Data Supplement for Leucht et al., "A Meta-Analysis of Head-to-Head Comparisons of Second-Generation Antipsychotics in the Treatment of Schizophrenia," American Journal of Psychiatry (doi: 10.1176/appi.ajp.2008.08030368)

Glossary of meta-analytic terms:

In this glossary we can only briefly describe some of the statistical terms used in the method section. The idea is to give some information to those readers who are not familiar with meta-analysis. For a full description of the formulas involved and for alternative methods the interested reader is directed to meta-analytic textbooks such as the Cochrane Handbook for Reviewers (1) or others (2,3). The following terms are explained in the sequence in which they occur in the manuscript.

Systematic review: In contrast to conventional narrative reviews where in the worst case an expert subjectively summarizes the literature he believes to be the most important, systematic reviews use explicit methods in a predefined way to avoid bias by changing the method later to make the results come out better. The search terms of the literature search are predefined and there are different sources for the search (electronic databases, pharmaceutical companies, reference lists of identified studies, authors of identified studies). Inclusion and exclusion criteria of the studies to be included are predefined. The search process is described in the manuscript. For quality assurance all important steps of the review process (study selection, data extraction, data entering) are undertaken by at least two reviewers (in our case even three). Usually meta-analysis (see below) is used to combine the results of the single studies and to obtain quantitative measures of effect.

The Cochrane Collaboration: A not-for-profit organisation with the aim to produce, disseminate and maintain systematic reviews of health care interventions (www.cochrane.org). The Cochrane Schizophrenia Group (4) supported the conduct of our review.

Cochrane Collaboration quality criteria:

It has been shown that there is a strong relationship between allocation concealment and direction of effect (5). Therefore, the method of allocation concealment is a crucial characteristic of trial quality. Following the rules of the Cochrane Schizophrenia Group (4) we only included studies which met quality criteria A or B according to the Cochrane handbook (1). The categories are defined below:

A. Low risk of bias (adequate allocation concealment, e.g. serially numbered, opaque, sealed envelopes; numbered or coded bottles or containers)

B. Moderate risk of bias (some doubt about the results, primarily studies stated to be randomized without further details)

C. High risk of bias (inadequate allocation concealment; e.g. alternate allocation).

More discussion on quality criteria can be found in the Cochrane handbook (1).

Jadad scale: The Jadad scale is probably the most widely used scale to assess the quality of randomized controlled trials (6). The scale includes three items that are directly related to bias reduction: randomization; blinding; description of withdrawals and drop outs. The score goes from 0 to 5. A study can be judged as having poor quality if it is awarded 2 points or less.

For the purpose of the current review we did not use the Jadad scale for including or excluding studies, but rather we used it to address study quality further by meta-regression (see below) and a sensitivity analysis (see below) excluding studies with a score of 2 or less. It should be noted, however, that all studies included were on the high quality end in any case (randomized, at least rater-blinded studies). Therefore, we could only examine good versus very good study quality.

Meta-analysis: Meta-analysis is a statistical technique to combine the results of a number of studies on the same question.

Effect size: An effect size is a statistical measure of the *magnitude* of a treatment effect (in contrast to the p-value which is an indicator of *probability*). There are effect size measures for dichotomous data or for continuous data (see below).

Mean difference and weighted mean difference: The mean difference is an effect size measure for continuous variables. Please note that the term “mean difference” is potentially confusing, because it is actually a “difference in means”. It is calculated as the mean in the comparison group minus the mean in the control group. For example, if the mean change from baseline to endpoint of the PANSS total score induced by antipsychotic A were -20, and that of antipsychotic B were -15, the mean difference would be -5 (calculated as -20 – (-15) = -5). When the mean differences of the single studies are combined in a meta-analysis, the results are usually weighted by the size or precision of the single studies. Therefore, the summary statistic is called “weighted mean difference”.

Hedges’s g: Often different scales are used to measure similar concepts, for example here the PANSS total score and the BPRS total score. A mean difference based on the PANSS (30 items, total score goes from 30 to 210) does obviously not mean the same as a mean difference based on the BPRS (18 items, total score goes from 18 to 126). Therefore, standardized mean differences (SMD) rather than mean differences need to be calculated to allow for meta-analytic combination. This standardization is generally achieved by dividing the mean difference by the pooled standard deviation of both groups according to the general formula: SMD = (mean group A – mean group B)/pooled standard deviation. Various modifications of this general formula exist (e.g. Cohen’s d, Hedges’s d, Hedges’s g etc). Hedges’s adjusted g is the formula used in this review and by the Cochrane Collaboration (1). It includes a correction factor for very small sample sizes (below 10 participants); in larger sample sizes the results are unaffected. When different studies are pooled they are again weighted according to a measure related to their sample size. The disadvantage of the standardized mean difference is that it does not express the results in the original units, but rather standard deviation units, the interpretation of which is less

intuitive. The description by Cohen is conventionally used for the interpretation of a standardized mean difference (e.g. Hedges's g). He said that an SMD of 0.20 is small, 0.50 is medium, and 0.80 is large (7). Nevertheless, this is no more than a rule of thumb and the interpretation can be different according to the situation.

Relative risk, risk difference and number-needed-to-treat (NNT):

The relative risk and the risk difference are effect size measures for dichotomous (yes/no) outcomes; in the current review, dropout due to inefficacy of treatment.

The risk difference is in a way the most straightforward method. It is the risk of one group minus the risk in the other group. For example, if 10% of the participants in the intervention group and 20% in the control group dropped out, then the risk difference is:

10% - 20% = |-10%| (or expressed in decimals 0.10 – 0.20 = |-0.10|)

The risk ratio uses the same numbers but divides rather than subtracts the risks. 10%/20% = 50% (or expressed in decimals 0.10/0.20 = 0.50). While risk differences may be more easily interpreted by clinicians, the advantage of the risk ratio is that in meta-analyses it accounts better for differences in baseline risk, e.g. if studies with higher and lower dropout rates are combined.

The number-needed-to-treat is the number of patients that must be treated with the new intervention to avoid one poor outcome. It is usually calculated as the inverse of the risk difference. In the example above, the risk difference in dropouts was 10%, thus NNT = 1/0.1 = 10. Ten patients would have to be treated with the intervention to avoid one dropout.

Fixed-effects versus random-effects model:

There are two general statistical models to combine different studies in a meta-analysis. Fixed-effects models assume that each study estimates exactly the same treatment effect, while random-effects models assume that the studies estimate treatment effects that follow a distribution across studies. There are arguments for and against both models. We chose a priori a random-effects model as the primary measure, but a fixed-effects model did not yield substantially different results.

Homogeneity test:

It is important to assess to what extent the results of the individual studies are consistent or differ. This assessment was performed by a chi-squared test of homogeneity. It examines whether observed differences in results are compatible with chance alone. As the test has low power in meta-analyses with few studies an alpha level of p=0.1 instead of 0.05 was used to indicate significant heterogeneity.

Meta-regression:

Meta-regression examines whether the effect sizes of the single studies are influenced by specific characteristics ('moderators') of the single studies. Meta-regression is in essence similar to simple regressions in which an outcome variable is predicted by one or several explanatory variables. In meta-analysis, however, the moderator variable is a characteristic of the individual

studies, not of the individual patients. This may markedly reduce the likelihood of identifying the effect of certain moderators. The moderator variable is often only the mean intensity of a moderator variable in a given study. There may be only modest differences between the mean intensity from study to study, but major differences in the individual patient outcome in each study. Since the individual data is not captured and the moderators reflect on the study level only, meta-regression can be insensitive to these effects. A further important difference compared to simple regressions is that in meta-regressions the individual studies are weighted by the precision of their original effect estimate.

Sensitivity analysis:

Sensitivity analyses are made to examine the robustness of results if some key decisions were changed. For example, we had a priori decided to include single-blind and double-blind studies. In a sensitivity analysis, we excluded the single-blind studies to examine whether including only double-blind studies would the results still be the same. Or in the primary analysis we included studies irrespective of their origin, but we examined in a sensitivity analysis whether excluding studies from China made a difference. Sensitivity analysis evaluates the effect of assumptions by doing separate analyses omitting studies which do not meet a certain criteria or adding studies that were excluded by a certain criteria. If the pattern of effect sizes are similar in different sensitivity analyses, then there is evidence that the findings are not dependent on a single assumption. If a sensitivity analysis eliminates studies, the power of detecting statistically significant differences is less. Attention should therefore also be directed to the pattern of effect sizes.

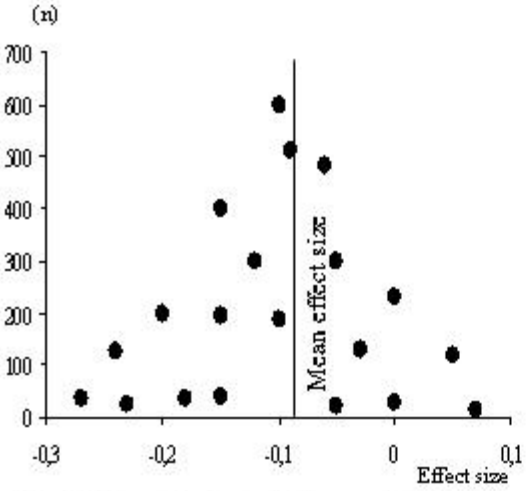
Publication bias:

Studies that did not show the desired results are less likely to be published, for example because a pharmaceutical sponsor is understandingly not interested in such a publication. In addition, journal editors may not be as interested in negative studies as in positive studies. Nevertheless, if only the positive studies are included in a review, the overall result must be too positive. Publication bias has also been called the ‘file-drawer problem’ in the sense that negative studies are put away in the file-drawer and never published. In this review two methods were applied to detect a potential publication bias, funnel-plots and fail-safe calculations (see below).

Funnel-plot:

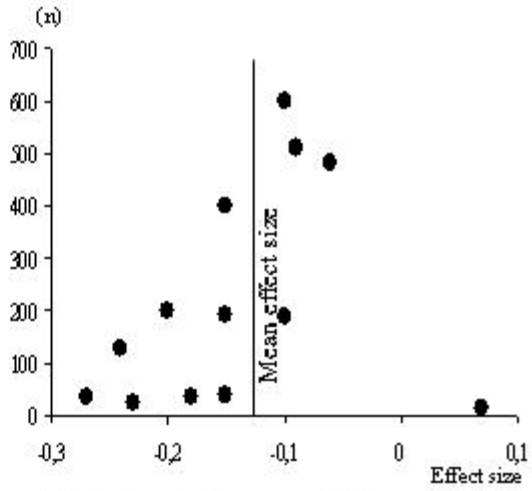
The funnel-plot method is a graphical method based on symmetry. The effect sizes of the single studies are plotted on the x-axis against some measure related to each study’s sample size on the y-axis. Large studies have a good precision and will present themselves on top close to the mean effect size while the smaller the studies get, the more they should scatter around the mean effect size. If all studies have been published, there should be a symmetrical figure resembling an inverted funnel. Egger et al. have developed at statistical test to assess funnel-plot asymmetry (8). If the funnel-plot is asymmetrical, it is possible that some unpublished studies exist (for illustration see the figure below). An asymmetrical funnel-plot is, however, not a proof for publication bias, because other reasons can have caused the asymmetry. Furthermore, if the number of studies is small the method’s power is low.

Figure a: Hypothetical funnel-plot <u>not</u> indicating potential publication bias



The effect sizes of the single studies were plotted on the x-axis, the studies' sample sizes on the y-axis. If all studies have been published a symmetrical figure resembling an inverted funnel results. Negative effect sizes reflect a superiority of the intervention group.

Figure b: Hypothetical funnel-plot indicating potential publication bias



Here the funnel-plot is asymmetrical, because studies in the lower right hand corner are missing. This suggests a relevant publication bias in the sense that smaller studies with results in favour of the control group have not been published.

<u>Fail-safe calculations:</u>

The "fail-safe calculation" by Orwin (9) estimates how many unidentified studies would have to exist to reverse statistical significance ($p>0.05$). If this number is so high that it is unlikely that so many unpublished studies exist, the results can be considered to be valid.

Supplemental Material I: Sensitivity Analyses

We performed a sensitivity analysis on pharmaceutical sponsorship and present it in detail below (supplemental Table I). It was especially important because we had previously shown that conclusions in abstracts systematically supported the sponsoring pharmaceutical company (10). The results do not suggest that the sponsor had a strong impact on the results. Only olanzapine was no longer superior to risperidone when studies sponsored by olanzapine's manufacturer were removed. But when studies sponsored by risperidone's manufacturer were removed as well, and only neutrally sponsored studies remained, olanzapine was again superior.

