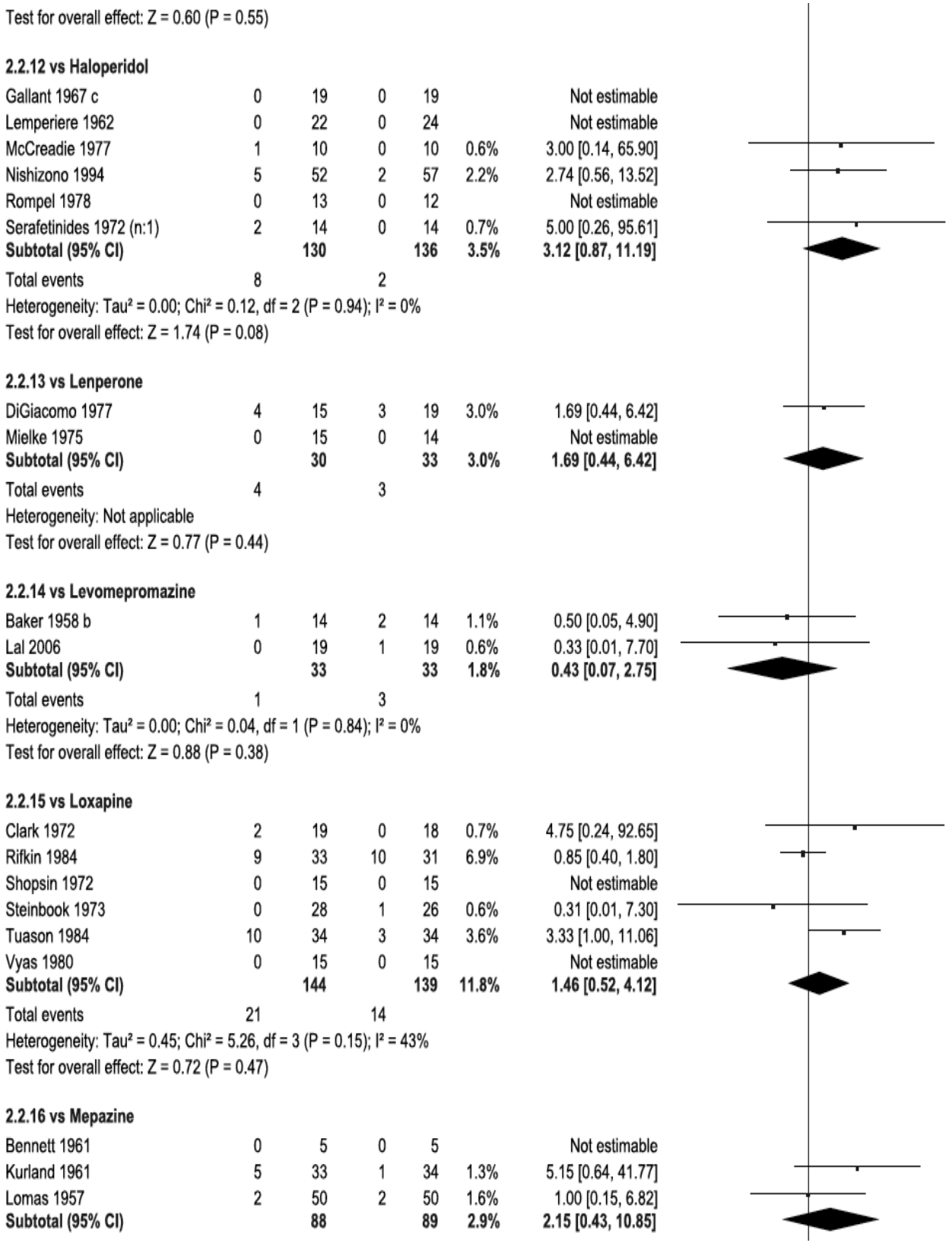
Chiu 1976	0	31	5	33	0.7%	0.10 [0.01, 1.68]
Gelenberg 1979	3	8	2	7	2.5%	1.31 [0.30, 5.73]
Hong 1997	2	19	2	21	1.7%	1.11 [0.17, 7.09]
Honigfeld 1984a	0	15	1	16	0.6%	0.35 [0.02, 8.08]
Honigfeld 1984b	18	76	6	75	5.8%	2.96 [1.24, 7.05]
Honigfeld 1984d	2	113	2	110	1.5%	0.97 [0.14, 6.79]
Howanitz 1999	2	18	3	24	2.0%	0.89 [0.17, 4.78]
Lieberman 2003b	6	83	2	81	2.3%	2.93 [0.61, 14.08]
Singer 1974	0	20	0	20		Not estimable
Subtotal (95% CI)		**383**		**387**	**17.1%**	**1.46 [0.78, 2.74]**
Total events	33		23			

Heterogeneity: Tau² = 0.12; Chi² = 8.20, df = 7 (P = 0.32); I² = 15%
Test for overall effect: Z = 1.19 (P = 0.23)

2.2.11 vs Fluphenazine

Clark 1971 a	0	23	0	20		Not estimable
Goldberg 1964	4	112	6	115	3.4%	0.68 [0.20, 2.36]
Subtotal (95% CI)		**135**		**135**	**3.4%**	**0.68 [0.20, 2.36]**
Total events	4		6			

Heterogeneity: Not applicable



Test for overall effect: Z = 0.60 (P = 0.55)

2.2.12 vs Haloperidol

Gallant 1967 c	0	19	0	19		Not estimable
Lemperiere 1962	0	22	0	24		Not estimable
McCreadie 1977	1	10	0	10	0.6%	3.00 [0.14, 65.90]
Nishizono 1994	5	52	2	57	2.2%	2.74 [0.56, 13.52]
Rompel 1978	0	13	0	12		Not estimable
Serafetinides 1972 (n:1)	2	14	0	14	0.7%	5.00 [0.26, 95.61]
Subtotal (95% CI)		**130**		**136**	**3.5%**	**3.12 [0.87, 11.19]**
Total events	8		2			

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%

Test for overall effect: Z = 1.74 (P = 0.08)

2.2.13 vs Lenperone

DiGiacomo 1977	4	15	3	19	3.0%	1.69 [0.44, 6.42]
Mielke 1975	0	15	0	14		Not estimable
Subtotal (95% CI)		**30**		**33**	**3.0%**	**1.69 [0.44, 6.42]**
Total events	4		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.77 (P = 0.44)

2.2.14 vs Levomepromazine

Baker 1958 b	1	14	2	14	1.1%	0.50 [0.05, 4.90]
Lal 2006	0	19	1	19	0.6%	0.33 [0.01, 7.70]
Subtotal (95% CI)		**33**		**33**	**1.8%**	**0.43 [0.07, 2.75]**
Total events	1		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

Test for overall effect: Z = 0.88 (P = 0.38)

2.2.15 vs Loxapine

Clark 1972	2	19	0	18	0.7%	4.75 [0.24, 92.65]
Rifkin 1984	9	33	10	31	6.9%	0.85 [0.40, 1.80]
Shopsin 1972	0	15	0	15		Not estimable
Steinbook 1973	0	28	1	26	0.6%	0.31 [0.01, 7.30]
Tuason 1984	10	34	3	34	3.6%	3.33 [1.00, 11.06]
Vyas 1980	0	15	0	15		Not estimable
Subtotal (95% CI)		**144**		**139**	**11.8%**	**1.46 [0.52, 4.12]**
Total events	21		14			

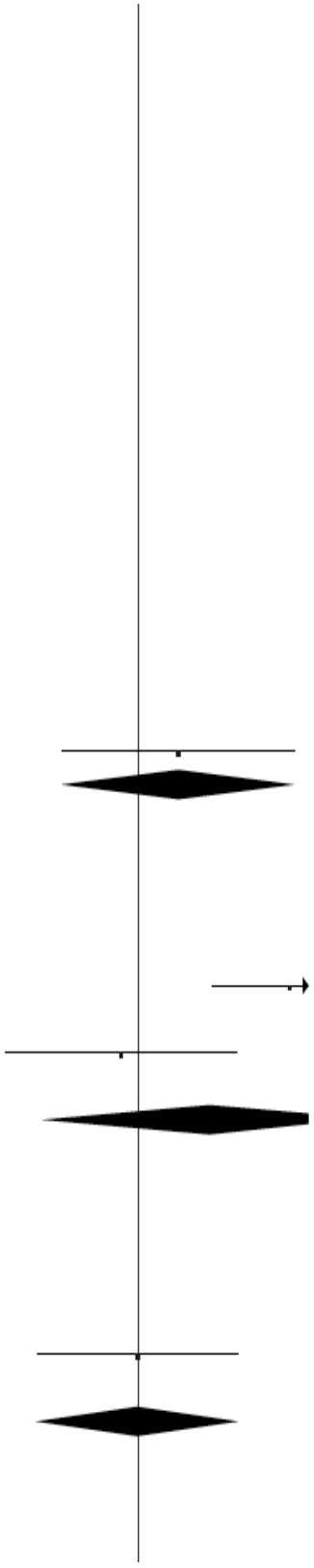
Heterogeneity: Tau² = 0.45; Chi² = 5.26, df = 3 (P = 0.15); I² = 43%

Test for overall effect: Z = 0.72 (P = 0.47)

2.2.16 vs Mepazine

Bennett 1961	0	5	0	5		Not estimable
Kurland 1961	5	33	1	34	1.3%	5.15 [0.64, 41.77]
Lomas 1957	2	50	2	50	1.6%	1.00 [0.15, 6.82]
Subtotal (95% CI)		**88**		**89**	**2.9%**	**2.15 [0.43, 10.85]**