Supplemental Table I: sensitivity analyses excluding studies sponsored by the respective pharmaceutical companies – PANSS total score (the antipsychotic of the pharmaceutical sponsor which was excluded from the analysis is highlighted in **bold** face)

Comparison	**Results: The results that, in contrast to the primary outcome, did *or* did not show a significant difference between groups are highlighted by bold face**
Amisulpride versus **olanzapine**	N = 2, n = 455, WMD 1.6, CI -2.3 to 5.5, p = 0.427
Amisulpride versus olanzapine	N = 2, n = 246, WMD -1.8, CI -19.0 to 15.3, p = 0.833
Amisulpride versus **risperidone**	N = 2, n = 291, WMD 0.4, CI -4.6 to 5.3, p = 0.880
Amisulpride versus risperidone	No data available
Amisulpride versus **ziprasidone**	No data available
Amisulpride versus ziprasidone	N = 1, n = 122, WMD -2.7, CI -8.9 to 3.5, p = 0.397
Aripiprazole versus **olanzapine**	N = 2, n = 794, WMD 5.0, CI 1.9 to 8.1, p = 0.002
Aripiprazole versus olanzapine	No data available
Aripiprazole versus **risperidone**	N = 2, n = 372, WMD 1.5, CI -3.0 to 6.0, p = 0.509
Aripiprazole versus risperidone	No data available
Clozapine versus **olanzapine**	N = 3, n = 180, WMD 1.2, CI -2.6 to 4.9, p = 0.549
Clozapine versus olanzapine	N = 7, n = 619, WMD 1.3, CI -1.3 to 4.0, p = 0.327
Clozapine versus **quetiapine**	N = 1, n = 27, WMD -0.2, CI -4.5 to 4.1, p = 0.934
Clozapine versus quetiapine	N = 1, n = 27, WMD -0.2, CI -4.5 to 4.1, p = 0.934
Clozapine versus **risperidone**	N = 4, n = 380, WMD -0.8, CI -6.5 to 4.9, p = 0.793
Clozapine versus risperidone	N = 4, n = 210, WMD 1.4, CI -2.6 to 5.5, p = 0.494
Clozapine versus **ziprasidone**	No data available

Clozapine versus ziprasidone	N = 1, n = 146, WMD 0.5, CI -6.7 to 7.7, p = 0.892
Clozapine versus **zotepine**	No data available
Clozapine versus zotepine	No data available
Olanzapine versus **quetiapine**	N = 7, n = 1243, WMD -4.4, CI -6.6 to -2.3, p < 0.001
Olanzapine versus quetiapine	N = 7, n = 1041, WMD -3.7, CI -5.7 to -1.7, p < 0.001
Olanzapine versus **risperidone***	N = 11, n = 1802, WMD -2.5, CI -5.1 to -0.9, p = 0.002
Olanzapine versus risperidone*	**N = 10, n = 1600, WMD -1.4, CI -3.1 to 0.2, p = 0.087**
Olanzapine versus **risperidone***	N = 7, n = 1037, WMD -2.1, CI -4.1 to -0.1, p = 0.043
Olanzapine versus **ziprasidone**	N = 4, n = 1291, WMD -8.3, CI -11.0 to –5.6, p < 0.001
Olanzapine versus ziprasidone	N = 3, n = 762, WMD -7.6, CI -10.9 to -4.4, p < 0.001
Quetiapine versus **risperidone**	N = 7, n = 1606, WMD 2.5, CI 0.4 to 4.7, p = 0.022
Quetiapine versus risperidone	N = 5, n = 1143, WMD 3.9, CI -0.0 to 7.8, p = 0.050
Quetiapine versus **ziprasidone**	N = 2, n = 710, WMD -0.1, CI -6.3 to 6.1, p = 0.974
Quetiapine versus ziprasidone	N = 2, n = 710, WMD -0.1, CI -6.3 to 6.1, p = 0.974
Risperidone versus **sertindole**	No data available
Risperidone versus sertindole	N = 2, n = 493, WMD -2.0, CI -12.2 to 8.2, p = 0.704
Risperidone versus **ziprasidone**	N = 2, n = 720, WMD -6.1, CI -9.5 to -2.7, p < 0.001
Risperidone versus ziprasidone	N = 3, n = 1016, WMD -4.6, CI -7.6 to -1.7, p = 0.002

*Olanzapine was not more efficacious than risperidone when studies sponsored by olanzapine's manufacturer were excluded. However, when only neutrally studies were included, olanzapine was again superior (p=0.043, see the third row with both olanzapine and risperidone in bolt print).

We also extensively performed other sensitivity analyses on the primary outcome excluding single blind studies, studies with a Jadad quality score <3, first episode studies, effectiveness studies, CATIE phase II (the same subjects were re-randomized) or Chinese studies. We also addressed first-episode studies and treatment resistant populations separately, we analyzed studies with clozapine doses higher than 400mg/day separately, and we analyzed clozapine studies of at least 3 or 6 months duration separately. We used a fixed effects model instead of the random effects model. It should be noted that by excluding studies in sensitivity analyses the number of studies is sometimes clearly reduced resulting in a loss of power. Nevertheless, the vast majority of these sensitivity analyses was consistent with the primary results. The few

exceptions where the results changed from statistically significant to not statistically significant or vice versa are presented below.

1. Excluding single-blind studies: No comparison of clozapine with zotepine available.

2. Excluding studies with a Jadad quality score <3: The degree as to how well a study is rated on the Jadad scale is partly related to how well the randomization and blinding procedures are documented. All our studies were randomized and at least single-blind and were in general good quality studies. Therefore, our analysis is really between good quality and very good quality. Olanzapine tended to be superior to aripiprazole, but the result was no longer significant, because one of the two studies was excluded (n=91, WMD -3, CI -12.2 to 6.2, p=0.52). It should be noted that the excluded study has to date only been incompletely presented on the internet (11). It was a large industry organized study of likely high quality, but the necessary information was not reported and we therefore had to give it a low quality score. No higher quality studies comparing clozapine with quetiapine, ziprasidone or zotepine were available.

3. Excluding first episode studies: not different from the primary results.

4. Excluding effectiveness studies or CATIE phase II: Risperidone was not significantly different from ziprasidone in the remaining 1 or 2 studies (N=1, n=296, WMD -1.5, CI -6.6 to 3.6, p=0.56; N=2, n=812, WMD -4.0, CI -8.4 to 0.3, p=0.07).

5. Excluding Chinese studies: No comparison of clozapine with zotepine available.

6. First-episode studies separately: The few first-episode studies showed no differences between groups (see discussion in main manuscript).

7. Studies in treatment resistant populations separately: One out of two studies comparing risperidone with sertindole was in treatment-resistant patients (12) and risperidone was superior (n = 321, WMD -6.9, CI -12.1 to -1.7, p= 0.009). In a single study (13) olanzapine tended to be superior to risperidone, but no longer significantly so (n=81, WMD -3.6, CI –13.3 to 6.1, p=0.47). The clozapine results did not change (see main manuscript).

8. The fixed effects model was less conservative in two occasions: clozapine was superior to risperidone for positive symptoms and olanzapine to ziprasidone for negative symptoms.

9. Clozapine doses higher than 400mg/day: clozapine was superior to risperidone (N=2, n=335, WMD -6.6, CI-11.5 to -1.7), but not olanzapine (N=2, n=154, WMD 2.4, CI-2.4 to 7.3). There was no data for other drugs.

Supplemental Table II: Results based on Hedges's g

We primarily analyzed the studies using weighted mean differences (WMD), since this preserves the original PANSS units, which are intuitively interpreted (e.g. a WMD of 5 means 5 points PANSS difference between the two groups). For a sensitivity analysis we used the standardized effect size (Hedges's g, SMD) to include a few more studies (13.3%) using scales other than the PANSS (generally BPRS). The results were very consistent. Only amisulpride was more efficacious than risperidone for negative symptoms (possibly due to increased power).

Only those comparisons with at least one additional study based on a rating scale other than the PANSS are shown. The results are shown only in one direction, for example, as amisulpride versus risperidone, but not again as risperidone versus amisulpride. But the results are symmetrical and only the sign needs to be changed to obtain the reverse result.

The original results based on weighted mean differences (WMD) are shown in the first row for comparison.

The results based on Hedges's g (SMD) are presented in the second row.

OVERALL SYMPTOMS	
Comparison	**Results**
Amisulpride versus risperidone	N = 2, n = 291, WMD 0.38, CI -4.6 to 5.3, p = 0.880 N = 3, n = 519, SMD -0.07, CI -0.24 to 0.10, p = 0.416
Clozapine versus olanzapine	N = 7, n = 619, WMD 1.3, CI -1.3 to 4.0, p = 0.327 N = 10, n = 731, SMD 0.11, CI -0.04 to 0.25, p = 0.147
Clozapine versus quetiapine	N = 4, n = 232, WMD 0.5, CI -1.9 to 2.9, p = 0.679 N = 5, n = 299, SMD 0.07, CI -0.15 to 0.30, p = 0.525
Clozapine versus risperidone	N = 5, n = 466, WMD -0.04, CI -5.1 to 5.0, p = 0.987 N = 8, n = 609, SMD -0.13, CI -0.32 to 0.06, p = 0.182
Olanzapine versus risperidone	N = 14, n = 2404, WMD -1.9, CI -3.3 to –0.6, p = 0.006 N = 16, n = 2438, SMD -0.11, CI -0.19 to -0.03, p = 0.007
Olanzapine versus ziprasidone	N = 4, n = 1291, WMD -8.3, CI -11.0 to –5.6, p < 0.001 N = 5, n = 1542, SMD -0.29, CI -0.41 to -0.16, p < 0.001
Quetiapine versus risperidone	N = 9, n = 1953, WMD 3.2, CI 1.1 to 5.4, p = 0.003 N = 10, n = 1978, SMD 0.19, CI 0.10 to 0.28, p < 0.001
POSITIVE SYMPTOMS	
Comparison	**Results**
Clozapine versus olanzapine	N = 6, n = 593, WMD 0.2, CI -1.2 to 0.9, p = 0.744 N = 9, n = 669, SMD -0.01, CI -0.17 to 0.14, p = 0.861
Clozapine versus risperidone	N = 4, n = 541, WMD -0.7, CI –2.4 to 1.0, p = 0.412 N = 6, n = 624, SMD -0.14, CI -0.34 to 0.06, p = 0.172
Olanzapine versus quetiapine	N = 6, n = 646, WMD –1.9, CI –2.7 to –1.1, p < 0.001 N = 7 n = 676, SMD -0.49, CI -0.75 to -0.23, p = 0.001
Quetiapine versus risperidone	N = 7, n = 1264, WMD 1.8, CI 1.2 to 2.5, p < 0.001 N = 8, n = 1289, SMD 0.45, CI -0.21 to 0.68, p < 0.001
Risperidone versus ziprasidone	N = 1, n = 204, WMD –2.5, CI –4.6 to –0.4, p = 0.021 N = 2, n = 500, SMD -0.02, CI –0.42 to –0.06, p= 0.010
NEGATIVE SYMPTOMS	
Comparison	**Results**
Amisulpride versus risperidone	N = 3, n = 519, WMD –1.0, CI –2.1 to 0.1, p = 0.078

	N = 3, n = 519, SMD -0.18, CI -0.36 to 0.01, p = 0.037
Clozapine versus olanzapine	N = 6, n = 593, WMD 0.6, CI -0.4 to 1.6, p = 0.227 N = 9, n = 669, SMD 0.03, CI -0.16 to 0.21, p = 0.770
Clozapine versus quetiapine	N = 2, n = 142, WMD 2.2, CI 1.0 to 3.5, p < 0.001 N = 3, n = 209, SMD 0.43, CI 0.11 to 0.74, p = 0.009
Clozapine versus risperidone	N = 4, n = 541, WMD -0.4, CI -1.8 to 1.0, p = 0.575 N = 7, n = 664, SMD -0.08, CI -0.23 to 0.07, p = 0.316
Olanzapine versus quetiapine	N = 6, n = 646, WMD -0.4, CI -1.2 to 0.3, p = 0.266 N = 7, n = 676, SMD -0.07, CI -0.23 to 0.07, p = 0.316
Quetiapine versus risperidone	N = 7, n = 1264, WMD -0.3, CI –1.9 to 1.3, p = 0.673 N = 8, n = 1298, SMD -0.06, CI -0.33 to 0.21, p = 0.663

Comment on Multiple Statistical Comparisons

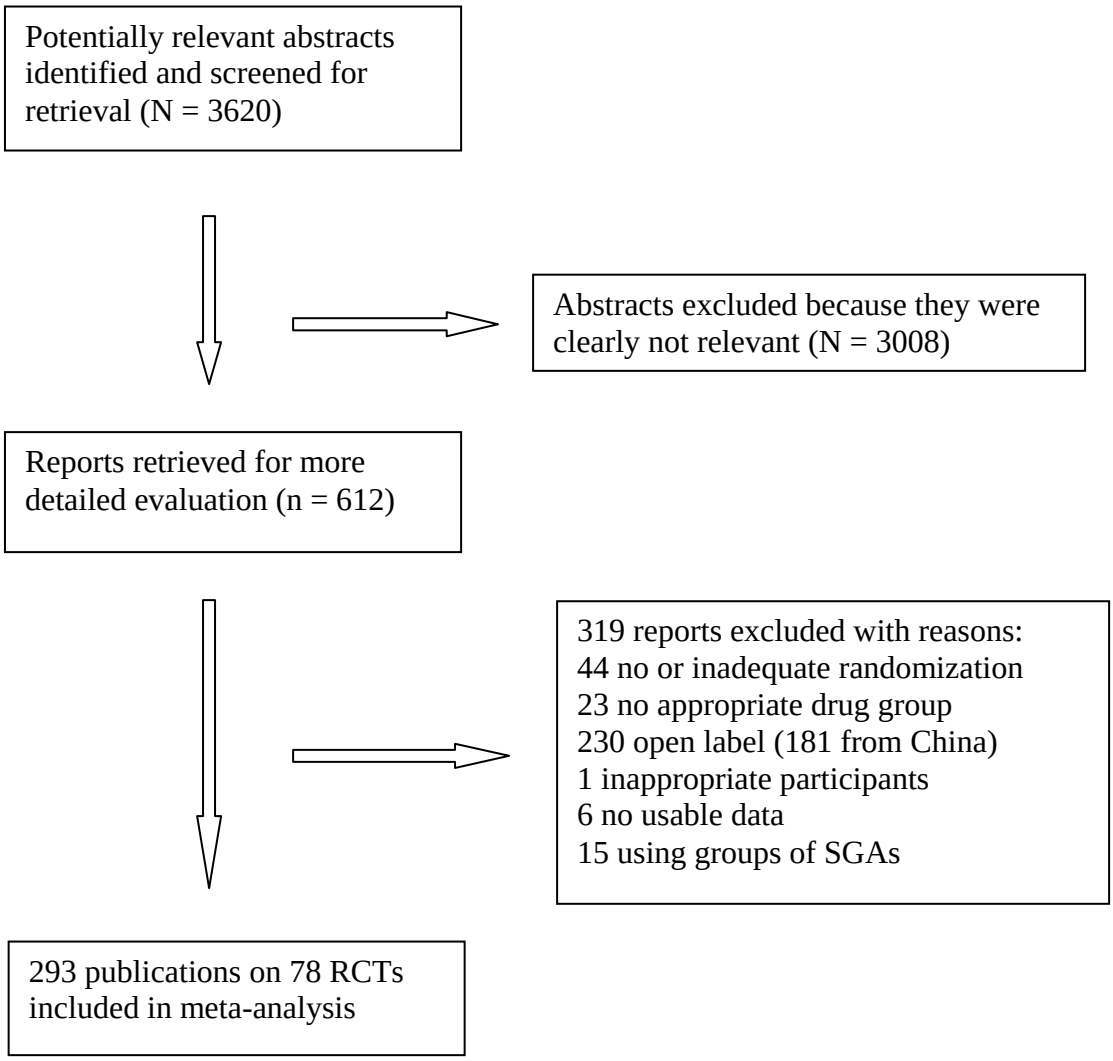
In meta-analysis, adjustments for multiple testing are usually not made and meta-analytic textbooks do not even report on it (1-3). In performing meta-analysis of multiple drugs, each with multiple outcomes, the matter is even more complicated. Unfortunately, a traditional correction for multiple testing is not appropriate here. For example, without any hypothesis, the Bonferroni method would expect that in one out of 20 comparisons a p-value below the conventional 0.05 level would occur by chance alone (14). In our case, there have been many well controlled prior studies with all the second-generation antipsychotics (SGAs). Controlled studies indicate that four SGAs – clozapine, amisulpride, olanzapine, risperidone - may be superior to first-generation antipsychotics (FGAs) (15). This evidence also indicates that five SGAs are about equally efficacious as FGAs. Therefore the prediction could be that the four SGAs previously shown to be superior to FGAs would be superior to the other five; and that the other five would be about equal to each other. It would be impossible to apply a correction for multiple testing which only addresses the probability that one of nine is significant. It has nothing to contribute to the prediction that four drugs will be superior to the other five; and that the other five will be approximately equally efficacious. It is further complicated by the fact that clozapine is more firmly established to really be superior than the other three.

There is also a problem of corrections for multiple testing applied to multiple outcomes (for example PANSS total, positive symptoms, etc). In order to make a correction for the fact that two or more outcomes may be correlated, it is important to know the correlation between the various measures in each study. These are not reported in the source literature that is extracted for the meta-analysis. Even if such a correction could be made, it is impossible to do a correction for multiple testing when you would predict that certain drugs would be superior and predict that others would be equal to the comparators. Since it is impossible to do Bonferroni (or similar) corrections, we can only restrict ourselves to general remarks. It may well be that a number of results were due to chance alone, but it is impossible to calculate which ones they are. But our results are remarkably consistent across several outcomes (except for negative symptoms) with sensitivity analyses supporting the validity of our findings. The results are also consistent in that, for example, olanzapine is significantly superior to a number of other SGAs, not only to one. As regards the sensitivity analyses, one expects loss of power as the number of studies in an analysis is restricted. Furthermore, in meta-analysis, sensitivity analyses are not made to dredge the data for statistical significances, but rather to examine the robustness of the results under different conditions. It is almost the opposite of data mining for a significant result.

The Bonferroni correction is most useful in considering blind screening of data sets for association because it estimates the chance that one out of many tests may be significant by change alone. In sensitivity analysis, one is evaluating whether an interesting result on the primary analysis also occurs under other assumptions. But when a result appears to be significant in the sensitivity analysis, which was not significant in the primary analysis, such a result is likely to be an artefact of multiple testing.

Supplemental Table III: Characteristics of included studies

Quality of Reports of Meta-analysis (QUORUM) flow-diagram describing the search process (16)



Author Sponsor's drug	Design	Participants	Interventions
Amisulpride versus Aripiprazole			
No study			
Amisulpride versus Clozapine			
No study			
Amisulpride versus Olanzapine			
Lecrubier et al. 2006 (17) Olanzapine	Allocation: random, no further details Blinding: double, no further details. Duration: 26 weeks. Design:parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia catatonic (n=11), disorganised (n=102) or residual (n=131), SANS severity score of 10 or more (excluding the item attention). N=245. Gender: 167 M, 78 F. Age: mean 37.4 years History: duration ill mean 11.2 years age at onset n.i.	1. Amisulpride: Fixed dose: 150 mg/day. N=70. 2. Olanzapine: Fixed dose: 5 mg/day. N=70. 3. Olanzapine: Fixed dose: 20 mg/day. N=70.
Mortimer et al. 2004 (18) Amisulpride	Allocation: random, computer-generated randomisation. Blinding: double, identical capsules. Duration: 24 weeks. Design: parallel. Location: multicenter. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia disorganised (n=33), paranoid (n=260) or undifferentiated (n=76) or schizophreniform disorder (n=8), dominant positive symptoms, BPRS of 36 or more, PANSS positive score higher than PANSS negative score. N=377. Gender: 245 M, 132 F. Age: 18-65 years, mean=37.8 years. History: duration ill mean=8.84 years, age at onset n.i.	1. Amisulpride: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 504 mg/day. N=189. 2. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 13 mg/day. N=188.
Vanelle and Douki 2006 (19) Amisulpride	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia and comorbid depression, disorganised (n=26), paranoid (n=32), undifferentiated (n=23) or residual (n=4). N=85. Gender: 54 M, 31 F. Age: 18-65 years (mean=34 years). History: duration ill n.i., age at onset n.i.	1. Amisulpride: Flexible dose. Allowed dose range: 200-600 mg/day. Mean dose: 471 mg/day. N=45. 2. Olanzapine: Flexible dose. Allowed dose range: 5-15 mg/day. Mean dose: 11.4 mg/day. N=40.

Wagner et al. 2005 (20) Olanzapine	Allocation: random, medication containers according to a pseudo-random computer algorithm. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV and ICD-10) schizophrenia, CGI of 4 or more, PANSS of 61 or more. N=52. Gender: 23 M, 13 F (of subjects with neuropsychological data, n=36). Age: 18-65 years, mean=36.3 years. History: duration ill mean=8.4 years (of subjects with neuropsychological data, n=36), age at onset 27.9 years (of subjects with neuropsychological data, n=36).	1. Amisulpride: Flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 511.1 mg/day. N=26. 2. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 15.0 mg/day. N=26.
Amisulpride versus Quetiapine			
No study			
Amisulpride versus Risperidone			
Hwang et al. 2003 (21) Amisulpride	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 6 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia disorganised (n=9), paranoid (n=22), undifferentiated (n=16). N=48. Gender: 20 M, 27 F Age: 18-65 years, mean=35.2 years. History: duration ill mean: 13.4 years, age at onset n.i.	1. Amisulpride: Flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 630 mg/day. N=23 2. Risperidone: Flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: 6.88 mg/day. N=25.
Möller et al. 2005 (22) Amisulpride	Allocation: random, no further details. Blinding: double, no further details. Duration: 6 weeks. Design: parallel. Location: n.i. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder or shared psychotic disorder. N=36. Gender: n.i. Age: 65 years or more. History: duration ill n.i., age at onset n.i.	1. Amisulpride: Flexible dose. Allowed dose range: 100-400 mg/day. Mean dose: n.i. N=24. 2. Risperidone: Flexible dose. Allowed dose range: 1-4 mg/day. Mean dose: n.i. N=12.
Peuskens et al. 1999 (23) Amisulpride	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient	Diagnosis: (DSM-IV) schizophrenia disorganised, paranoid or undifferentiated, BPRS of 36 or more. N=228. Gender: 137 M, 91 F. Age: 18-65 years, mean =36.5 years History: duration ill mean 9.1 years, age at onset n.i.	1. Amisulpride: Fixed dose: 800 mg/day. N=115. 2. Risperidone: Fixed dose: 8 mg/day. N=113.

Sechter et al. 2002 (24) Amisulpride	Allocation: random, no further details. Blinding: double, no further details. Duration: 26 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) chronic schizophrenia disorganised (n=37), paranoid (n=227), residual (n=19) or undifferentiated (n=27), PANSS between 60 and 120, recent worsening of symptoms. N=310. Gender: 170 M, 140 F. Age: 18-65 years, mean=38.4 years. History: duration ill mean=11.8 years, age at onset n.i.	1. Amisulpride: Flexible dose. Allowed dose range: 400-1000 mg/day. Mean dose: 683 mg/day. N=152. 2. Risperidone: Flexible dose. Allowed dose range: 4-10 mg/day. Mean dose: 6.92 mg/day. N=158.
Amisulpride versus Sertindole			
No study			
Amisulpride versus Ziprasidone			
Olié et al. 2006 (25) Ziprasidone	Allocation: random, no further datails. Blinding: double, no further details. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: outpatient.	Diagnosis: (DSM-III-R) chronic schizophrenia, PANSS negative subscore at least 6 points higher than PANSS positive subscore. N=123. Gender: 79 M, 44 F. Age: 18-64 years, mean=39 years. History: duration ill n.i., age at onset n.i.	1. Amisulpride: Flexible dose. Allowed dose range: 100-200 mg/day. Mean dose: 144.7mg/day. N=63. 2. Ziprasidone: Flexible dose. Allowed dose range: 80-160 mg/day. Mean dose: 118.0 mg/day. N=60.
Amisulpride versus Zotepine			
No study			
Aripiprazole versus Clozapine			
No study			
Aripiprazole versus Olanzapine			
Study BMS CN138003 2005 (11) Aripiprazole	Allocation:random nfd Blinding:double Duration:52 weeks first 6 weeks observed Design:parallel Location:multicentre Setting: in and outpatients	Diagnosis: acute schizophrenia PANSS of 60 or more Gender:n.i. Age:n.i. History: duration ill, age at onset: n.i.	1. Aripiprazole Fixed/flexible dose (15, 20, 30 mg) Mean dose: n.i. N=355 2. Olanzapine Fixed/flexible dose (10,15,20mg) Mean dose:n.i. N=348

McQuade et al. 2004 (26) Aripiprazole	Allocation: random, no further details. Blinding: double, no further details. Duration: 26 weeks. Design: parallel. Location: multicentre. Setting: originally inpatient	Diagnosis: (DSM-IV) schizophrenia disorganised (n=17), paranoid (n=271), residual (n=3) or undifferentiated (n=26), in acute relapse. PANSS total score of 60 or more. N=317. Gender: 229 M, 88 F. Age: >17 years, mean=38.4 years. History: duration ill n.i., age at first hospitalisation mean=24.50 years.	1. Aripiprazole: Flexible dose. Allowed dose range: 15-30 mg/day. Mean dose: 25.1 mg/day. N=156. 2. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 16.5 mg/day. N=161.
Aripiprazole versus Quetiapine			
No study			
Aripirazole versus Risperidone			
Chan et al. 2007 (27) Aripiprazole	Allocation: random, permuted block randomisation stratified by centre. Blinding: double, identical capsules. Duration: 4 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia (n=80) or schizoaffective disorder (n=3), acute relapse. PANSS total score of 60 or more. N=83. Gender: 45 M, 38 F. Age: 18-65 years, mean =35.2 years History: duration ill n.i., age at onset n.i.	1. Aripiprazole: Fixed dose: 15 mg/day. N=49. 2. Risperidone: Fixed dose: 6 mg/day. N=34.
Potkin et al. 2003 (28) Aripiprazole	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 4 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia (n=289) or schizoaffective disorder (n=115), hospitalised due to an acute relapse, response to previous antipsychotic treatment other than clozapine, PANSS of 60 or more. N=404. Gender: 283 M, 121 F. Age: 18-65 years, mean=38.9 years. History: duration ill n.i., age at onset n.i.	1. Aripiprazole: Fixed dose: 20 mg/day. N=101. 2. Aripiprazole: Fixed dose: 30 mg/day. N=101. 3. Risperidone: Fixed dose: 6 mg/day. N=99.
Aripiprazole versus Sertindole			
No study			
Aripiprazole versus Ziprasidone			
No study			
Aripiprazole versus Zotepine			
No study			

Clozapine versus Olanzapine			
Bitter et al. 2003 (29) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 18 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia, non-response to, or intolerance of standard antipsychotic therapy, BPRS of 42 or more. N=147 (enrollment population N=150). Gender: 88 M, 59 F. Age: 18-65 years, mean=37.6 years. History: duration ill n.i., age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 100-500 mg/day. Mean dose: 216.2 mg/day. N=72 (enrollment population N=74). 2. Olanzapine: Flexible dose. Allowed dose range: 5-25 mg/day. Mean dose: 17.2 mg/day. N=75 (enrollment population N=74).
Conley et al. 2003 (30) Neutral sponsor	Allocation: random, no further details. Blinding: double, no further details. Duration: 16 weeks (first 8 weeks observed). Design: cross-over. Location: n.i. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia, resistance to previous treatment. BPRS of 45 or more. CGI of 4 or more. N=13. Gender: 8 M, 5 F. Age: mean= 37.58 years. History: duration ill n.i., age at onset n.i.	1. Clozapine: Fixed dose: 450 mg/day. N=5. 2. Olanzapine: Fixed dose: 50 mg/day. N=8.
Krakowski et al. 2006 (31) Neutral sponsor	Allocation: random, block radomisation (block size of 3). Blinding: double, no further details. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia (n=71) or schizoaffective disorder (n=39), persistent aggression. N=110. Gender: 90 M, 20 F. Age: 18-60 years, mean: 34 years. History: duration ill mean:15.5 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.5 mg/day (at the end of the last 6 weeks). N=37. 2. Haloperidol: Flexible dose. Allowed dose range: 10-30 mg/day. Mean dose: 23.3 mg/day (at the end of the last 6 weeks). N=36. 3. Olanzapine: Flexible dose. Allowed dose range: 10-35 mg/day. Mean dose: 24.7 mg/day (at the end of the last 6 weeks). N=37.