Total events	7		3			
Heterogeneity: Tau² = 0.32; Chi² = 1.30, df = 1 (P = 0.25); I² = 23%						
Test for overall effect: Z = 0.93 (P = 0.35)						
2.2.17 vs Mesoridazine						
Douglas 1969	0	32	0	32		Not estimable
Freeman 1969	0	25	0	25		Not estimable
Freeman 1973	0	25	0	25		Not estimable
Tetreault 1969 a	0	15	0	15		Not estimable
Subtotal (95% CI)		**97**		**97**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.18 vs Metiapine						
Simpson 1973 b	0	5	0	5		Not estimable
Subtotal (95% CI)		**5**		**5**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.19 vs Molindone						
Serafetinides 1972 (n:2)	1	15	0	15	0.6%	3.00 [0.13, 68.26]
Subtotal (95% CI)		**15**		**15**	**0.6%**	**3.00 [0.13, 68.26]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
2.2.20 vs Olanzapine						
Conley 1998	6	42	1	420	1.3%	60.00 [7.40, 486.60]
Dossenbach 2007	0	12	0	27		Not estimable
Kostakoglu 2001	0	10	1	20	0.6%	0.64 [0.03, 14.36]
Loza 1999	0	14	0	27		Not estimable
Subtotal (95% CI)		**78**		**494**	**2.0%**	**7.15 [0.08, 667.86]**
Total events	6		2			
Heterogeneity: Tau² = 8.92; Chi² = 5.87, df = 1 (P = 0.02); I² = 83%						
Test for overall effect: Z = 0.85 (P = 0.40)						
2.2.21 vs Oxypertine						
Claghorn 1970 a	0	20	0	20		Not estimable
Goldberg 1970 a	1	20	1	20	0.8%	1.00 [0.07, 14.90]
van Praag 1975 a	0	19	0	21		Not estimable
Subtotal (95% CI)		**59**		**61**	**0.8%**	**1.00 [0.07, 14.90]**
Total events	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						



2.2.22 vs Penfluridol

Chouinard 1976	7	19	3	14	3.7%	1.72 [0.54, 5.50]
Wang 1982	0	20	0	21		Not estimable
Subtotal (95% CI)		**39**		**35**	**3.7%**	**1.72 [0.54, 5.50]**
Total events	7		3			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.91 (P = 0.36)

2.2.23 vs Perphenazine

Bennett 1961	0	5	0	0		Not estimable
Subtotal (95% CI)		**5**		**0**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable

2.2.24 vs Pimozide

Anumonye 1976	0	12	0	12		Not estimable
Chouinard 1982 b	0	20	0	20		Not estimable
Kolivakis 1974	0	25	0	26		Not estimable
Pecknold 1982	1	10	0	10	0.6%	3.00 [0.14, 65.90]
Umene 1972	1	46	0	46	0.6%	3.00 [0.13, 71.78]
Wilson 1982 a	4	22	1	21	1.3%	3.82 [0.46, 31.43]
Subtotal (95% CI)		**135**		**135**	**2.6%**	**3.40 [0.74, 15.67]**
Total events	6		1			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 2 (P = 0.99); $I^2 = 0\%$

Test for overall effect: Z = 1.57 (P = 0.12)

2.2.25 vs Piperacetazine

Gallant 1970 a	0	13	0	13		Not estimable
Gallant 1970 b	0	8	0	8		Not estimable
Johnson 1970	0	13	0	13		Not estimable
Small 1970	3	15	1	14	1.3%	2.80 [0.33, 23.86]
Subtotal (95% CI)		**49**		**48**	**1.3%**	**2.80 [0.33, 23.86]**
Total events	3		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.94 (P = 0.35)

2.2.26 vs Prochlorperazine

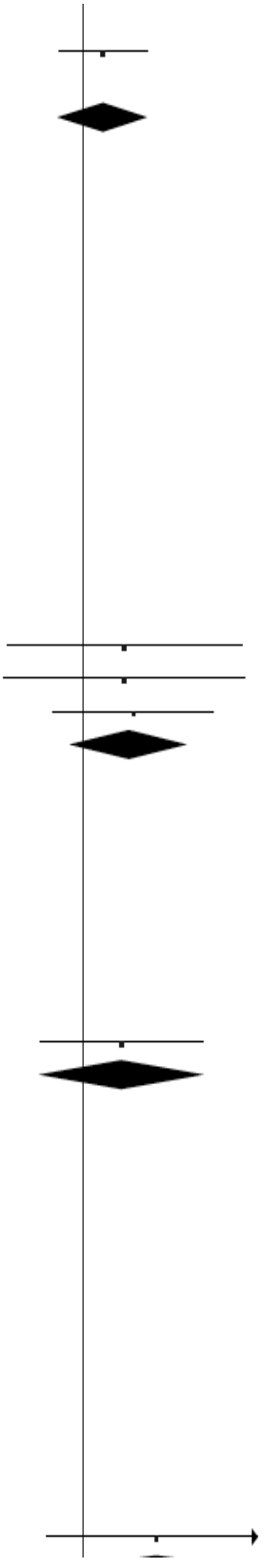
Bennett 1961	0	5	0	5		Not estimable
Wilson 1961	0	2	0	2		Not estimable
Subtotal (95% CI)		**7**		**7**		**Not estimable**
Total events	0		0			