Meltzer et al. 2003 (32) Clozapine	Allocation: random, no further details Blinding: single, rater-blinded. Duration: 104 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia (n=609) or schizoaffective disorder (n=371), high suicidal risk. N=980. Gender: 602 M, 378 F. Age: 18-65 years, mean=37.1 years. History: duration ill n.i., age at onset mean=24.7 years.	1. Clozapine: Flexible dose. Allowed dose range: 200-900 mg/day. Mean dose: 274.2 mg/day. N=490. 2. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 16.6 mg/day. N=490.
Moresco et al. 2004 (33) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: singlecentre. Setting: inpatient	Diagnosis: (DSM-IV) schizophrenia, treatment resistance to two previous antipsychotic medications. BPRS score of 27 or more. N=23. Gender: 16 M, 7 F. Age: 18 years or more, mean =36.2 years History: duration ill n.i., age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 300-400 mg/day. Mean dose: 325.4 mg/day. N=12. 2. Olanzapine: Flexible dose. Allowed dose range: 15-20 mg/day. Mean dose: 18.3 mg/day. N=11.
Naber et al. 2005 (34) Olanzapine	Allocation: random, computer-generated randomisation. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient, initially inpatient.	Diagnosis: (DSM-IV) schizophrenia, non-response to, or intolerance of standard antipsychotic therapy, BPRS of 24 or more. N=114. Gender: 69 M, 45 F. Age: 18-65 years, mean=34.0 years. History: duration ill n.i., age at onset 26.9 years.	1. Clozapine: Flexible dose. Allowed dose range: 100-400 mg/day. Mean dose: 209 mg/day. N=57. 2. Olanzapine: Flexible dose. Allowed dose range: 5-25 mg/day. Mean dose: 16.2 mg/day. N=57.
Shaw et al. 2006 (35) Neutral sponsor	Allocation: random, random-numbers chart, blocks of 4. Blinding: double, identical capsules. Duration: 8 weeks. Design: parallel. Location: n.i. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia, treatment resistant to two previous antipsychotics, IQ of 70 or more. N=25. Gender: 15 M, 10 F. Age: 7-16 years, mean =12.3 years. History: duration ill mean =3.2 years, age at onset mean =9.1 years	1. Clozapine: Flexible dose. Allowed dose range: 150-500 mg/day. Mean dose: 327 mg/day. N=12. 2. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 18.1 mg/day. N=13.
Tollefson et al. 2001 (36) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 18 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia catatonic (n=3), disorganised (n=34), paranoid (n=101), residual (n=8) or undifferentiated (n=34), previous treatment resistance, BPRS of 45 or more. N=180. Gender: 115 M, 65 F. Age: 18-70 years, mean=38.6 years. History: duration ill n.i., age at onset mean=22.8 years.	1. Clozapine: Flexible dose. Allowed dose range: 200-600 mg/day. Mean dose: 303.6 mg/day. N=90. 2. Olanzapine: Flexible dose. Allowed dose range: 15-25 mg/day. Mean dose: 20.5 mg/day. N=90.

Volavka et al. 2002 (13) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 14 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) chronic schizophrenia (n=135) or schizoaffective disorder (n=22), suboptimal response to previous treatment, PANSS of 60 or more. N=167. Gender: 133 M, 24 F. Age: 18-60 years, mean=40.8 years. History: duration ill mean=19.5 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 526.6 mg/day (at the end of the last 6 weeks). N=40. 2. Haloperidol: Flexible dose. Allowed dose range: 10-30 mg/day. Mean dose: 25.7 mg/day (at the end of the last 6 weeks). N=37. 3. Olanzapine: Flexible dose. Allowed dose range: 10-40 mg/day. Mean dose: 30.4 mg/day (at the end of the last 6 weeks). N=39. 4. Risperidone: Flexible dose. Allowed dose range: 4-16 mg/day. Mean dose: 11.6 mg/day (at the end of the last 6 weeks). N=41.
Atmaca et al. 2003 (37) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 6 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia. N=56. Gender: 24 M, 29 F. Age: 19-46 years, mean=30.8 years. History: duration ill mean=6.1 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: n.i. Mean dose: 207.1 mg/day. N=14. 2. Olanzapine: Flexible dose. Allowed dose range: n.i. Mean dose: 15.7 mg/day. N=14. 3. Quetiapine: Flexible dose. Allowed dose range: n.i. Mean dose: 535.7 mg/day. N=14. 4. Risperidone: Flexible dose. Allowed dose range: n.i. Mean dose: 6.7 mg/day. N=14.
Wang et al. 2002 (38) Unclear	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: singlecentre. Setting: in- and outpatient.	Diagnosis: (CCMD-3) schizophrenia. N=61. Gender: 29 M, 32 F. Age: mean=27,9 years, History: duration ill mean=4.2 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 25-400 mg/day. Mean dose: n.i. N=31. 2. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: n.i. N=30.

Kumra et al. 2007 (39) Neutral sponsor	Allocation: computer generated randomization list handled by research pharmacist. Blinding: double. Duration: 12 weeks. Design: parallel. Location: two centres. Setting: inpatient.	Diagnosis: (Kiddie-SADS) schizophrenia, schizoaffective disorder. N=39. Gender: 21 M, 18 F. Age: mean=15.6 years. History: treatment refractory (2 unsuccesful adequate antipsychotic drug trials, BPRS > 35, at least 2 psychotic symptoms moderate or more).	1. Clozapine: Flexible dose. Maximum dose: 900mg/day Mean dose: 403.1. N=18 2. Olanzapine: Flexible dose. Maximum dose 30mg/day, mean dose 26.2. N=21
Clozapine versus Quetiapine			
Atmaca et al. 2003 (37) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 6 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia. N=56. Gender: 24 M, 29 F. Age: 19-46 years, mean=30.8 years. History: duration ill mean clozapine=6.1 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: n.i. Mean dose: 207.1 mg/day. N=14. 2. Olanzapine: Flexible dose Allowed dose range: n.i. Mean dose: 15.7 mg/day. N=14. 3. Quetiapine: Flexible dose. Allowed dose range: n.i. Mean dose: 535.7 mg/day. N=14. 4. Risperidone: Flexible dose. Allowed dose range: n.i. Mean dose: 6.7 mg/day. N=14.
Li 2003 (40) Unclear	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 8 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (CCMD-2) schizophrenia. N=76. Gender: n.i. Age: mean=35.5 years, History: duration ill: mean=5.92 years, age at onset n.i.	1. Clozapine: Allowed dose range: start with 25 mg, in two weeks supposed dose, n.f.d. Mean dose: 325 mg/day. N=38. 2. Quetiapine: Allowed dose range: start with 25 mg, in two weeks supposed dose, n.f.d. Mean dose: 375 mg/day. N=38.
Li and Feng 2005 (41) Unclear	Allocation: random, no further details. Blinding: double, no further details. Duration: 12 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (CCMD-3) schizophrenia. N=67. Gender: n.i.. Age: mean=26.18 years. History: duration ill mean =0.5 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 100-550 mg/day. Mean dose: 255.96 mg/day. N=34. 2. Quetiapine: Flexible dose. Allowed dose range: 150-650 mg/day. Mean dose: 362.09 mg/day. N=33.

Li et al. 2002 (42) Unclear	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: singlecentre. Setting: in- and outpatient.	Diagnosis: (CCMD-3) first episode schizophrenia. N=63. Gender: M n.i., F n.i. Age: mean =29 years. History: duration ill mean=0.64 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 25-750 mg/day. Mean dose: 270.5 mg/day. N=31. 2. Quetiapine: Flexible dose. Allowed dose range: 25-750 mg/day. Mean dose: 478.5 mg/day. N=32.
Liu et al. 2004 (43) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 12 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (CCMD-3) schizophrenia. N=72. Gender: n.i. M, n.i. F. Age: mean=37.2 years, History: duration ill mean clozapine=9 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: initial dose: 50 mg/day, after 10 days: 400-600 mg/day. Mean dose: n.i. N=36 2. Quetiapine: Flexible dose. Allowed dose range: initial dose: 100 mg/day, after 10 days: 400-700 mg/day. Mean dose: n.i. N=36
Clozapine versus Risperidone			
Atmaca et al. 2003 (37) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 6 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia. N=56. Gender: 24 M, 29 F. Age: 19-46 years, mean=30.8 years. History: duration ill mean=6.1 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: n.i. Mean dose: 207.1 mg/day. N=14. 2. Olanzapine: Flexible dose. Allowed dose range: n.i. Mean dose: 15.7 mg/day. N=14. 3. Quetiapine: Flexible dose. Allowed dose range: n.i. Mean dose: 535.7 mg/day. N=14. 4. Risperidone: Flexible dose. Allowed dose range: n.i. Mean dose: 6.7 mg/day. N=14.

Volavka et al. 2002 (13) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 14 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) chronic schizophrenia (n=135) or schizoaffective disorder (n=22), suboptimal response to previous treatment, PANSS of 60 or more. N=167. Gender: 133 M, 24 F. Age: 18-60 years, mean=40.8 years. History: duration ill mean=19.5 years, age at onset: n.i.	1. Clozapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 526.6 mg/day (at the end of the last 6 weeks). N=40. 2. Haloperidol: Flexible dose. Allowed dose range: 10-30 mg/day. Mean dose: 25.7 mg/day (at the end of the last 6 weeks). N=37. 3. Olanzapine Flexible dose. Allowed dose range: 10-40 mg/day. Mean dose: 30.4 mg/day (at the end of the last 6 weeks). N=39. 4. Risperidone: Flexible dose. Allowed dose range: 4-16 mg/day. Mean dose: 11.6 mg/day (at the end of the last 6 weeks). N=41.
Azorin et al. 2001 (44) Clozapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia catatonic (n=4), disorganised (n=46), paranoid (n=140), residual (n=15) or undifferentiated (n=51), poor previous treatment response, CGI of 4 or more, BPRS of 45 or more. N=273. Gender: 182 M, 74 F. Age: 18-65 years, mean=38.6 years. History: duration ill mean n.i., age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 200-900 mg/day. Mean dose: 642 mg/day (of completers, n=100). N=138. 2. Risperidone: Flexible dose. Allowed dose range: 2-15 mg/day. Mean dose: 9 mg/day (of completers, n=101). N=135.
Bondolfi et al. 1998 (45) Risperidone	Allocation: random, no further details. Blinding: double, double-dummy protocol. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-III-R) chronic schizophrenia disorganised (n=24), paranoid (n=50), residual (n=5) or undifferentiated (n=7), non-response to, or intolerance of previous antipsychotic treatment, PANSS between 60 and 120. N=86. Gender: 61 M, 25 F. Age: 18-65 years, mean=37.3 years. History: age at first hospitalisation mean=25.5 years, age at onset mean=23.3 years.	1. Clozapine: Flexible dose. Allowed dose range: 0-600 mg/day. Mean dose: 291.2 mg/day (at week 6). N=43. 2. Risperidone: Flexible dose. Allowed dose range: 0-12 mg/day. Mean dose: 6.4 mg/day (at week 6). N=43.

Breier et al. 1999 (46) Neutral sponsor	Allocation: random, no further details. Blinding: double, no further details. Duration: 6 weeks. Design: parallel. Location: singlecentre. Setting: n.i.	Diagnosis: (DSM-IV) chronic schizophrenia, BPRS positive subscore of 8 or more, SANS of 20 or more, following a baseline fluphenazine treatment. N=29. Gender: 19 M, 10 F. Age: 18-55 years, mean =35 years. History: duration ill mean=12.5 years, age at onset mean =22.5.	1. Clozapine: Flexible dose. Allowed dose range: 200-600 mg/day. Mean dose: 403.6 mg/day. N=14. 2. Risperidone: Flexible dose. Allowed dose range: 2-9 mg/day. Mean dose: 5.9 mg/day. N=15.
Ren et al. 2001 (47) Neutral sponsor	Allocation: random, no further detials. Blinding: double, ball drawing out of box. Duration: 12 weeks. Design: parallel. Location: singlecentre. Setting: outpatient.	Diagnosis: (CCMD-3) schizophrenia. N=120. Gender: n.i. M, n.i. F. Age: mean=34.5 years. History: duration ill mean=6.3 years, age at onset mean =22.6 years.	1. Clozapine: Allowed dose range: n.i. Mean dose: 350 mg/day. N=60. 2. Risperidone: Allowed dose range: n.i. Mean dose: 3.2 mg/day. N=60.
Zhou et al. 2000 (48) Unclear	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 8 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (CCMD-2) schizophrenia. N=40. Gender: 23 M, 17 F. Age: mean=28.3 years. History: duration ill mean =3 years, age at onset n.i.	1. Clozapine: Fixed and flexible dose (first 2 weeks) Allowed dose range: 25-300 mg/day (first 2 weeks), then 300 mg/day fixed. Mean dose: n.i. N=20. 2. Risperidone: Fixed and flexible dose (first 2 weeks). Allowed dose range: 1-6 mg/day (first 2 weeks), then 6 mg/day fixed. Mean dose: n.i. N=20.
Heinrich et al. 1994 (49) Neutral sponsor	Allocation: random, no further details. Blinding: double, same amount of capsules. Duration: 4 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (ICD-9) acute schizophrenia catatonic (n=1), disorganised (n=1), paranoid (n=47), unspecified (n=2) or schizoaffective psychosis schizodominant type (n=8) plus (n=1 not specified). N=60. Gender: 31 M, 28 F. Age: 18-65 years. History: duration ill n.i., age at onset n.i.	1. Clozapine: Fixed dose: 400 mg/day. N=20. 2. Risperidone: Fixed dose: 4 mg/day. N=20. 3. Risperidone: Fixed dose: 8 mg/day. N=20.
McGurk et al. 2005 (50) Neutral sponsor	Allocation: random, no further details. Blinding: double, no further details. Duration: 29 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder, treatment resistance, moderate severity score on BPRS or SANS. N=97. Gender: 77 M, 20 F. Age: 18-60 years, mean=41.9 years. History: duration ill n.i., age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 12.5-800 mg/day (target dose: 500 mg/day from day 28 on). Mean dose: n.i. N=47. 2. Risperidone: Flexible dose. Allowed dose range: 1-16 mg/day (target dose: 6 mg/day from day 15 on). Mean dose: n.i. N=50.

Wahlbeck et al. 2000 (51) Neutral sponsor	Allocation: random, computer-generated randomisation. Blinding: single, rater-blinded. Duration: 10 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient (initially inpatient).	Diagnosis: (DSM-IV) schizophrenia, resistance to previous treatment. N=20. Gender: 10 M, 9 F. Age: 24-55 years, mean=36.2 years. History: duration ill mean clozapine=12.6 years, mean risperidone=13.1 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 25-600 mg/day. Mean dose: 385 mg/day. N=11. 2. Risperidone: Flexible dose. Allowed dose range: 2-10 mg/day.Mean dose: 7.8 mg/day. N=9.
Daniel et al. 1996 (52) Risperidone	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 12 weeks (6 weeks observed). Design: cross-over. Location: n.i. Setting: outpatient.	Diagnosis: (DSM-III-R) chronic schizophrenia (n=16) or schizoaffective disorder (n=4). N=20. Gender: 7 M, 13 F. Age: 22-51 years, mean=33.8 years. History: duration ill n.i., age at onset mean=22.7 years.	1. Clozapine: Flexible dose. Allowed dose range: 75-800 mg/day. Mean dose: 375 mg/day. N=10. 2. Risperidone: Flexible dose. Allowed dose range: 1-10 mg/day. Mean dose: 6.1 mg/day. N=10.
Clozapine versus Sertindole			
No study			
Clozapine versus Ziprasidone			
Sacchetti et al. 2006 (53) Ziprasidone	Allocation: random, no further details. Blinding: double, no further details. Duration: 18 weeks. Design: parallel. Location: n.i. Setting: n.i.	Diagnosis: schizophrenia, non-response to, or intolerance of 3 previous antipsychotic treatment trials. N=146. Gender: 101 M, 45 F. Age: mean=40 years. History: duration ill n.i., age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 250-600 mg/day. Mean dose: 345.7 mg/day. N=73. 2. Ziprasidone: Flexible dose. Allowed dose range: 80-160 mg/day. Mean dose: 130.4 mg/day. N=73.
Clozapine versus Zotepine			
Lin et al. 2003 (54) Unclear	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 12 weeks. Design: parallel. Location: n.i. Setting: inpatient.	Diagnosis: schizophrenia, BPRS >30, clozapine treatment for more than 5 months. N=59. Gender: n.i. Age: 20-65 years. History: duration ill n.i., age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: n.i. Mean dose: 387.1 mg/day. N=24. 2. Zotepine: Flexible dose. Allowed dose range: n.i. Mean dose: 377.1 mg/day. N=35.

Meyer-Lindenberg et al. 1997 (55) Zotepine	Allocation: random, no further details. Blinding: double, no further details. Duration: 6 weeks. Design: parallel. Location: n.i. Setting: n.i.	Diagnosis: (DSM-III-R) schizophrenia catatonic, hebephrenic, paranoid or residual, BPRS >40 after washout phase, no previous treatment with either medication. N=50. Gender: n.i. M, n.i. F. Age: 18-60 years. History: duration ill n.i., age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 150-450 mg/day. Mean dose: n.i. N=25. 2. Zotepine: Flexible dose. Allowed dose range: 150-450 mg/day. Mean dose: n.i. N=25.
Olanzapine versus Quetiapine			
Atmaca et al. 2003 (37) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 6 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia. N=56. Gender: 24 M, 29 F. Age: 19-46 years (mean=30.8 years). History: duration ill mean=6.1 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: n.i. Mean dose: 207.1 mg/day. N=14. 2. Olanzapine: Flexible dose. Allowed dose range: n.i. Mean dose: 15.7 mg/day. N=14. 3. Quetiapine: Flexible dose. Allowed dose range: n.i. Mean dose: 535.7 mg/day. N=14. 4. Risperidone: Flexible dose. Allowed dose range: n.i. Mean dose: 6.7 mg/day. N=14.
Kinon et al. 2006 (56) Olanzapine	Allocation: random, computer-generated randomisation. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: multicentre. Setting: outpatient.	Diagnosis: (DSM-IV) schizophrenia (n=230), schizoaffective disorder (n=116), prominent negative symptoms. N=346. Gender: 228 M, 118 F. Age: mean=41.1 years, History: duration ill mean=20.5 years	1. Olanzapine Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 15.6 mg/day. N=171. 2. Quetiapine Flexible dose Allowed dose range: 300-700 mg/day. Mean dose: 455.8 mg/day. N=175.
Riedel et al. 2007 (57) Olanzapine	Allocation: random, no further details, Blinding: double Duration: 8 week Design: parallel Setting: inpatient	Diagnosis: (DSM-IV) schizophrenia, acute episode (N= 52, 33 observed) Gender: 21 M/ 12 F Age:18-65 years, mean = 35.6 years, History duration ill mean= 6.6 years	1. Olanzapine:flexible Allowed dose range: 10-20mg Mean Dose: 15,82 mg. N= 17 2. Quetiapine: flexible Allowed Dose range 400-800 mg Mean dose 586,86 mg. N= 16

Lieberman et al. 2005 (58) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Gender: 1080 M, 380 F. Age: 18-65 years, mean=40.6 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.1 mg/day. N=336. 2. Perphenazine: Flexible dose. Allowed dose range: 8-32 mg/day. Mean dose: 20.8 mg/day. N=261. 3. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 543.4 mg/day. N=337. 4. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day. Mean dose: 3.9 mg/day. N=341. 5. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day. Mean dose: 112.8 mg/day. N=185.
Stroup et al. 2006 (59) Neutral sponsor	Allocation: random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re-randomised. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: n.i. Setting: in- and outpatient.	Diagnosis: (DSM-IV) chronic schizophrenia. N=444. Gender: 308 M, 136 F. Age: 18-65 years, mean=40.9 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.5 mg/day. N=68. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.2 mg/day. N=63. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day.Mean dose: 4.1 mg/day. N=70. 4. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day.Mean dose: 115.9 mg/day. N=137.
Sirota et al. 2006 (60) Quetiapine	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 12 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia, PANSS negative subscore >15, SANS >60. N=40. Gender: 32 M, 8 F. Age: 21-64 years, mean=37.2 years History: duration ill mean=14.6 years, age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 16.0 mg/day. N=21. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 637.2 mg/day. N=19.

Švestka et al. 2003 (61) Neutral sponsor	Allocation: random, no further details. Blinding:double, no further details. Duration: 6 weeks. Design: parallel. Location: n.i. Setting: inpatient.	Diagnosis: (ICD-10) acute schizophrenia (n=32), schizoaffective disorder (n=10). N=42. Gender: 0 M, 42 F. Age: mean=35.78 years. History: duration ill mean=7.05 years, age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 19.5 mg/day. N=20. 2. Quetiapine: Flexible dose. Allowed dose range: 50-700 mg/day. Mean dose: 677.3 mg/day. N=22.
Ozguven et al. 2004 (62) Neutral sponsor	Allocation: random, no further details Blinding: single Duration: 6 weeks Design: parallel Location, Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia Gender: 8M, 22F. Age, history, duration ill: not indicated	1. Olanzapine: Mean dose: 20.0mg/day. N= 15 2. Quetiapine: Mean dose: 833,3 mg/day. N= 15
McEvoy et al. 2007 (63) Quetiapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 52 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia (n=231), schizophreniform disorder (n=115) or schizoaffective disorder (n=54), first episode, psychotic symptoms for 1 month to 5 years, PANSS psychosis and CGI-S score of 4 or more. N=400. Gender: 292 M, 108 F. Age: 16-40 years, mean=24.5 years. History: duration ill mean=1.08 years, age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 11.7 mg/day. N=133. 2. Quetiapine: Flexible dose. Allowed dose range: 100-800 mg/day. Mean dose: 506 mg/day. N=134. 3. Risperidone: Flexible dose. Allowed dose range: 0.5-4 mg/day. Mean dose: 2.4 mg/day. N=133.
Mori et al. 2004 (64) Unclear	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks (last 4 weeks observed). Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia disorganised (n=23), paranoid (n=10), undifferentiated (n=34). N=77. Gender: 39 M, 38 F. Age: 28-84 years, mean=59.9 years. History: duration ill mean=34.51 years, age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 16.5 mg/day. N=20. 2. Perospirone: Flexible dose. Allowed dose range: 4-48 mg/day. Mean dose: 37.3 mg/day. N=18. 3. Quetiapine: Flexible dose. Allowed dose range: 50-750 mg/day. Mean dose: 432.5 mg/day. N=20. 4. Risperidone: Flexible dose. Allowed dose range: 1-12 mg/day. Mean dose: 7.37 mg/day. N=19.

McEvoy et al. 2006 (65) Neutral	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 52 weeks (26 weeks observed, because of small group sizes. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, inadequate efficacy in previous study, clozapine treatment (n=49) was open-label. N=99 (observed N=50). Gender: 80 M, 19 F. Age: 18-65 years (mean=39.7 years). History: duration ill n.i., age at onset: n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 23.4 mg/day. N=19. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 642.9 mg/day. N=15. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6 mg/day. Mean dose: 4.8 mg/day. N=16.
Voruganti et al 2007 (66) Quetiapine	Allocation: random,no further details. Blinding: single, rater-blinded Duration: 52 weeks Design: parallel	Diagnosis: schizophrenia, N= 86, no further details	1. Olanzapine: Flexible dose: Mean Dose: 17,2 mg/day. N=42 2. Quetiapine: Flexible Dose. Mean Dose: 612, 8 mg/day. N=43
Sacchetti et al. 2004 (67) Quetiapine	Allocation: random, no further details. Blinding: single (rater-blinded). Duration: 16 weeks (8 weeks observed). Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia, PANSS total score of 70 or more, PANSS positive subscore of 4 or more on at least 2 items N=75 Age: 18-65 years History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 14.6 mg/day. N=25 2. Quetiapine: Flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 602.4 mg/day. N=25 3. Risperidone: Flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: 4.3 mg/day. N=25

Olanzapine versus Risperidone			
Atmaca et al. 2003 (37) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 6 weeks. Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia. N=56. Gender: 24 M, 29 F. Age: 19-46 years, mean=30.8 years. History: duration ill mean=6.1 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: n.i. Mean dose: 207.1 mg/day. N=14. 2. Olanzapine: Flexible dose. Allowed dose range: n.i. Mean dose: 15.7 mg/day. N=14. 3. Quetiapine: Flexible dose. Allowed dose range: n.i. Mean dose: 535.7 mg/day. N=14. 4. Risperidone: Flexible dose. Allowed dose range: n.i. Mean dose: 6.7 mg/day. N=14.
Canive et al. 2000 (68) Olanzapine	Allocation: random Blinding: double Duration: 18 weeks, first 8 week treatment period observed Design: cross –over Location: not indicated Setting: inpatient/outpatient	Diagnosis: (DSM-IV) schizophrenia N= 15 Age 18-65 years, mean =42 years History, duration ill: n. i	1. Olanzapine: fixed, 15 mg/day. N= 5 2. Risperidone: fixed 6mg/day N= 4
Wynn et al. 2007 (69) Risperidone	Allocation: random Blinding: double Duration: 8 weeks Design: parallel Location: not indicated Setting: inpatient/outpatient	Diagnosis: (DSM-IV) schizophrenia N= 51 Age 18-60 years, mean age 48,8 years. History, duration ill: n. i.	1. Olanzapine: fixed, 15 mg/da.y N= 21 2. Risperidone: fixed 4mg/day. N= 19 3. Haloperidol: fixed 8mg/day. N= 11

Volavka et al. 2002 (13) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 14 weeks. Design: parallel. Location: multicentre. Setting: inpatient	Diagnosis: (DSM-IV) chronic schizophrenia (n=135) or schizoaffective disorder (n=22), suboptimal response to previous treatment, PANSS of 60 or more. N=167. Gender: 133 M, 24 F Age: 18-60 years, mean=40.8 years History: duration ill mean=19.5 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 526.6 mg/day (at the end of the last 6 weeks). N=40. 2. Haloperidol: Flexible dose. Allowed dose range: 10-30 mg/day. Mean dose: 25.7 mg/day (at the end of the last 6 weeks). N=37. 3. Olanzapine: Flexible dose. Allowed dose range: 10-40 mg/day. Mean dose: 30.4 mg/day (at the end of the last 6 weeks). N=39. 4. Risperidone: Flexible dose. Allowed dose range: 4-16 mg/day. Mean dose: 11.6 mg/day (at the end of the last 6 weeks). N=41.
McEvoy et al. 2007 (63) Quetiapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 52 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia (n=231), schizophreniform disorder (n=115) or schizoaffective disorder (n=54), first episode, psychotic symptoms for 1 month to 5 years, PANSS psychosis and CGI-S score of 4 or more. N=400. Gender: 292 M, 108 F. Age: 16-40 years, mean=24.5 years. History: duration ill mean risperidone=1.08 years, age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 11.7 mg/day. N=133. 2. Quetiapine: Flexible dose. Allowed dose range: 100-800 mg/day. Mean dose: 506 mg/day. N=134. 3. Risperidone: Flexible dose. Allowed dose range: 0.5-4 mg/day. Mean dose: 2.4 mg/day. N=133.
Mori et al. 2004 (64) Unclear	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks (last 4 weeks observed). Design: parallel. Location: singlecentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia disorganised (n=23), paranoid (n=10), undifferentiated (n=34). N=77. Gender: 39 M, 38 F. Age: 28-84 years, mean=59.9 years. History: duration ill mean=34.51 years, age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 16.5 mg/day. N=20. 2. Perospirone: Flexible dose. Allowed dose range: 4-48 mg/day. Mean dose: 37.3 mg/day. N=18. 3. Quetiapine: Flexible dose. Allowed dose range: 50-750 mg/day. Mean dose: 432.5 mg/day. N=20. 4. Risperidone: Flexible dose. Allowed dose range: 1-12 mg/day. Mean dose: 7.37 mg/day. N=19.

McEvoy et al. 2006 (65) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 52 weeks (26 weeks observed, because of small group size. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, inadequate efficacy in previous study, clozapine treatment (n=49) was open-label. N=99. Gender: 80 M, 19 F. Age: 18-65 years, mean=39.7 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 23.4 mg/day. N=19. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 642.9 mg/day. N=15. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6 mg/day. Mean dose: 4.8 mg/day. N=16.
Sacchetti et al. 2004 (67) Quetiapine	Allocation: random, no further details. Blinding: single (rater-blinded). Duration: 16 weeks (8 weeks observed). Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia, PANSS total score of 70 or more, PANSS positive subscore of 4 or more on at least 2 items N=75 Age: 18-65 years History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 14.6 mg/day N=25 2. Quetiapine: Flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 602.4 mg/day N=25 3.Risperidone: Flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: 4.3 mg/day N=25
Conley et al. 2001 (70) Risperidone	Allocation: random, stratified by site. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia (n=325) paranoid (n=213) or schizoaffective disorder (n=52), PANSS between 60 and 120. N=377. Gender: 274 M, 103 F. Age: 18-64 years, mean=40.0 years. History: duration ill mean=16 years, age at onset mean=24.1 years.	1. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 13.1 mg/day. N=189. 2. Risperidone: Flexible dose. Allowed dose range: 2-6 mg/day. Mean dose: 4.7 mg/day. N=188.
Dollfus et al. 2005 (71) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia with post-psychotic depression. PANSS positive subscore of 28 or less N=76. Gender: 53 M, 23 F. Age: 18-65 years, mean=39.3 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 5-15 mg/day. Mean dose: n.i. N=36 2. Risperidone: Flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: n.i. N=40.