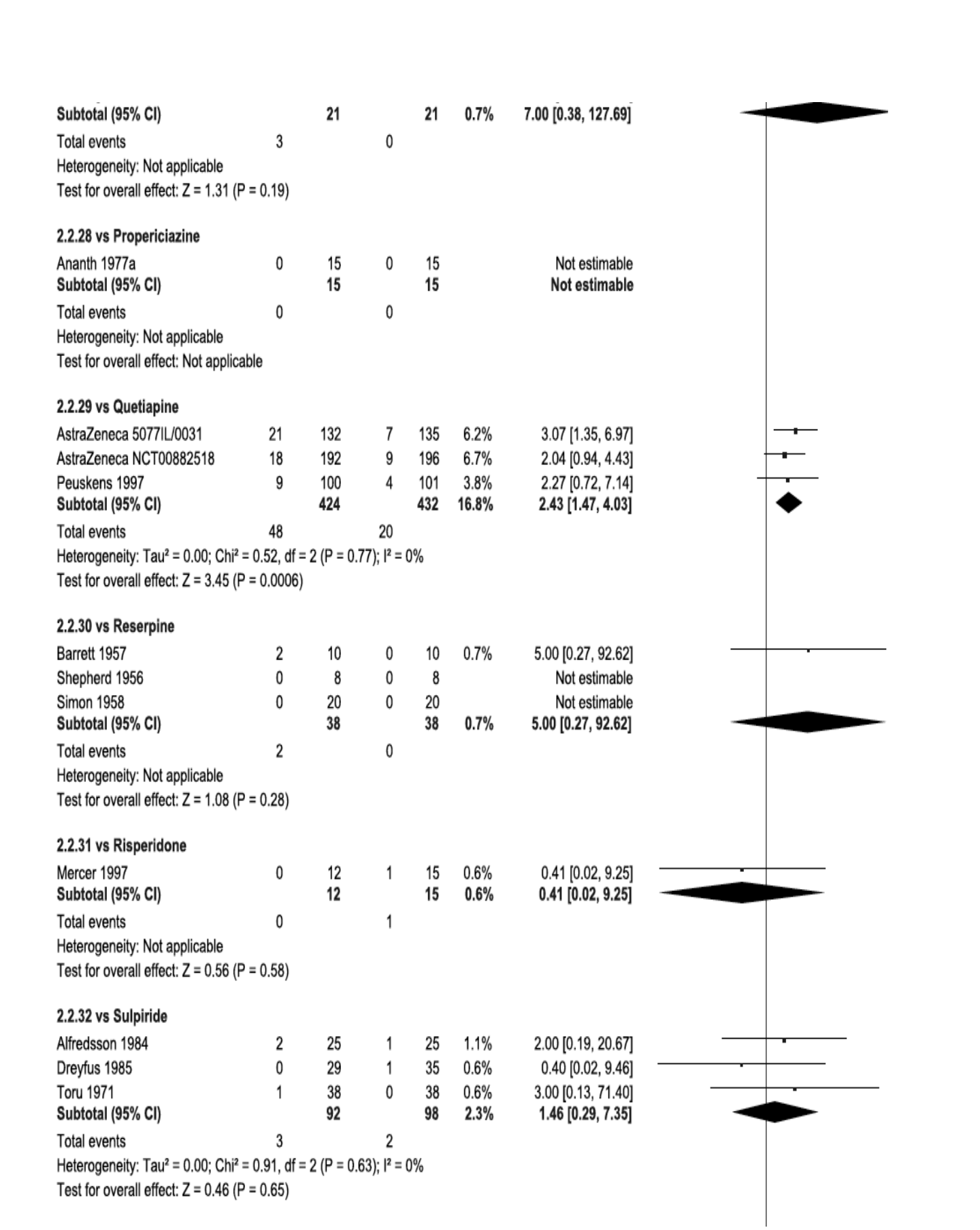
Heterogeneity: Not applicable

Test for overall effect: Not applicable

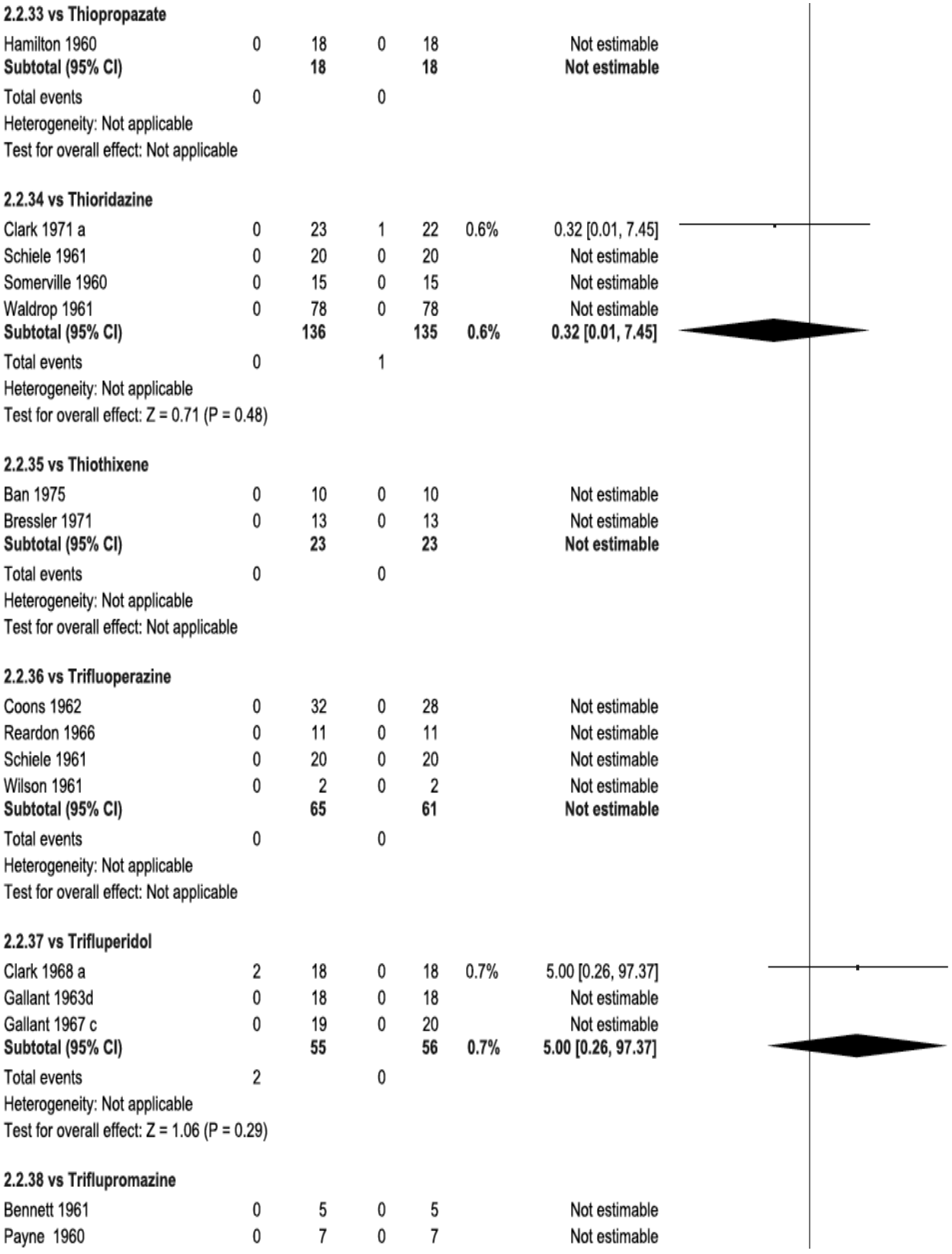
2.2.27 vs Promazine

Fleming 1959	3	21	0	21	0.7%	7.00 [0.38, 127.69]

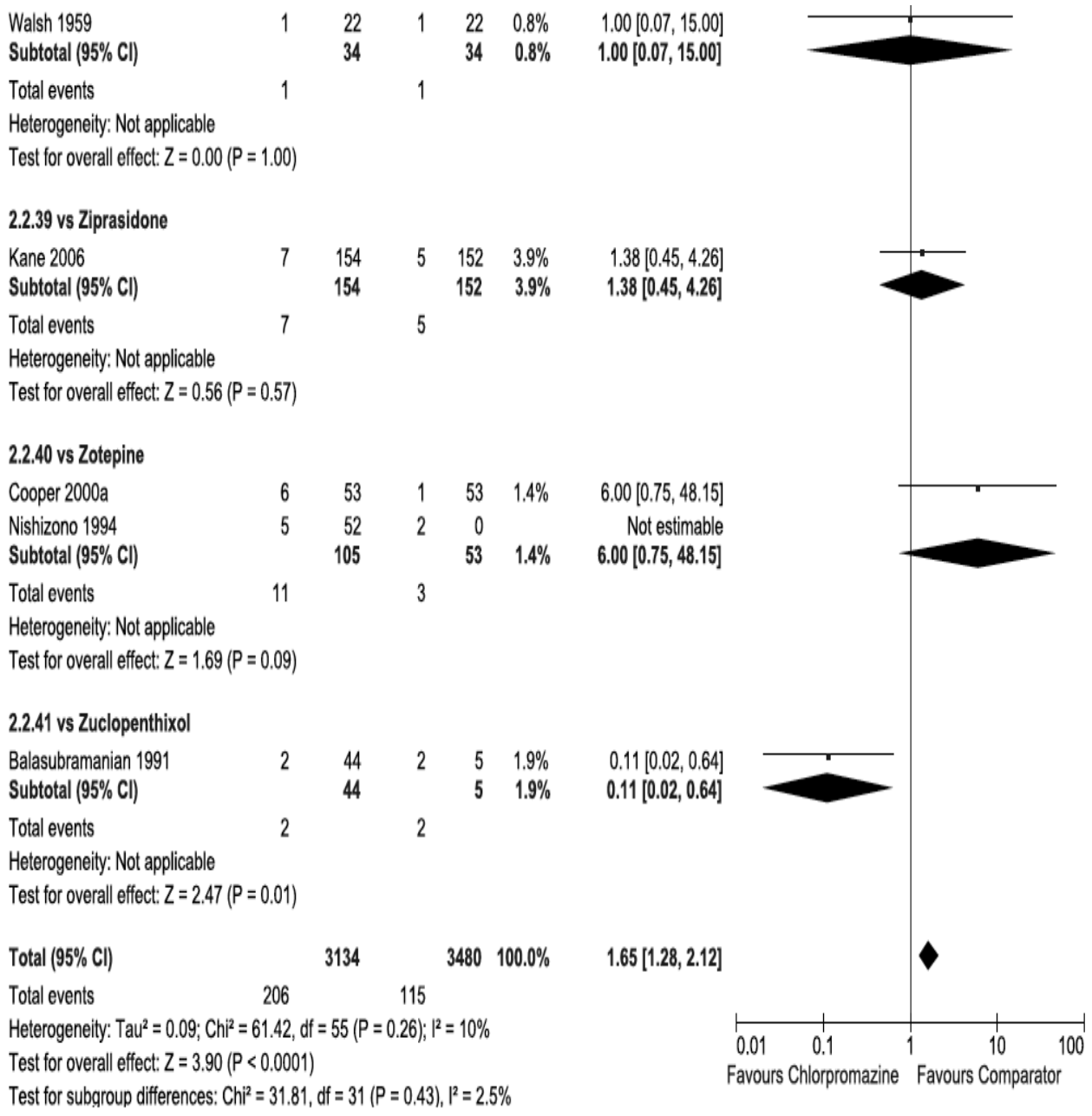




Subtotal (95% CI)		**21**		**21**	**0.7%**	**7.00 [0.38, 127.69]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
2.2.28 vs Propericiazine						
Ananth 1977a	0	15	0	15		Not estimable
Subtotal (95% CI)		**15**		**15**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.29 vs Quetiapine						
AstraZeneca 5077IL/0031	21	132	7	135	6.2%	3.07 [1.35, 6.97]
AstraZeneca NCT00882518	18	192	9	196	6.7%	2.04 [0.94, 4.43]
Peuskens 1997	9	100	4	101	3.8%	2.27 [0.72, 7.14]
Subtotal (95% CI)		**424**		**432**	**16.8%**	**2.43 [1.47, 4.03]**
Total events	48		20			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.52$, df = 2 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 3.45 (P = 0.0006)						
2.2.30 vs Reserpine						
Barrett 1957	2	10	0	10	0.7%	5.00 [0.27, 92.62]
Shepherd 1956	0	8	0	8		Not estimable
Simon 1958	0	20	0	20		Not estimable
Subtotal (95% CI)		**38**		**38**	**0.7%**	**5.00 [0.27, 92.62]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
2.2.31 vs Risperidone						
Mercer 1997	0	12	1	15	0.6%	0.41 [0.02, 9.25]
Subtotal (95% CI)		**12**		**15**	**0.6%**	**0.41 [0.02, 9.25]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
2.2.32 vs Sulpiride						
Alfredsson 1984	2	25	1	25	1.1%	2.00 [0.19, 20.67]
Dreyfus 1985	0	29	1	35	0.6%	0.40 [0.02, 9.46]
Toru 1971	1	38	0	38	0.6%	3.00 [0.13, 71.40]
Subtotal (95% CI)		**92**		**98**	**2.3%**	**1.46 [0.29, 7.35]**
Total events	3		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.91$, df = 2 (P = 0.63); $I^2 = 0\%$						
Test for overall effect: Z = 0.46 (P = 0.65)						



2.2.33 vs Thiopropazate						
Hamilton 1960	0	18	0	18		Not estimable
Subtotal (95% CI)		**18**		**18**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.34 vs Thioridazine						
Clark 1971 a	0	23	1	22	0.6%	0.32 [0.01, 7.45]
Schiele 1961	0	20	0	20		Not estimable
Somerville 1960	0	15	0	15		Not estimable
Waldrop 1961	0	78	0	78		Not estimable
Subtotal (95% CI)		**136**		**135**	**0.6%**	**0.32 [0.01, 7.45]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
2.2.35 vs Thiothixene						
Ban 1975	0	10	0	10		Not estimable
Bressler 1971	0	13	0	13		Not estimable
Subtotal (95% CI)		**23**		**23**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.36 vs Trifluoperazine						
Coons 1962	0	32	0	28		Not estimable
Reardon 1966	0	11	0	11		Not estimable
Schiele 1961	0	20	0	20		Not estimable
Wilson 1961	0	2	0	2		Not estimable
Subtotal (95% CI)		**65**		**61**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.37 vs Trifluperidol						
Clark 1968 a	2	18	0	18	0.7%	5.00 [0.26, 97.37]
Gallant 1963d	0	18	0	18		Not estimable
Gallant 1967 c	0	19	0	20		Not estimable
Subtotal (95% CI)		**55**		**56**	**0.7%**	**5.00 [0.26, 97.37]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
2.2.38 vs Triflupromazine						
Bennett 1961	0	5	0	5		Not estimable
Payne 1960	0	7	0	7		Not estimable