Gureje et al. 2003 (72) Olanzapine	Allocation: random, computer-generated randomisation. Blinding: double, double-dummy design. Duration: 30 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, schizoaffective disorder or schizophreniform disorder, BPRS total score of 36 or more. N=65. Gender: 38 M, 27 F. Age: 18 years or more, mean =35.2 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 17.2 mg/day. N=32. 2. Risperidone: Flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: 6.6 mg/day. N=33.
Jeste et al. 2003 (73) Risperidone	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient	Diagnosis: (DSM-IV) schizophrenia (n=149) or schizoaffective disorder (n=26), PANSS between 50 and 120. N=176. Gender: 62 M, 113 F. Age: 60 years or more, mean =71.2 years. History: duration ill mean=34.7 years.	1. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 11.1 mg/day. N=89. 2. Risperidone: Flexible dose. Allowed dose range: 1-3 mg/day. Mean dose: 1.9 mg/day. N=87.
Keefe et al. 2006 (74) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 52 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder. N=414. Gender: 282 M, 132 F. Age: 18-55 years, mean=39 years. History: duration ill n.i., age at onset n.i.	1. Haloperidol: Flexible dose. Allowed dose range: 2-19 mg/day. Mean dose: 8.2 mg/day. N=97. 2. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 12.3 mg/day. N=159. 3. Risperidone: Flexible dose. Allowed dose range: 2-10 mg/day. Mean dose: 5.2 mg/day. N=158.
Purdon et al. 2000 (75) Olanzapine	Allocation: random, computer-generated randomisation. Blinding: double, no further details. Duration: 54 weeks. Design: parallel. Location: multicentre. Setting: outpatient.	Diagnosis: (DSM-IV) schizophrenia, in early phase. N=65. Gender: 46 M, 19 F. Age: 18-65 years, mean=28.9 years. History: duration ill mean=2.6 years, age at onset mean=25.5 years.	1. Haloperidol: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 9.70 mg/day. N=23. 2. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 11.00 mg/day. N=21. 3. Risperidone: Flexible dose. Allowed dose range: 4-10 mg/day. Mean dose: 6.00 mg/day. N=21.

Robinson et al. 2005 (76) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 16 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-IV) first episode schizophrenia (n=84), schizophreniform disorder (n=19) or schizoaffective disorder (n=9). N=120. Gender: 78 M, 34 F. Age: 16-40 years, mean=23.3 years . History: duration ill mean=2.2 years, age at onset mean=20.7 years.	1. Olanzapine: Flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 11.8 mg/day. N=60. 2. Risperidone: Flexible dose. Allowed dose range: 1-6 mg/day. Mean dose: 3.9 mg/day. N=60.
Sikich et al. 2004 (77) Neutral sponsor	Allocation: random, computer-generated randomisation. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient	Diagnosis: (K-SADS-P or DSM-IV) schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, major depression with psychotic features or bipolar affective disorder with psychotic features, schizophrenia spectrum (n=26), affective disorders (n=24) subjects selected because of prominent positive psychotic symptoms. N=51. Gender: 30 M, 21 F. Age: 8-19 years, mean=14.8 years. History: duration ill n.i., age at onset mean=12.4 years.	1. Haloperidol: Flexible dose. Allowed dose range: 1-8 mg/day. Mean dose: 5.0 mg/day. N=15. 2. Olanzapine: Flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 12.3 mg/day. N=16. 3. Risperidone: Flexible dose. Allowed dose range: 0.5-6 mg/day. Mean dose: 4.0 mg/day. N=20.
Tran et al. 1997 (78) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 28 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia (n=277), schizophreniform disorder, schizoaffective disorder, BPRS score of 42 or more. N=339. Gender: 220 M, 119 F. Age: 18-65 years, mean=36.21 years. History: duration ill n.i., age at onset mean=23.7 years.	1. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 17.2 mg/day. N=172. 2. Risperidone: Flexible dose. Allowed dose range: 4-12 mg/day. Mean dose: 7.2 mg/day. N=167.
van Nimwegen et al. 2006 (79) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 6 weeks. Design: parallel. Location: n.i. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia, schizophreniform disorder or schizoaffective disorder, all first episode N=131. Gender: 106 M, 25 F. Age: mean =24.75 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 5-20 mg/day. Mean dose: 10.95 mg/day. N=64. 2. Risperidone: Flexible dose. Allowed dose range: 1-5 mg/day. Mean dose: 2.96 mg/day.N=67.
Wang et al. 2006 (80) Risperidone	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 22 weeks (last 12 weeks observed). Design: parallel. Location: multicentre. Setting: outpatient.	Diagnosis: (DSM-IV) schizophrenia (n=24), schizoaffective disorder (n=12). N=36. Gender: 17 M, 19 F. Age: mean=47.0 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: n.i. Mean dose: 13.8 mg/day. N=17. 2. Risperidone: Flexible dose. Allowed dose range: n.i. Mean dose: 5.3 mg/day. N=19.

Lieberman et al. 2005 (58) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Gender: 1080 M, 380 F. Age: 18-65 years, mean=40.6 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.1 mg/day. N=336. 2. Perphenazine: Flexible dose. Allowed dose range: 8-32 mg/day. Mean dose: 20.8 mg/day. N=261. 3. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 543.4 mg/day. N=337. 4. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day. Mean dose: 3.9 mg/day. N=341. 5. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day. Mean dose: 112.8 mg/day. N=185.
Stroup et al. 2006 (59) Neutral sponsor	Allocation: random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re-randomised. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: n.i. Setting: in- and outpatient.	Diagnosis: (DSM-IV) chronic schizophrenia. N=444. Gender: 308 M, 136 F. Age: 18-65 years, mean=40.9 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.5 mg/day. N=68. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.2 mg/day. N=63. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day.Mean dose: 4.1 mg/day. N=70. 4. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day.Mean dose: 115.9 mg/day. N=137.
Svestka et al. 2003 (81) Neutral sponsor	Allocation: random, no further details Blinding: double Duration: 6 weeks Design: parallel Setting: inpatient	Diagnosis: (ICD-10) first episode, acute schizophrenia, schizoaffective disorder; N=42. Age, history, duration ill: no further details .	Olanzapine: no further details Risperidone:no further details
Olanzapine versus Sertindole			
No study			

Olanzapine versus Ziprasidone			
Lieberman et al. 2005 (58) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Gender: 1080 M, 380 F. Age: 18-65 years, mean=40.6 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.1 mg/day. N=336. 2. Perphenazine: Flexible dose. Allowed dose range: 8-32 mg/day. Mean dose: 20.8 mg/day. N=261. 3. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 543.4 mg/day. N=337. 4. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day. Mean dose: 3.9 mg/day. N=341. 5. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day. Mean dose: 112.8 mg/day. N=185.
Stroup et al. 2006 (59) Neutral sponsor	Allocation: random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re-randomised. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: n.i. Setting: in- and outpatient.	Diagnosis: (DSM-IV) chronic schizophrenia. N=444. Gender: 308 M, 136 F. Age: 18-65 years, mean=40.9 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.5 mg/day. N=68. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.2 mg/day. N=63. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day.Mean dose: 4.1 mg/day. N=70. 4. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day. Mean dose: 115.9 mg/day. N=137.
Breier et al. 2005 (82) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 28 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient	Diagnosis: (DSM-IV) schizophrenia, BPRS of 42 or more, CGI-S of 4 or more. N=548. Gender: 352 M, 196 F. Age: 18-75 years, mean=39.2 years. History: duration ill n.i., age at onset mean=23.4 years	1. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 15.27 mg/day. N=277. 2. Ziprasidone: Flexible dose. Allowed dose range: 80-160 mg/day. Mean dose: 115.96 mg/day. N=271.

Kinon et al. 2006 (83) Olanzapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 24 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia or schizoaffective disorder, dominant depressive symptoms, MADRS of 16 or more. N=394. Gender: M n.i., F n.i. Age: 18-60 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Fixed dose: 10, 15 or 20 mg/day. N=202. 2. Ziprasidone: Fixed dose: 80, 120 or 160 mg/day. N=192.
Simpson et al. 2004 (84) Ziprasidone	Allocation: random, no further details. Blinding: double, no further details. Duration: 6 weeks. Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) acute schizophrenia (n=170) or schizoaffective disorder (n=99). CGI-S score of 4 or more, CGI-I score of 3 or more. N=269. Gender: 176 M, 93 F. Age: 18-55 years, mean =37.7 years. History: duration ill mean=14.7, age at onset mean=22.9 years.	1. Olanzapine: Flexible dose. Allowed dose range: 5-15 mg/day. Mean dose: 11.3 mg/day. N=133. 2. Ziprasidone: Flexible dose. Allowed dose range: 80-160 mg/day. Mean dose: 129.9 mg/day. N=136.
Svestka et al. 2005 (85) Neutral sponsor	Allocation: random, no further details Blinding: double Duration: 6 weeks Design: parallel Setting: inpatient	Diagnosis: (ICD-10) acute schizophrenia, schizoaffective disorder. N=42. Age, history, duration ill: not indicated	Olanzapine: no further details Ziprasidone: no further details
Olanzapine versus Zotepine			
No study			

Quetiapine versus Risperidone			
Lieberman et al. 2005 (58) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Gender: 1080 M, 380 F. Age: 18-65 years, mean=40.6 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.1 mg/day. N=336. 2. Perphenazine: Flexible dose. Allowed dose range: 8-32 mg/day. Mean dose: 20.8 mg/day. N=261. 3. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 543.4 mg/day. N=337. 4. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day. Mean dose: 3.9 mg/day. N=341. 5. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day. Mean dose: 112.8 mg/day. N=185.
McEvoy et al. 2006 (65) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 52 weeks (26 weeks observed, because of small group sizes . Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, inadequate efficacy in previous study, clozapine treatment (n=49) was open-label. N=99. Gender: 80 M, 19 F. Age: 18-65 years, mean=39.7 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 23.4 mg/day. N=19. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 642.9 mg/day. N=15. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6 mg/day. Mean dose: 4.8 mg/day. N=16
McEvoy et al. 2007 (63) Quetiapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 52 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia (n=231), schizophreniform disorder (n=115) or schizoaffective disorder (n=54), first episode, psychotic symptoms for 1 month to 5 years, PANSS psychosis and CGI-S score of 4 or more. N=400. Gender: 292 M, 108 F. Age: 16-40 years, mean=24.5 years. History: duration ill mean=1.08 years, age at onset n.i.	1.Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 23.4 mg/day. N=19. 2.Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 642.9 mg/day. N=15. 3.Risperidone: Flexible dose. Allowed dose range: 1.5-6 mg/day. Mean dose: 4.8 mg/day. N=16.

Stroup et al. 2006 (59) Neutral sponsor	Allocation: random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re-randomised. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: n.i. Setting: in- and outpatient.	Diagnosis: (DSM-IV) chronic schizophrenia. N=444. Gender: 308 M, 136 F. Age: 18-65 years, mean=40.9 years. History: duration ill n.i., age at onset n.i.	1.Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.5 mg/day. N=68. 2.Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.2 mg/day. N=63. 3.Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day.Mean dose: 4.1 mg/day. N=70. 4.Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day.Mean dose: 115.9 mg/day. N=137.
Mori et al. 2004 (64) Unclear	Allocation: random, no further details. Blinding: single (rater-blinded). Duration: 16 weeks (8 weeks observed). Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia disorganised (n=23), paranoid (n=10), undifferentiated (n=34). N=77. Gender: 39 M, 38 F. Age: 28-84 years, mean=59.9 years. History: duration ill mean=34.51 years, age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 2.5-20 mg/day. Mean dose: 16.5 mg/day. N=20. 2. Perospirone: Flexible dose. Allowed dose range: 4-48 mg/day. Mean dose: 37.3 mg/day. N=18. 3. Quetiapine: Flexible dose. Allowed dose range: 50-750 mg/day. Mean dose: 432.5 mg/day. N=20. 4. Risperidone: Flexible dose. Allowed dose range: 1-12 mg/day. Mean dose: 7.37 mg/day. N=19
Sacchetti et al. 2004 (67) Quetiapine	Allocation: random, no further details. Blinding: single (rater-blinded). Duration: 16 weeks (8 weeks observed). Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia, PANSS total score of 70 or more, PANSS positive subscore of 4 or more on at least 2 items N=75 Age: 18-65 years History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 10-20 mg/day. Mean dose: 14.6 mg/day. N=25. 2. Quetiapine: Flexible dose. Allowed dose range: 400-800 mg/day. Mean dose: 602.4 mg/day N=25. 3.Risperidone: Flexible dose. Allowed dose range: 4-8 mg/day. Mean dose: 4.3 mg/day. N=25

Conley et al. 2005 (86) Neutral sponsor	Allocation: random, no further details. Blinding: double, no further details. Duration: 12 weeks. Design: parallel. Location: n.i. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia, persistant positive psychotic symptoms, treatment resistance. N=38 (N=27 observed). Gender: n.i. Age: 18-65 years, mean=45.1 years. History: duration ill n.i., age at onset n.i.	1. Fluphenazine: Fixed dose: 12.5 mg/day. N=9 (of observed cases). 2. Quetiapine: Fixed dose: 400 mg/day. N=6 (of observed cases) 3. Risperidone: Fixed dose: 4 mg/day. N=12 (of observed cases).
Potkin et al. 2006 (87) Risperidone	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 6 weeks (2 weeks observed). Design: parallel. Location: multicentre. Setting: inpatient.	Diagnosis: (DSM-IV) schizophrenia (n=341) disorganised, paranoid or undifferentiated or schizoaffective disorder, CGI-S of 5 or more, recent exacerbation. N=382. Gender: 251 M, 131 F. Age: 18-65 years, mean=34.8 years. History: duration ill n.i., age at onset n.i.	1. Quetiapine Flexible dose. Allowed dose range: 50-800 mg/day. Mean dose: 523.8 mg/day (after 2 weeks). (579.5 mg/day, after 6 weeks). N=156. 2. Risperidone: Flexible dose. Allowed dose range: 1-6 mg/day. Mean dose: 4.32 mg/day (after 2 weeks). (4.7 mg/day, after 6 weeks). N=153.
Riedel et al. 2005 (88) Quetiapine	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 12 weeks. Design: parallel. Location: n.i. Setting: partially in- and outpatient	Diagnosis: (DSM-IV or ICD-10) schizophrenia, predominant negative symptoms, CGI of 4 or more, PANSS negative subscore of 21 or more. N=44. Gender: 27 M, 17 F. Age: mean=35 years, History: duration ill mean 4 years, age at onset: mean=31.1 years.	1. Quetiapine: Flexible dose. Allowed dose range: 50-800 mg/day. Mean dose: 589.7 mg/day. N=22. 2. Risperidone: Flexible dose. Allowed dose range: 2-8 mg/day. Mean dose: 4.9 mg/day. N=22.
Atmaca et al. 2003 (37) Neutral sponsor	Allocation: random, no further details. Blinding: single, rater-blinded. Duration: 6 weeks. Design: parallel. Location: singlecentre. Setting: inpatient	Diagnosis: (DSM-IV) schizophrenia. N=56. Gender: 24 M, 29 F. Age: 19-46 years, mean=30.8 years. History: duration ill mean 6.1 years, age at onset n.i.	1. Clozapine: Flexible dose. Allowed dose range: n.i. Mean dose: 207.1 mg/day. N=14. 2. Olanzapine: Flexible dose. Allowed dose range: n.i. Mean dose: 15.7 mg/day. N=14. 3. Quetiapine: Flexible dose. Allowed dose range: n.i. Mean dose: 535.7 mg/day. N=14. 4. Risperidone: Flexible dose. Allowed dose range: n.i. Mean dose: 6.7 mg/day. N=14.