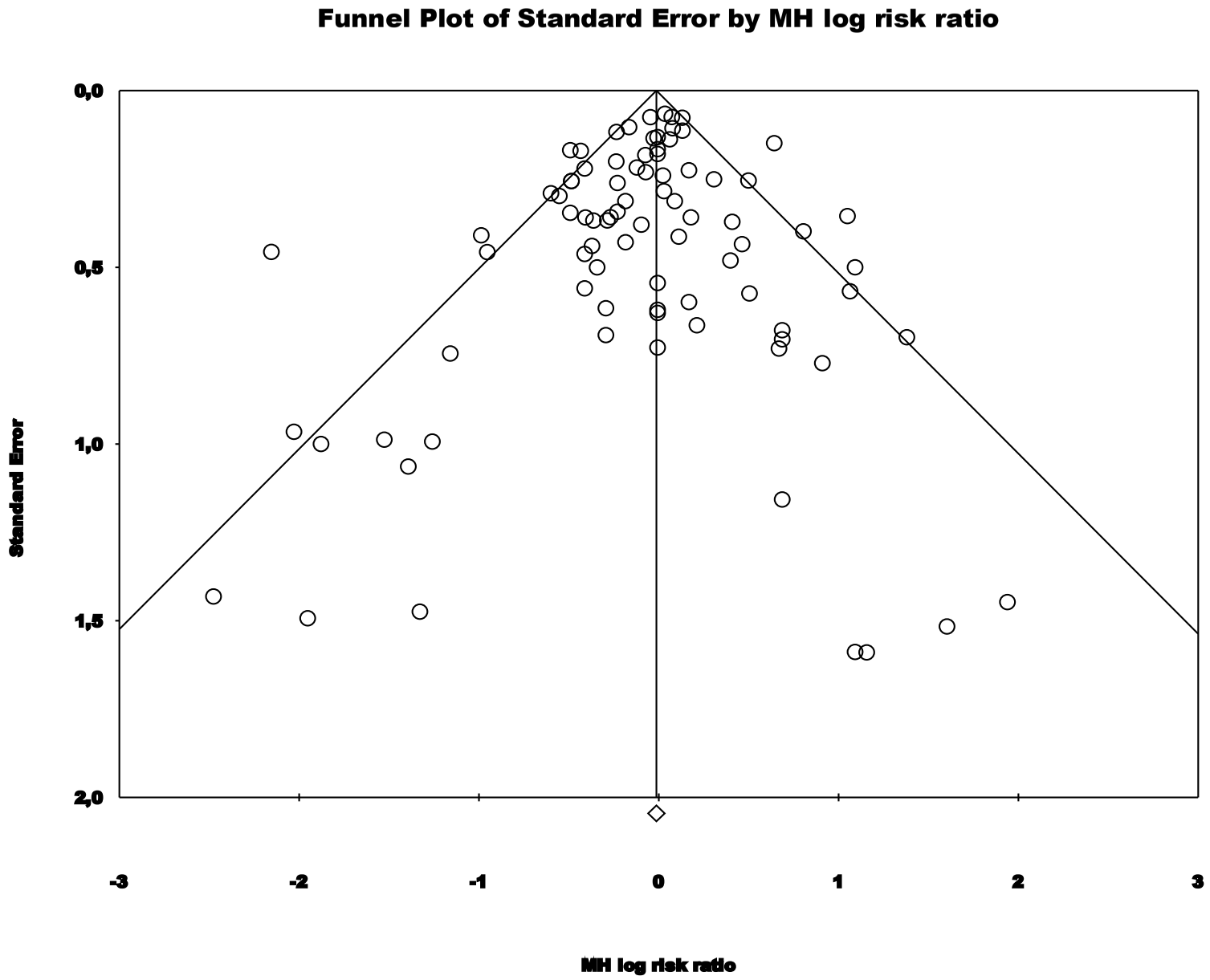


M-H= Maentel-Haenszel, CI= Confidence Interval, vs= versus

eFigure 7: Meta-regression analysis with chlorpromazine/clozapine dose ratio as a moderator

Outcome was response to treatment. Circle size represents weight each study was given in the analysis.

eFigure 8: Funnel plot of all trials for the outcome response to treatment



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Imputation of response rates from means and standard deviations in schizophrenia

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ABSTRACT

Missing outcome data is a major threat in meta-analytical studies of schizophrenia. Most clinical trials in psychiatry report only continuous outcome measures and express the effect of an intervention as a difference of means. However, these results are difficult to interpret for clinicians. Converting continuous data to binary response rates is one possible solution to the problem. Based on means and standard deviations for a continuous outcome, we examined the performance of an imputation method to define a dichotomous outcome using original individual patients' data from 16 randomized trials (6276 participants) comparing antipsychotic drugs in schizophrenia. We concluded that the imputed values re-captured in a reasonable degree the observed values providing a simple and practical alternative methodological choice for imputation of missing binary data in schizophrenia trials; nevertheless, the imputation method tended to introduce biases, especially for extreme risks and large treatment differences.

1. Introduction

Schizophrenia trials typically measure the efficacy of an intervention using the mean of a validated rating scale such as the Brief Psychiatric Rating Scale or the Positive and Negative Syndrome Scale (PANSS) at endpoint (or the mean change from baseline to endpoint). Binary results in the form of the number of responders based on a specific cut-off point (e.g., an at least 20% reduction from baseline in the PANSS scale) are useful for both statistical and clinical reasons. From a statistical point of view, such a dichotomization eliminates the need for the linearity assumption, and, although it decreases statistical power, it makes data summarization more efficient (Altman et al., 1994; Royston et al., 2000; Streiner, 2002; Mazumdar et al., 2003; Altman and Royston, 2006). From a clinical point of view, dichotomization allows for simple risk classification, assists in making treatment recommendations, in estimating prognosis and in setting diagnostic criteria, and, most importantly, enhances the interpretation of results. For example, the percentage responders in both groups (e.g., 10% and 20%) and a resulting response ratio (two times more responders in the second group) can be understood more intuitively than a difference of e.g., 10 points on the PANSS total score, despite recent efforts to translate the results of such rating scales for clinical practice (Leucht et al., 2005a,b; Levine et al., 2008; Schennach-Wolff et al., 2010). This is important for single RCTs, but even more so for meta-analyses which aim to summarize all RCT data and to present clinically useful indices such as risk differences or odds ratios (ORs) and the number-needed-to-treat (NNT) which are based on dichotomous outcomes. Unfortunately, response data are not consistently reported in trials leading to a major limitation for meta-analyses which attempt to present a summary of all available studies and not only a subset of them. To overcome this limitation, Furukawa et al. (2005) explored an imputation strategy to estimate response rates from means and standard deviations at endpoint and yielded excellent results in depression and anxiety trials. The aim of the current study was to determine whether this method is also applicable to schizophrenia trials. To this end, rigorous statistical methods (Furukawa et al., 2005; Furukawa and Leucht, 2011) were applied to a collection of studies for which individual patient data were available.

2. Methods

We compared the actual observed response rates and ORs with the ones imputed by the Furukawa et al. (2005) method using individual data of 6276 patients from 37 arms of 16 randomized controlled

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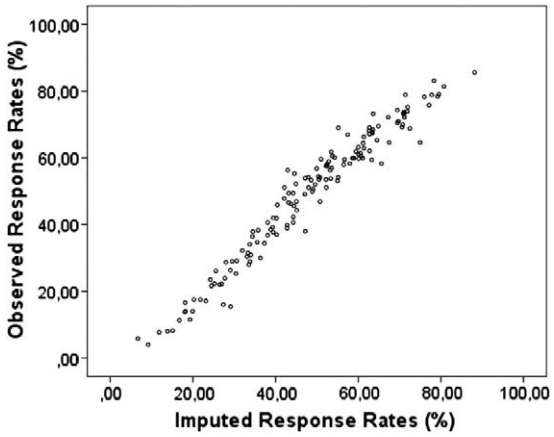

Fig. 1. Comparison of the observed versus imputed response rates.

trials (RCTs) (Beasley et al., 1996, 1997; Moller et al., 1997; Tollefson et al., 1997; Tran et al., 1997; Puech et al., 1998; Wetzel et al., 1998; Peuskens et al., 1999; Carriere et al., 2000; Colonna et al., 2000; Sechter et al., 2002; Lieberman et al., 2003a,b; Breier et al., 2005; Keefe et al., 2006; Kinon et al., 2006) that compared the efficacy of olanzapine or amisulpride with other antipsychotics or placebo in schizophrenia. Treatment efficacy was measured using the PANSS scale in the olanzapine studies and the Brief Psychiatric Rating Scale (BPRS) in the amisulpride studies. Four response cut-offs that are frequently used in the schizophrenia literature (Leucht et al., 2007) (at least 20%, 30%, 40%, and 50% reduction of the PANSS/BPRS total score from baseline) were applied leading to 148 response rate- and 116 OR-comparisons. We included all cut-offs and both scales together in the primary analysis, but examined every cut-off and scale separately in a sensitivity analysis. All studies were analyzed at endpoint using intention-to-treat data (last-observation-carried forward method).

2.1. Description of the imputation strategy

The imputation method (Furukawa et al., 2005) assumes a normal distribution of the rating scale, with a mean μ and a standard deviation SD. The values μ and SD can either refer to endpoint or change from baseline scores. Response is defined as a minimum percentage reduction α% from baseline score b to endpoint, where α% often is 20%, 30%, 40% or 50%. If response rates are not indicated, they could be estimated by the imputation method which proposes a common raw response threshold x for the patients of the same arm, based on the mean of their baseline scores. This raw threshold x for response criterion α% reduction is given by:

$$x = b(1-\alpha\%). \quad (1)$$

The expected percentage of responders P is calculated as the area under the normal curve left to x and is directly derived from the Z-score which is calculated as:

$$\text{Z-score} = (x-\mu)/SD. \quad (2)$$

Then, to estimate the OR between groups 1 and 2, we simply use the well-known formula:

$$OR = \frac{P_1/(1-P_1)}{P_2/(1-P_2)} \quad (3)$$

where P_1, P_2 are the response rates in groups 1 and 2 respectively.

2.2. Assessment of the performance of the imputation method

Since evaluating agreement adequately is practically impossible using a single test (Chinn, 1990; Keating and Matyas, 1998; Rankin and Stokes, 1998), we used a set of criteria to assess the performance of the imputation method. When normality was required to apply some of the methods, we used the logarithmic transformation of the measurements. Because four different cut-off points were considered and applied in the same arm in order to derive the response rates and the ORs, we applied statistical methods to account for repeated measurements (Donner, 1984). In a sensitivity analysis, we assessed each scale and each cut-off point separately.

2.2.1. The concordance correlation coefficient (CCC)

The concordance correlation coefficient (CCC) by Lin (1989) is commonly used in the evaluation of agreement between two methods when the data are measured repeatedly (King et al., 2007). The CCC is equivalent to the ANOVA intraclass correlation coefficient (ICC), a general relative measurement of consistency and agreement (Shrout and Fleiss, 1979), frequently used in medical literature (Furukawa et al., 2005; Furukawa and Leucht, 2011; da Costa et al., 2012). As ICC fails to incorporate the effect of the repeated measurements in the random error, CCC was applied in the primary analysis of the pooled cut-offs and ICC in the subgroup analysis of each cut-off separately. The correlation coefficient ranges from −1 (perfect negative agreement) to 1 (perfect positive agreement). Its appropriateness has been contested, among other reasons, by the claim that it does not distinguish between random error and bias (Bland and Altman, 1990; Rankin and Stokes, 1998).

Table 1
Regression of the logarithms of response rates and subgroup analyses. *t*-Tests and *p*-values refer to hypothesis of β = 1. Non-statistically significant results are in bold (*p*-value > 0.05).

Analysis	No. of comparisons	β (95% CI)	Std. error	*t*-Test	*p*-Value	R^2	MSE
Regression analysis (linear regression analysis with repeated measurements)							
Total	148	1.24 (1.19, 1.29)	0.03	8	0.00	0.95	0.02
Subgroup analysis by rating scale (linear regression analysis with repeated measurements)							
BPRS	56	0.81 (0.72, 0.89)	0.04	−4.75	0.00	0.86	0.01
PANSS	92	1.28 (1.22, 1.34)	0.03	9.33	0.00	0.96	0.02
Subgroup analysis by cut-off (simple regression analysis)							
20%	37	1.14 (1.06, 1.21)	0.04	3.50	0.00	0.96	0.02
30%	37	1.08 (1.03, 1.13)	0.03	2.67	0.01	0.98	0.01
40%	37	1.07 (1.03, 1.12)	0.02	3.50	0.00	0.98	0.02
50%	37	1.08 (1.02, 1.13)	0.03	2.67	0.01	0.98	0.04

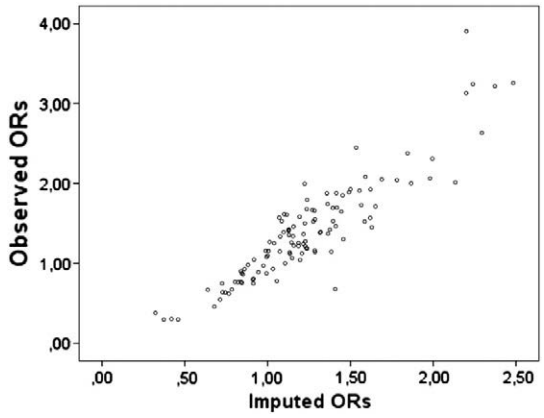

Fig. 2. Comparison of the observed versus imputed ORs. ORs = odds ratios.

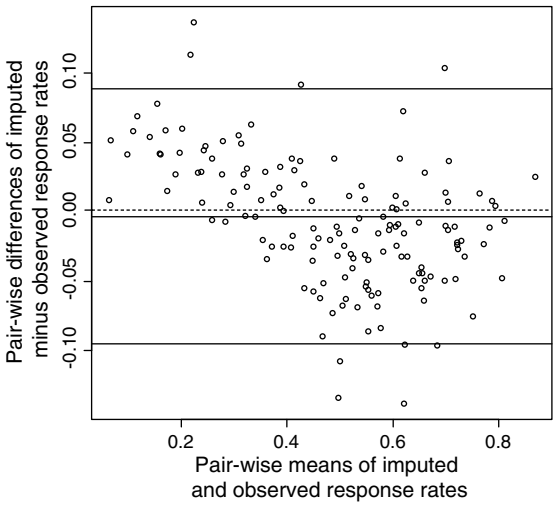

Fig. 3. 95% limits of agreement for the pooled response rates. The dashed horizontal line at zero represents the optimal difference between imputed minus observed response rates, the middle solid line represents the expected values of the difference between imputed minus observed response rates whereas the upper and lower solid lines represent the 95% limits of agreement.

2.2.2. Predictive accuracy

Predictive accuracy measures the maximal preservation of true values and implies other forms of accuracy such as ranking accuracy, distributional accuracy, estimation accuracy and imputation plausibility. It has been identified as a key parameter by the Euredit project (an EU sponsored project with the objective to develop tests for the validation of imputation methods (Chambers, 2001)). Predictive accuracy is assessed by a regression approach which examines how close the imputed value to the observed one is. For all cut-offs combined, we applied linear regression analysis with repeated measurements (Donner, 1984), followed by testing whether the slope β equals 1 (as we would expect in a case of perfect agreement). We also calculated the regression mean square error (MSE), which reflects the sampling error, and the R^2, which measures the proportion of the variance in Y "explained" by the variation in X (Appendix A).

A good imputation method would have a slope β not significantly different from 1, low MSE and R^2 close to one.

2.2.3. In the "limits of agreement"

In the "limits of agreement" method by Bland and Altman, the differences of imputed and observed values were plotted on the y-axis and their means on the x-axis, taking into account the repetition of measurements for each cut-off (Bland and Altman, 1986, 1999). This plot allowed us to investigate any possible relationship between the error introduced by the imputation method and the true values and, unlike CCC, distinguished between random error and bias. Provided that the differences were normally distributed, the agreement between the true and the imputed values could be considered reasonable if the 95% confidence interval of their difference was clinically acceptable.

3. Results

3.1. The CCC

The CCC for response rates (in natural logarithms) was 0.93 with 95% confidence intervals of 0.91 to 0.95 for both scales and all cut-offs. Respectively, for ORs (in natural logarithms), the CCC was 0.87 with 95% confidence intervals of 0.77 to 0.93, demonstrating a strong association of the observed and imputed values.

3.2. Predictive accuracy (linear regression model)

3.2.1. Response rates in individual arms

Fig. 1 shows the scatter plot between the actually observed response rates (P_{Ob}) versus the imputed ones (P_{Im}) in each arm of each trial. The regression coefficient was 1.24 and it was significantly different from 1 (p-value < 0.001), although the value R^2 was high (0.95) (Table 1). For example and based on this coefficient, the corresponding imputed value of an observed response rate of 20% would be 13.6%, 50% would be 42.3% and 80% would be 75.8%.

3.2.2. Odds ratios in individual trials

Fig. 2 shows the scatter plot between the actually observed ORs versus the imputed ones for each trial. The linear regression model

Table 2
Regression of the logarithms of ORs and subgroup analyses. t-Tests and p-values refer to hypothesis of β = 1. Non-statistically significant results are in bold (p-value > 0.05). ORs = odds ratios.

Analysis	No. of comparisons	β (95% CI)	Std. error	t-Test	p-Value	R^2	MSE
Regression analysis (linear regression analysis with repeated measurements)							
Total	116	1.25 (1.14, 1.36)	0.06	4.17	0.00	0.86	0.03
Subgroup analysis by rating scale (linear regression analysis with repeated measurements)							
BPRS	**28**	**0.97** (**0.62**, **1.33**)	**0.18**	**−0.17**	**0.87**	**0.71**	**0.03**
PANSS	88	1.28 (1.17, 1.40)	0.06	4.67	0.00	0.86	0.03
Subgroup analysis by cut-off (simple regression analysis)							
20%	29	1.32 (1.16, 1.47)	0.07	4.57	0.00	0.92	0.03
30%	29	1.37 (1.22, 1.52)	0.07	5.28	0.00	0.92	0.02
40%	29	1.35 (1.18, 1.52)	0.08	4.37	0.00	0.90	0.03
50%	**29**	**1.13** (**0.90**, **1.37**)	**0.12**	**1.08**	**0.29**	**0.78**	**0.06**

coefficient was 1.25. The *t*-test for $\beta = 1$ resulted in *p*-value < 0.001 and the value R^2 was 0.86 (Table 2). For example, based on the equation for both scales, an observed OR of 0.6 would be imputed by 0.53, 0.9 by 0.88 and 2.5 by 3.14.

3.3. "Limits of agreement"

3.3.1. Response rates

The mean difference between imputed minus observed response rates was 0.7% and the classical limits of agreement were −8.4% to 9.8% (response rates were normally distributed). The visual inspection of the Bland–Altman plot for response rates revealed clearly that the direction and the quantity of the error introduced by the imputation method were related to the magnitude of response rates; when observed response rates were high, the imputation method underestimated the response rates and, vice versa, when the observed response rates were low, the imputation method overestimated them (Fig. 3). According to Bland and Altman (1999) such a relationship between differences and magnitude of response rates results in limits of agreement wider apart than they should be; thus, Bland and Altman recommended a regression of the differences on their average (in natural logarithms). In our case, this technique produced non-parallel, linear regression lines as limits of agreement since the SD of differences was not reasonably constant over the mean response rate (Fig. 4). The mean difference in log scale was 0.02, the SD was 0.09 and the regression based 95% limits of agreement were upper limit $= -0.07 - 0.18 \times \log\ (P_{Im} \times P_{Ob})$ to lower limit $= -0.27 - 0.06 \times \log\ (P_{Im} \times P_{Ob})$. Thus, by back-transforming, the average imputed value could differ from the observed one by 1.05 times with regression based 95% limits of agreement between 0.76 $(P_{Im} \times P_{Ob})^{-0.06}$ and 0.93 $(P_{Im} \times P_{Ob})^{-0.18}$ times.

3.3.2. Odds ratios in individual trials

The Bland–Altman plot for log ORs from both scales and all cut-offs together is shown in Fig. 5. Again, the direction and the quantity of the error introduced by the imputation method were related to the mean ORs; when the observed ORs were larger than 1, the imputation method tended to underestimate the ORs, whereas, when the observed ORs were lower than 1, the imputation method tended to overestimate them, leading to conservative estimates regarding the efficacy comparison of two interventions. Moreover, the plot suggested that the imputation method performed better when the observed differences between treatment effects were not large resulting in log OR around 0. The log transformed data produced a mean difference of −0.06 and limits of agreement of −0.35 to 0.24, which by back-transformation provided a geometric mean ratio of 0.94 with limits of agreement of 0.71 to 1.27. Thus, the imputed values exceeded the observed ones by between 0.71 and 1.27 times. When the regression approach was applied to deal with the relationship between the differences and the magnitude of log ORs as suggested by Bland and Altman, two parallel linear regression lines as limits of agreement resulted (Fig. 6). The mean difference in log scale was −0.06, the SD was 0.12 and the regression based 95% limits of agreement were lower limit $= -0.25 - 0.15 \times \log\ (OR_{Im} \times OR_{Ob})$ to upper limit $= 0.22 - 0.15 \times \log\ (OR_{Im} \times OR_{Ob})$. Thus, by back-transforming, the average imputed value could differ from the observed one by 0.93 times with 95% limits of agreement between 0.78 $(OR_{Im} \times OR_{Ob})^{-0.15}$ and 1.25 $(OR_{Im} \times OR_{Ob})^{-0.15}$ times.

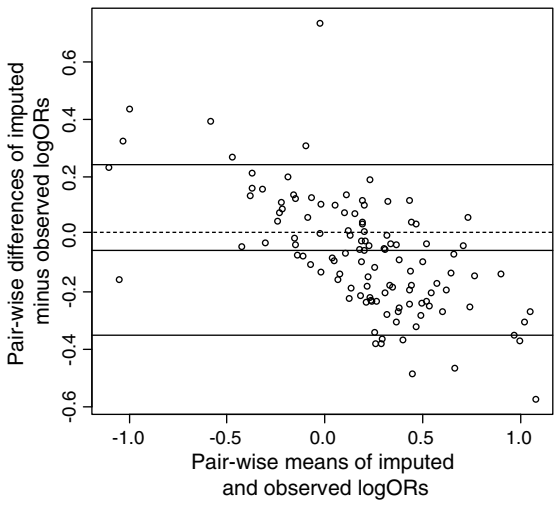

Fig. 5. 95% limits of agreement for the pooled ORs in natural logarithms. The dashed horizontal line at zero represents the optimal difference between imputed minus observed ORs, the middle solid line represents the expected values of the difference between imputed minus observed ORs whereas the upper and lower solid lines represent the 95% limits of agreement (all values in natural logarithms). ORs = odds ratios.