Zhong et al. 2006 (89) Quetiapine	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient, initially inpatient.	Diagnosis: (DSM-IV) schizophrenia, PANSS of 60 or more. N=673. Gender: 510 M, 163 F. Age: 18-65 years, mean=39.9 years. History: duration ill n.i., age at onset n.i.	1. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day.Mean dose: 525 mg/day. N=338. 2. Risperidone: Flexible dose. Allowed dose range: 2-8 mg/day. Mean dose: 5.2 mg/day. N=335.
Quetiapine versus Sertindole			
No Study			
Quetiapine versus Ziprasidone			
Lieberman et al. 2005 (58) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Gender: 1080 M, 380 F. Age: 18-65 years, mean=40.6 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.1 mg/day. N=336. 2. Perphenazine: Flexible dose. Allowed dose range: 8-32 mg/day. Mean dose: 20.8 mg/day. N=261. 3. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 543.4 mg/day. N=337. 4. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day. Mean dose: 3.9 mg/day. N=341. 5. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day. Mean dose: 112.8 mg/day. N=185.

Stroup et al. 2006 (59) Neutral sponsor	Allocation: random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re-randomised. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: n.i. Setting: in- and outpatient.	Diagnosis: (DSM-IV) chronic schizophrenia. N=444. Gender: 308 M, 136 F. Age: 18-65 years, mean=40.9 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.5 mg/day. N=68. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.2 mg/day. N=63. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day.Mean dose: 4.1 mg/day. N=70. 4. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day.Mean dose: 115.9 mg/day. N=137.
Quetiapine versus Zotepine			
No study			
Risperidone versus Sertindole			
Azorin et al. 2006 (90) Sertindole	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, catatonic (n=6), disorganised (n=48), paranoid (n=100) or undifferentiated (n=32), at least moderately ill on CGI-S. N=187. Gender: 113 M, 73 F. Age: 18-65 years. History: duration ill n.i., age at onset n.i.	1. Risperidone: Flexible dose. Allowed dose range: 4-10 mg/day. Mean dose: 6.6 mg/day. N=89. 2. Sertindole: Flexible dose. Allowed dose range: 12-24 mg/day. Mean dose: 16.2 mg/day. N=98.
Kane et al. 2005 (12) Sertindole	Allocation: random, no further details. Blinding: double, no further details. Duration: 12 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-IV) schizophrenia, treatment resistance, PANSS total score of 60 or more. N=321. Gender: 250 M, 71 F. Age: 18-55 years, mean=38.8 years. History: duration ill n.i., age at onset mean=22.1 years.	1. Risperidone: Flexible dose. Allowed dose range: 6-12 mg/day. Mean dose: 9.0 mg/day. N=105. 2. Sertindole: Flexible dose.Allowed dose range: 12-24 mg/day. Mean dose: 18.1 mg/day. N=216.

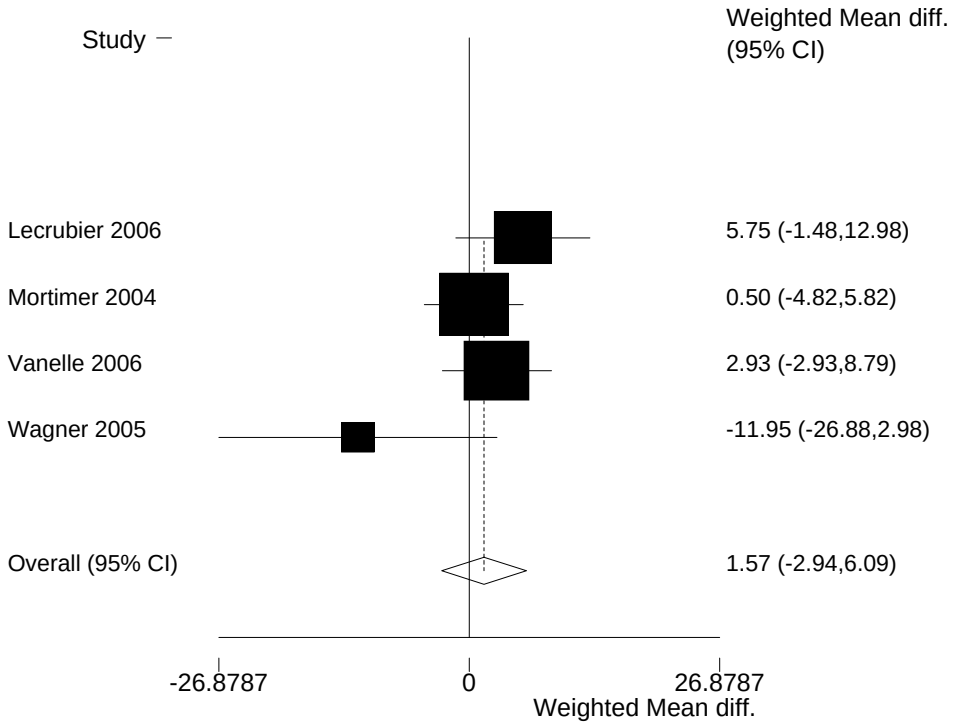
Risperidone versus Ziprasidone			
Lieberman et al. 2005 (58) Neutral sponsor	Allocation: random, no further details. Blinding: double, identical capsules. Duration: 78 weeks. Design: parallel. Location: multicentre. Setting: in- and outpatient.	Diagnosis: (DSM-IV) schizophrenia, previously more than one schizophrenic episode, responder. N=1493. Gender: 1080 M, 380 F. Age: 18-65 years, mean=40.6 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.1 mg/day. N=336. 2. Perphenazine: Flexible dose. Allowed dose range: 8-32 mg/day. Mean dose: 20.8 mg/day. N=261. 3. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 543.4 mg/day. N=337. 4. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day. Mean dose: 3.9 mg/day. N=341. 5. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day. Mean dose: 112.8 mg/day. N=185.
Stroup et al. 2006 (59) Neutral sponsor	Allocation: random, 2 steps of randomisation before and after availability of ziprasidone, subjects received other medication than in previous phase 1 treatment. Re-randomised. Blinding: double, identical capsules. Duration: 26 weeks. Design: parallel. Location: n.i. Setting: in- and outpatient.	Diagnosis: (DSM-IV) chronic schizophrenia. N=444. Gender: 308 M, 136 F. Age: 18-65 years, mean olanzapine=40.9 years. History: duration ill n.i., age at onset n.i.	1. Olanzapine: Flexible dose. Allowed dose range: 7.5-30 mg/day. Mean dose: 20.5 mg/day. N=68. 2. Quetiapine: Flexible dose. Allowed dose range: 200-800 mg/day. Mean dose: 565.2 mg/day.N=63. 3. Risperidone: Flexible dose. Allowed dose range: 1.5-6.0 mg/day. Mean dose: 4.1 mg/day. N=70. 4. Ziprasidone: Flexible dose. Allowed dose range: 40-160 mg/day.Mean dose: 115.9 mg/day. N=137.
Addington et al. 2004 (91) Ziprasidone	Allocation: random, no further details. Blinding: double, no further details. Duration: 8 weeks. Design: parallel. Location: multicentre. Setting: n.i.	Diagnosis: (DSM-III-R) schizophrenia (n=260) or schizoaffective disorder (n=36), acute exacerbation, PANSS total score of 60 or more. N=296. Gender: 215 M, 81 F. Age: 18-64 years. History: duration ill n.i., age at onset mean=24.9 years.	1. Risperidone: Flexible dose. Allowed dose range: 6-10 mg/day. Mean dose: 7.4 mg/day. N=147. 2. Ziprasidone: Flexible dose. Allowed dose range: 80-160 mg/day. Mean dose: 114.2 mg/day. N=149.

Risperidone versus Zotepine
No study
Sertindole versus Ziprasidone
No Study
Sertindole versus Zotepine
No study
Ziprasidone versus Zotepine
No study

N= number of patients, M = male, F = female, PANSS = Positive and Negative Syndrome Scale, BPRS = Brief Psychiatric Rating Scale, MADRS = Montgomery Asberg Depression Rating Scale, SANS = Scale for the Assessment of Negative Symptoms, CGI = Clinical Global Impression, EPS = extrapyramidal symptoms, ICD 9/10 = International Classification of Diseases, 9th/10th Revision, DSM-III-R, -IV = different versions of the Diagnostic and Statistical Manual of Mental Disorders, CCMD-2, -3 = Chinese Classification of Mental Disorders $2^{nd}/3^{rd}$ Revision, n.i. = not indicated

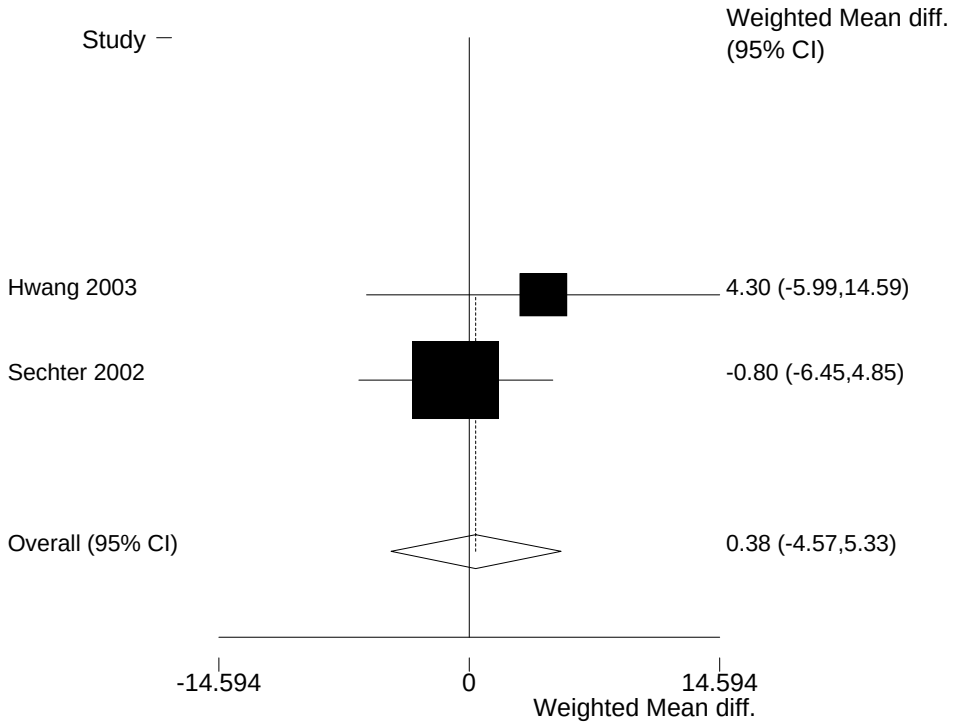
Figures I. 1. a – I. 8. e : PANSS total score (weighted mean difference, WMD)

Figure I. 1. a: PANSS total score - Amisulpride versus Olanzapine




```
N=701
Heterogeneity chi-squared =   4.78 (d.f. = 3) p = 0.189
Estimate of between-study variance Tau-squared =  7.7295
Test of WMD=0 : z= 0.68 p = 0.494
```

Figure I. 1. b: PANSS total score - Amisulpride versus Risperidone

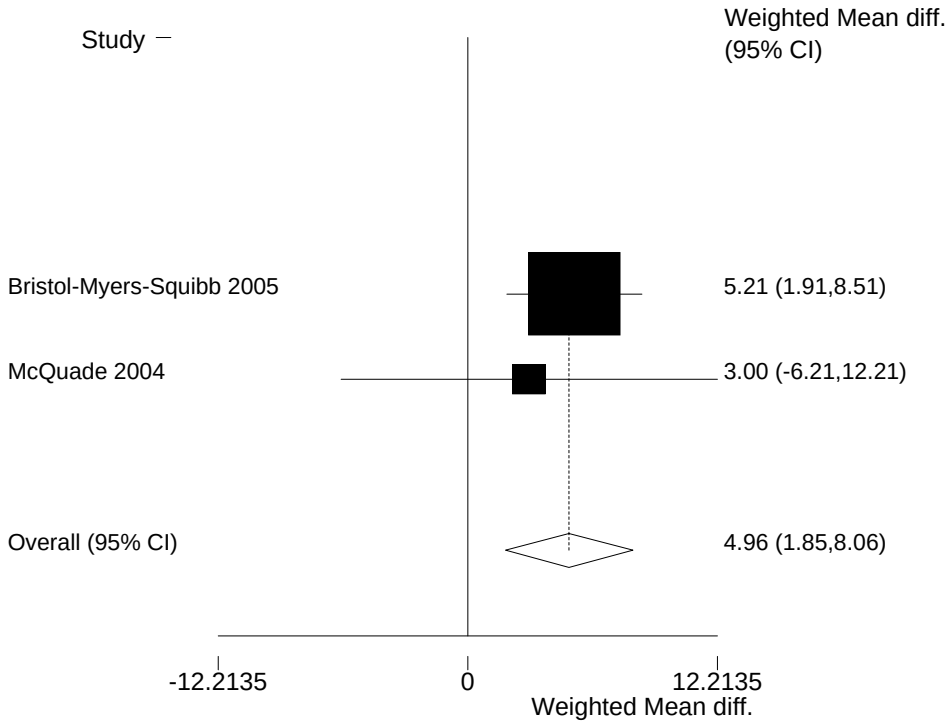



```
N=291
Heterogeneity chi-squared =   0.72 (d.f. = 1) p = 0.395
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.15 p = 0.880
```