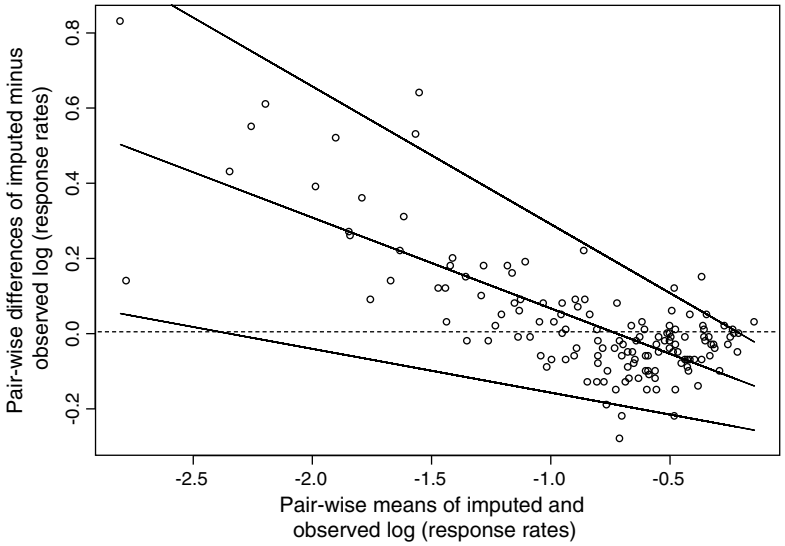

Fig. 4. Regression based 95% limits of agreements for the pooled response rates in natural logarithms. The dashed horizontal line at zero represents the optimal difference between imputed minus observed response rates, the middle solid line represents the expected values of the difference between imputed minus observed response rates whereas the upper and lower solid lines represent the regression based limits of agreement (all values in natural logarithms).

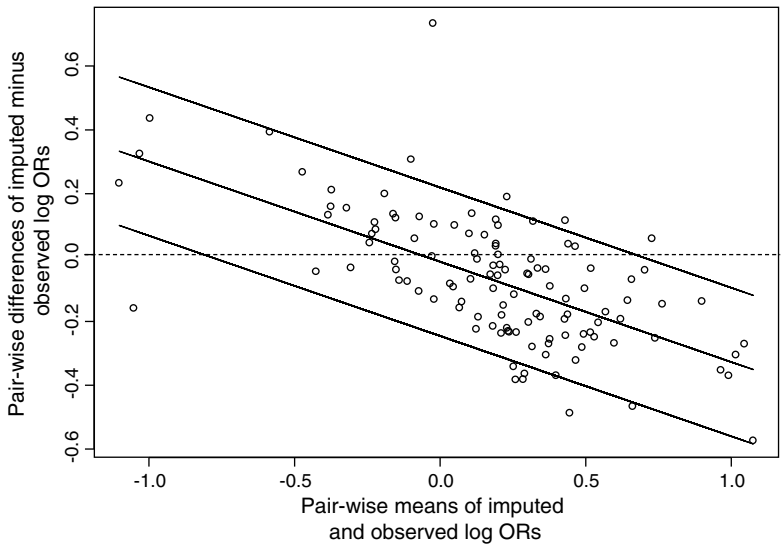

Fig. 6. Regression based 95% limits of agreements for the pooled ORs in natural logarithms. The dashed horizontal line at zero represents the optimal difference between imputed minus observed ORs, the middle solid line represents the expected values of the difference between imputed minus observed ORs whereas the upper and lower solid lines represent the regression based limits of agreement (all values in natural logarithms). ORs = odds ratios.

The results of sensitivity analyses analyzing PANSS derived and BPRS derived response rates and ORs separately, and each response cut-off separately, found similar effects as the overall results (see Tables 1 & 2 and online supplement).

4. Discussion

When full data sets are available, meta-analysis can be performed and its results can be presented without a problem. Unfortunately, this is hardly the case. Many trials report results only as differences in means of value scales. These measures are not only difficult to interpret from a clinical perspective, but are also excluded from the analysis of response (binary) data, leading to a substantial loss of power and precision. In addition, the analysis may be biased if unreported data are related to the true clinical outcome. Thus, an alternative approach is urgently needed to manage this information when performing a meta-analysis.

Furukawa's method is based on an assumption of normal distribution as in Suissa (1991), who however had another objective; he tried to avoid dichotomization of the continuous outcome and attempted to estimate the risk of an event from means and standard deviations without using the original response rates. Apart from Furukawa's and Suissa's methods, there are three other available conversion methods by Kraemer and Kupfer (2006), Hasselblad and Hedges (1995) and Cox and Snell (1989). Kraemer and Kupfer's method allows the direct conversion of SMDs into risk differences (Kraemer and Kupfer, 2006) whereas Hasselblad and Hedges' method and Cox and Snell's method allow the direct conversion of SMDs into odds ratios (Cox and Snell, 1989; Hasselblad and Hedges, 1995). In practice, these methods are often less useful, because many meta-analytic software such as the Cochrane Collaboration's RevMan do not allow entering odds ratios directly. Intrigued by the work of Furukawa et al. (2005), we decided to empirically examine whether the imputation method proposed for depression and anxiety trials could also be applied in schizophrenia trials. However, Furukawa et al. (2005) and Furukawa and Leucht (2011) used only the intraclass correlation coefficient (ICC) to assess the performance of the imputation method which does not distinguish between random error and bias. Indeed, if we had evaluated the method only with the correlation coefficient and its expansion CCC, we would have found excellent agreement as only the Euredit criteria and the Bland–Altman method showed the weaknesses of the imputation method. Overall, our findings suggested that the imputed values re-captured the observed (true) values to a reasonable extent, providing a simple and practical method for the imputation of missing binary data in schizophrenia trials. Nevertheless, the examined imputation method tended to introduce bias in the direction of overestimation for low values and underestimation for high values. This direction of bias leads to conservative estimates when two interventions are compared, the usual goal of a meta-analysis.

The main advantage of our study lies in its empirical design. Few published studies have assessed the performance of methods using large, empirical datasets; most of them have used simulated data. Given that all imputation methods depend on inherently untestable assumptions (Horton et al., 2010), evaluations based on empirical data are crucial.

In the practical implementation, we should pay attention to another important detail. The percentage PANSS/BPRS reduction is often miscalculated (Obermeier et al., 2011), since the minimum score of 30/18 respectively, when the 1–7 scoring system is used, is often not subtracted, leading to underestimation of reported response rates (Leucht et al., 2007; Obermeier et al., 2010). For that reason, we subtracted the 30/18 minimum points of the PANSS/BPRS for all calculations of the percentage reduction from baseline (Leucht et al., 2005a; Schennach-Wolff et al., 2010). Thus, when missing response rates are imputed, it needs to know which scoring system was used and all mean scores must be accordingly adjusted by subtracting from them the minimum score.

We conclude that the imputation method works best for medium degrees of percentage response, but is biased in very high and very low response rates. Meta-analyses applying the method should be accompanied by sensitivity analyses excluding the imputed values. Excel sheets containing the necessary formula can be obtained from our websites (Estimating % PANSS or BPRS responders from the mean and sd.xls, http://www.cfdm.de/index.php?option=com_content&task=view&id=15&Itemid=29).

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Contributors

M.T. Samara and S. Leucht designed the study; M.T. Samara, L.M. Spineli and G. Salanti analyzed the data; M.T. Samara, T.A. Furukawa, R.R. Engel, J.M. Davis and S. Leucht contributed to the interpretation of the results. M.T. Samara and S. Leucht drafted the manuscript and all other authors critically reviewed the manuscript. All authors saw and approved the final version of the manuscript.

Conflict of interest

Stefan Leucht has received honoraria for consulting/advisory boards from Alkermes, BristolMyersSquibb, EliLilly, Janssen, Johnson&Johnson, and MedAvante, Roche, lecture honoraria from AstraZeneca, BristolMyersSquibb, EliLilly, EssexPharma, Janssen, Johnson&Johnson, Lundbeck Institute, Pfizer, and SanofiAventis, and EliLilly has provided medication for a trial with SL as the primary investigator. T.A. Furukawa has received honoraria for speaking at CME meetings sponsored by Asahi Kasei, EliLilly, GlaxoSmithKline, Mochida, MSD, Otsuka, Pfizer, Shionogi and Tanabe-Mitsubishi. He is a diplomate of the Academy of Cognitive Therapy. He has received royalties from Igaku-Shoin, Seiwa-Shoten and Nihon Bunka Kagaku-sha. He is on the advisory board for Sekisui Chemicals and Takeda Science Foundation. The Japanese Ministry of Education, Science, and Technology, the Japanese Ministry of Health, Labor and Welfare, and the Japan Foundation for Neuroscience and Mental Health have funded his research projects. The other authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2013.10.029.

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D. Publications
Online supplement

Appendix A. Supplementary data

- Linear regression analysis with repeated measurements of the form $Y_{ij} = \beta \times \mathrm{X}_{ij} + \varepsilon_{ij}$ (Donner 1984), where i is the trial and j is the cut-off, followed by testing whether the slope β equals 1 was applied. If the t-test for $\beta = 1$ did not result in a significant difference, then the regression mean square error (MSE) was calculated:

$$MSE = \frac{(yy - xy^2 / xx)}{N - 2} \qquad (4)$$

where $yy = \sum_{i=1}^{n}\sum_{j=1}^{k}(Y_{ij} - \overline{Y})^2$, $xy = \sum_{i=1}^{n}\sum_{j=1}^{k}(Y_{ij} - \overline{Y})(X_{ij} - \overline{X})$, $xx = \sum_{i=1}^{n}\sum_{j=1}^{k}(X_{ij} - \overline{X})^2$,

$$\overline{Y} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{k} Y_{ij}}{N}, \quad \overline{X} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{k} X_{ij}}{N}, \quad N = n \times k,$$

n is the number of trials and k is the number of cut-offs.

D. Publications
Online supplement

CORRELATION COEFFICIENT RESULTS

Web table 1: Response rates (in natural logarithms)

Subgroup analysis	**Number of comparisons**	**CCC or ICC**	**95% CI**
By rating scale		*CCC (for repeated measurements)*	
BPRS	56	0.72	(0.53, 0.84)
PANSS	92	0.90	(0.86, 0.93)
By cut-off point		*ICC (for single measurements)*	
20%	37	0.89	0.80, 0.94
30%	37	0.94	0.89, 0.97
40%	37	0.95	0.90, 0.97
50%	37	0.93	0.87, 0.96

Note: CCC: concordance correlation coefficient; ICC: intraclass correlation coefficient; CI: confidence interval

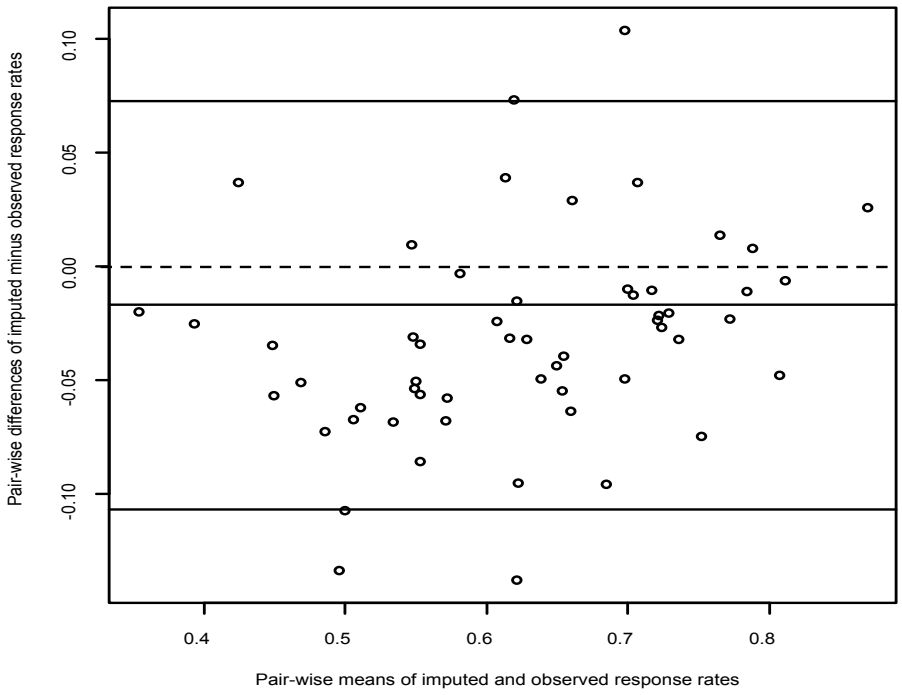
Web table 2: Odds ratios (in natural logarithms)

Subgroup analysis	**Number of comparisons**	**CCC or ICC**	**95% CI**
By rating scale		*CCC (for repeated measurements)*	
BPRS	28	0.72	(0.45, 0.87)
PANSS	88	0.88	(0.77, 0.94)
By cut-off point		*ICC (for single measurements)*	
20%	29	0.90	0.79, 0.95
30%	29	0.89	0.76, 0.95
40%	29	0.88	0.74, 0.94
50%	29	0.83	0.67, 0.92

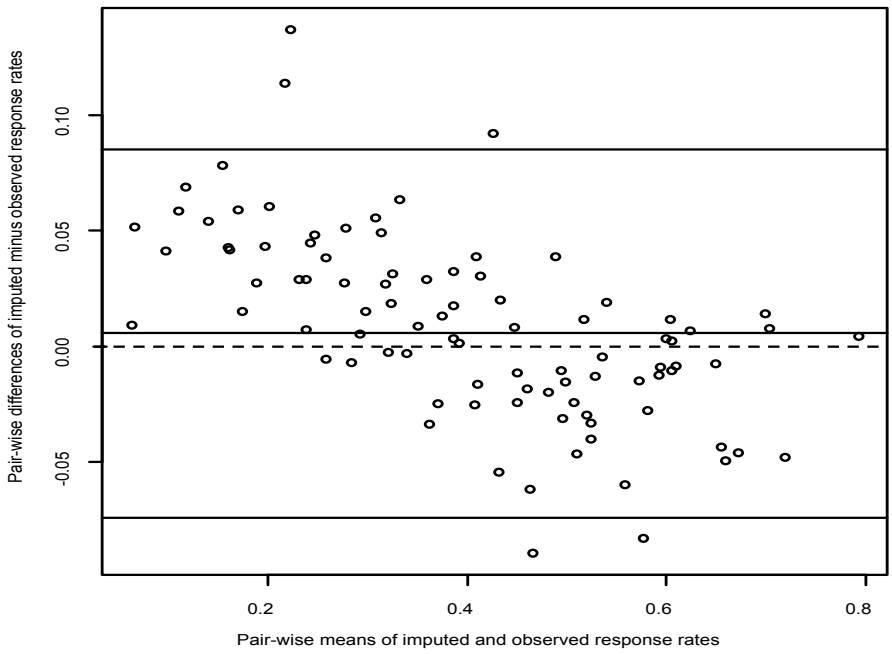
Note: CCC: concordance correlation coefficient; ICC: intraclass correlation coefficient; CI: confidence interval

*The CCC is interpreted similarly with ICC.

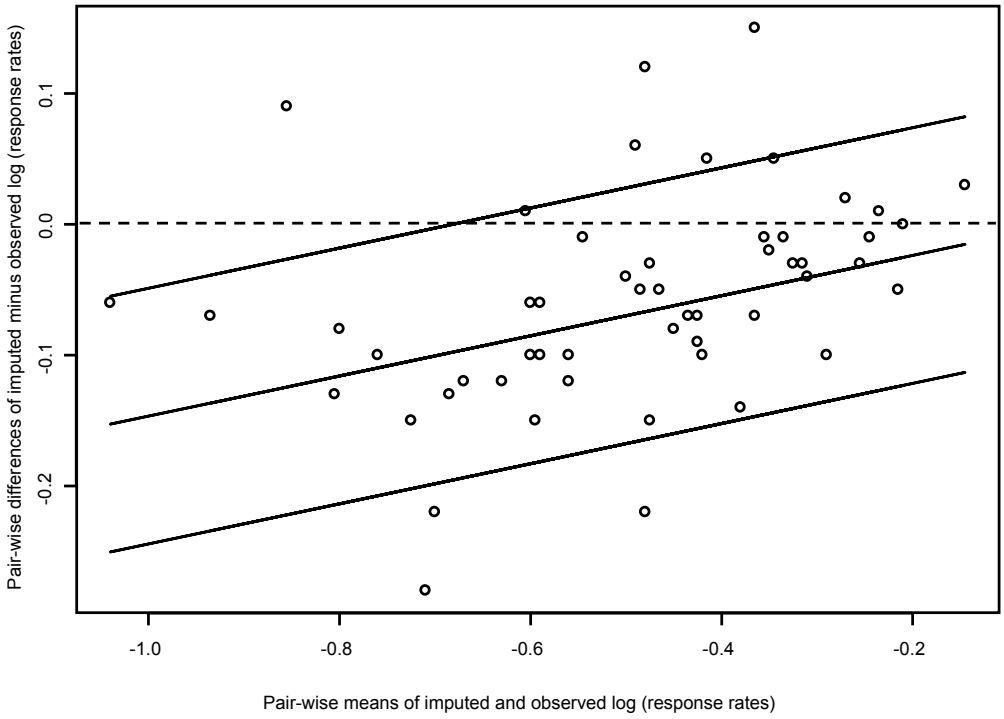
Web figure 1: For BPRS scale, 95% limits of agreement of response rates.



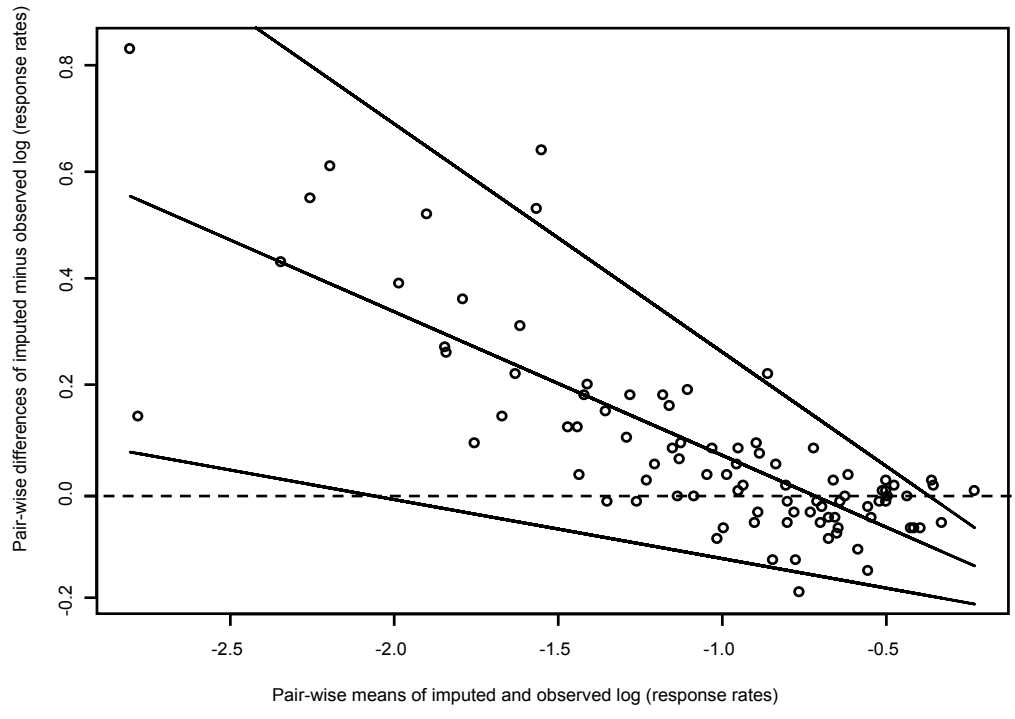
Web figure 2: For PANSS scale, 95% limits of agreement of response rates.



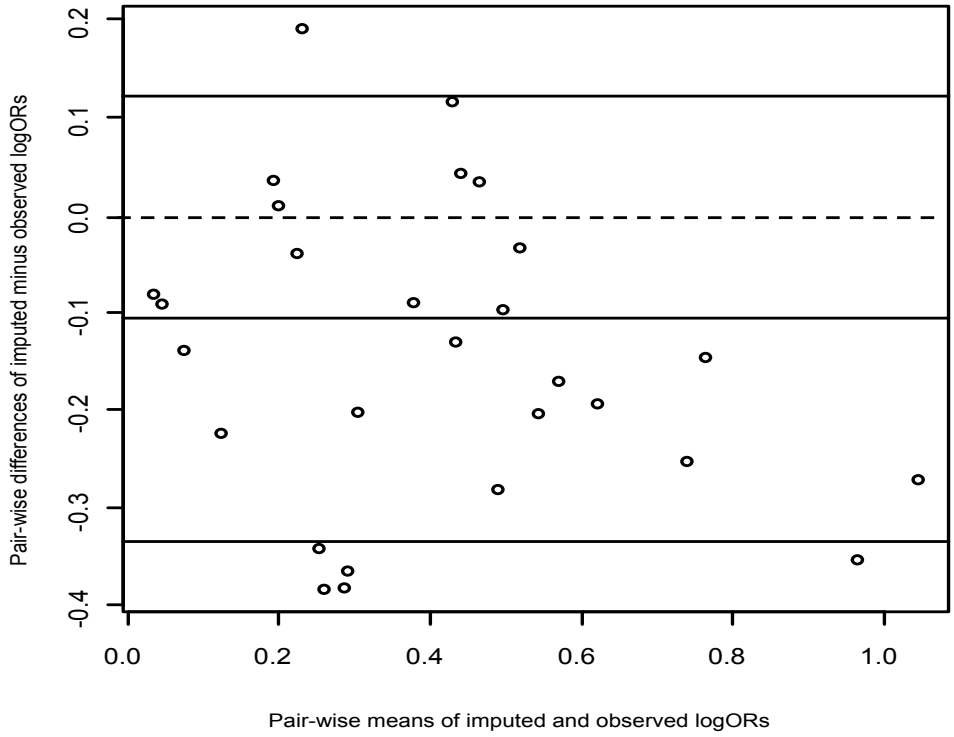
Web figure 3: For BPRS scale, regression based limits of agreement of response rates in natural logarithms.



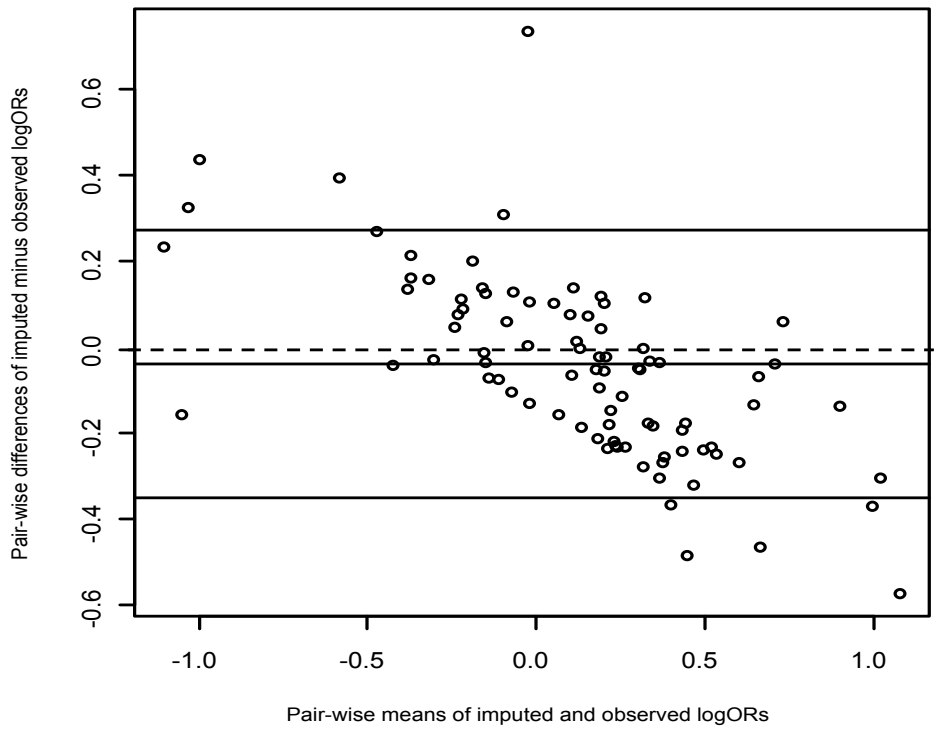
Web figure 4: For PANSS scale, regression based limits of agreement of response rates in natural logarithms.



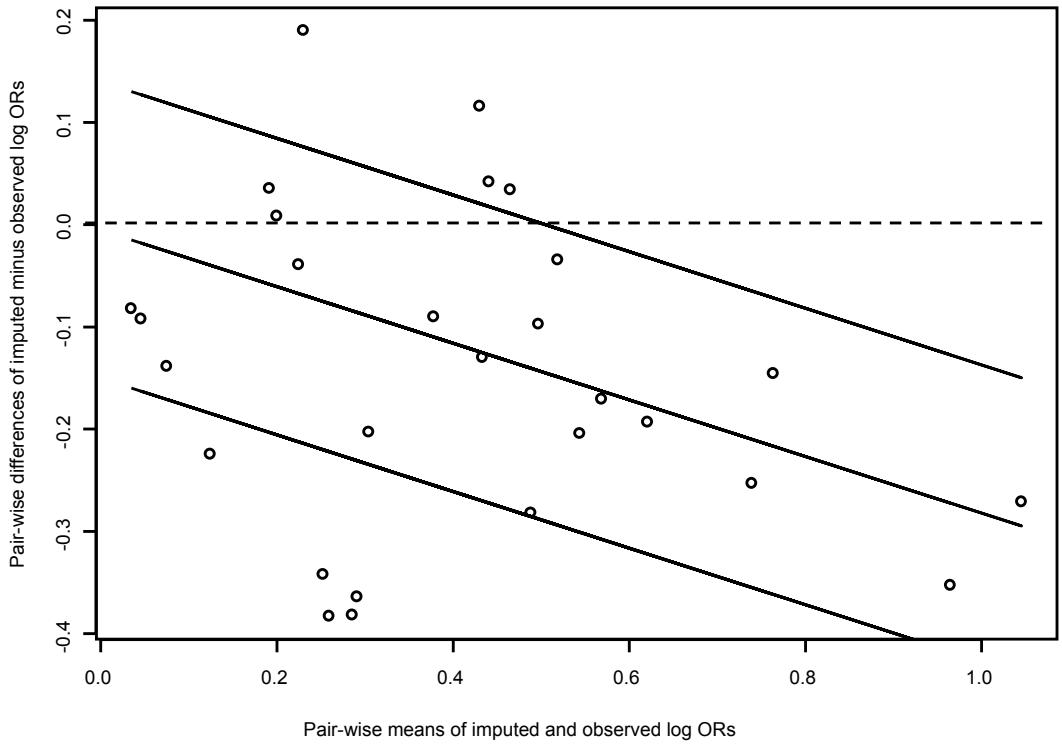
Web figure 5: For BPRS scale, 95% limits of agreement of odds ratios (ORs) in natural logarithms .



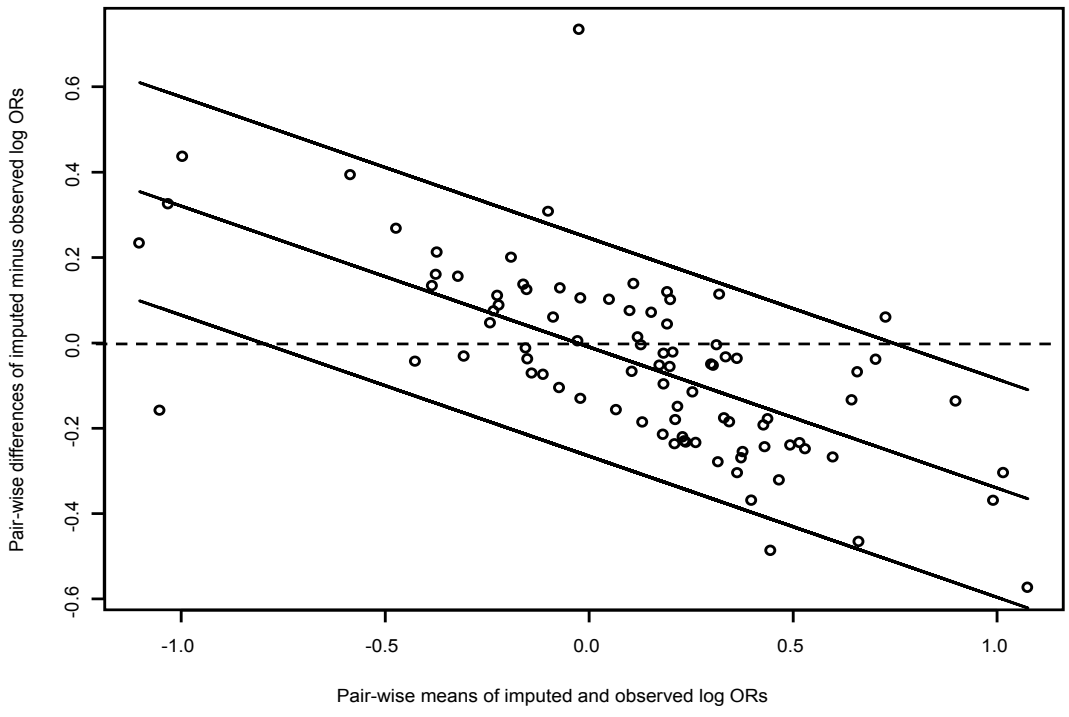
Web figure 6: For PANSS scale, 95% limits of agreement of odds ratios (ORs) in natural logarithms .



Web figure 7: For BPRS scale, regression based limits of agreement of odds ratios (ORs) in natural logarithms.



Web figure 8: For PANSS scale, regression based limits of agreement of odds ratios (ORs) in natural logarithms.



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8. **Miscellaneous.**

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8.4 No amendment or waiver of any terms is binding unless set forth in writing and signed by the parties. The Rightsholder and CCC hereby object to any terms contained in any writing prepared by the User or its principals, employees, agents or affiliates and purporting to govern or otherwise relate to the licensing transaction described in the Order Confirmation, which terms are in any way inconsistent with any terms set forth in the Order Confirmation and/or in these terms and conditions or CCC's standard operating procedures, whether such writing is prepared prior to, simultaneously with or subsequent to the Order Confirmation, and whether such writing appears on a copy of the

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