Figure I. 1. c: PANSS total score - Amisulpride versus Ziprasidone

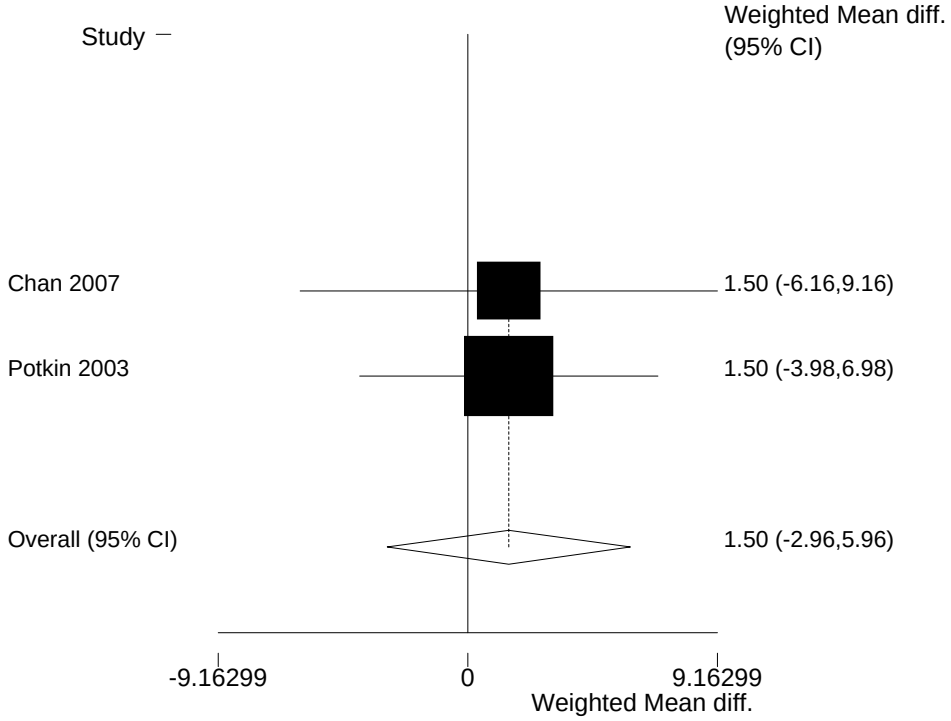
```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Olie 2006        |     -2.7    -8.94949   3.54949
-----------------+---------------------------------
  I-V pooled WMD |     -2.7    -8.94949   3.54949
-----------------+---------------------------------
N=122
Test of WMD=0 : z= 0.85 p = 0.397
```

Figure I. 2. a: PANSS total score - Aripiprazole versus Olanzapine



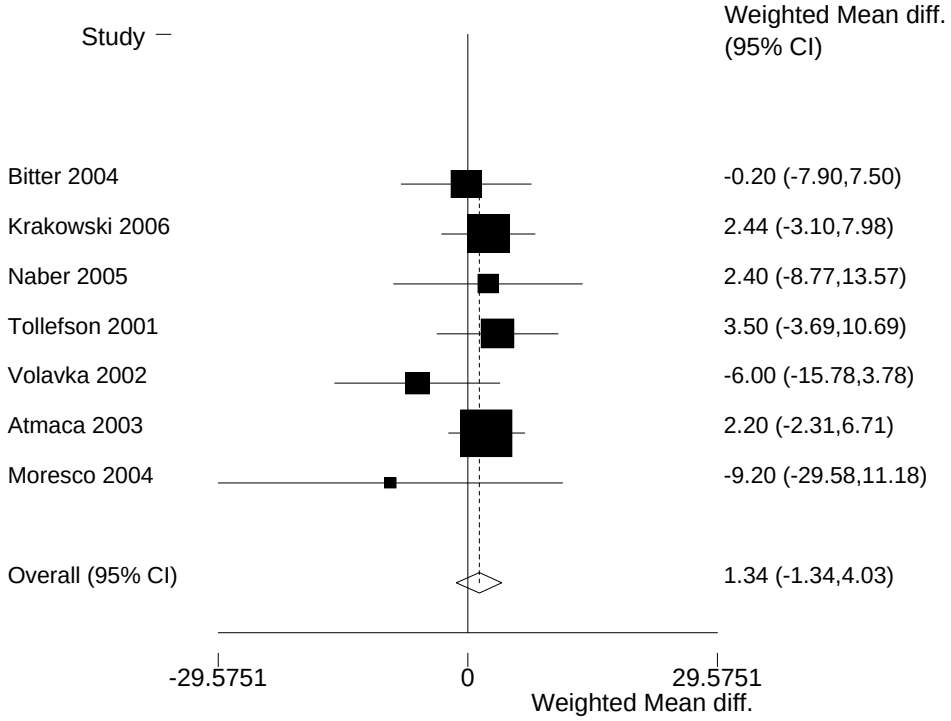
N=794
Heterogeneity chi-squared = 0.20 (d.f. = 1) p = 0.658
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 3.13 p = 0.002

Figure I. 2. b: PANSS total score - Aripiprazole versus Risperidone



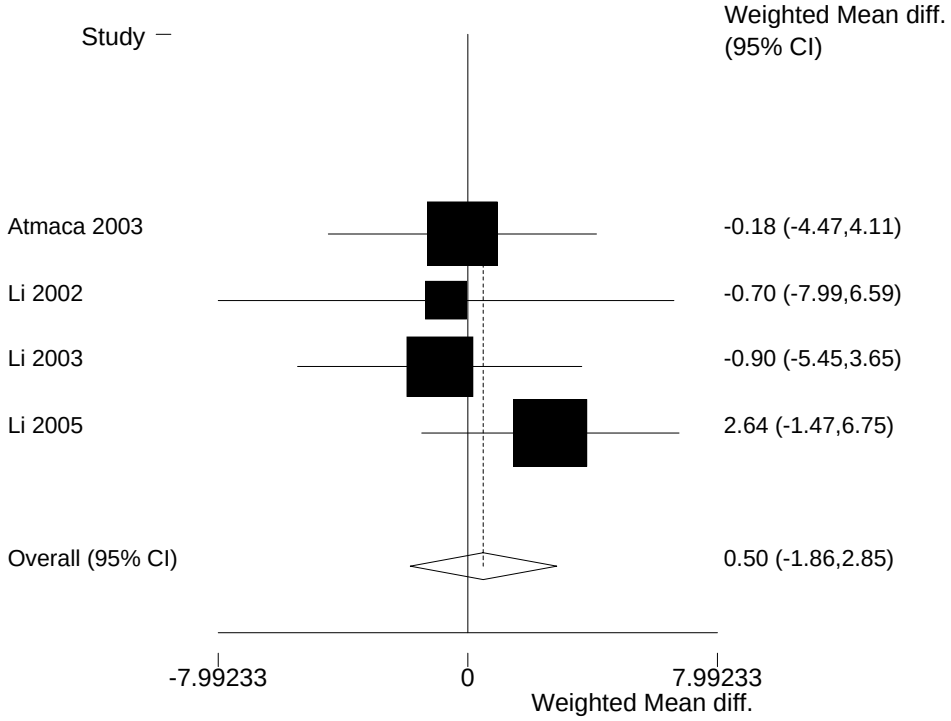

```
N=372
Heterogeneity chi-squared =   0.00 (d.f. = 1) p = 1.000
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.66 p = 0.509
```

Figure I. 3. a: PANSS total score - Clozapine versus Olanzapine



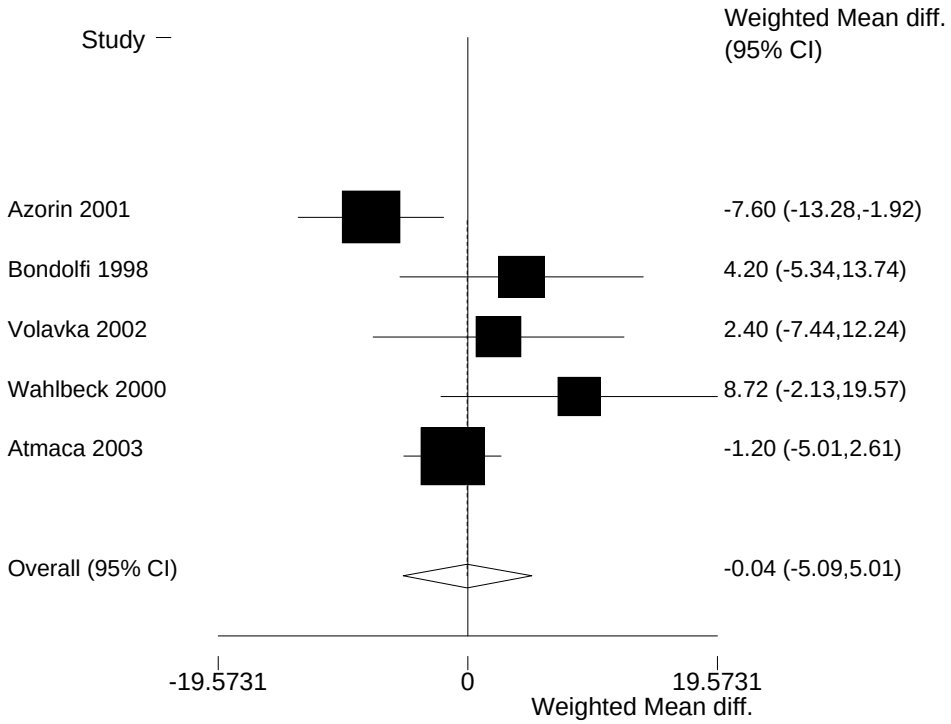
N=619
Heterogeneity chi-squared = 4.02 (d.f. = 6) p = 0.674
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.98 p = 0.327

Figure I. 3. b: PANSS total score - Clozapine versus Quetiapine




```
N=232
Heterogeneity chi-squared =   1.61 (d.f. = 3) p = 0.658
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.41 p = 0.679
```

Figure I. 3. c: PANSS total score - Clozapine versus Risperidone

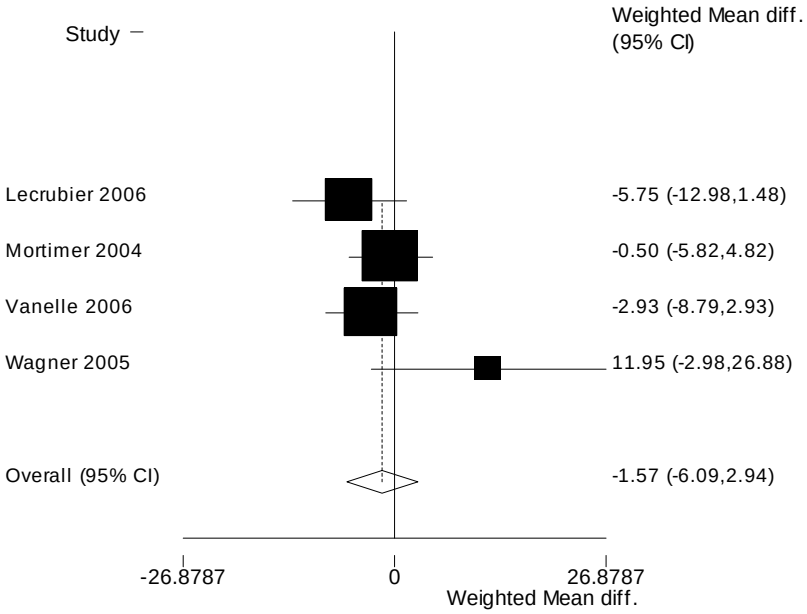



```
N=466
Heterogeneity chi-squared =   9.81 (d.f. = 4) p = 0.044
Estimate of between-study variance Tau-squared = 18.1717
Test of WMD=0 : z= 0.02 p = 0.987
```

Figure I. 3. d: PANSS total score - Clozapine versus Ziprasidone

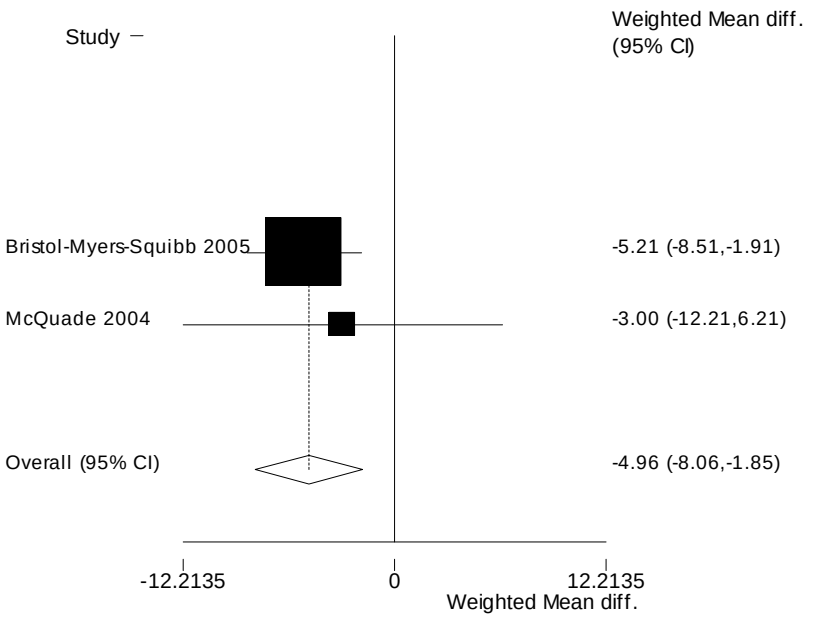
```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Sacchetti 2006   |       .5     -6.7187    7.7187
-----------------+---------------------------------
  I-V pooled WMD |       .5     -6.7187    7.7187
-----------------+---------------------------------
N=146
Test of WMD=0 : z= 0.14 p = 0.892
```

Figure I. 4. a: PANSS total score - Olanzapine versus Amisulpride



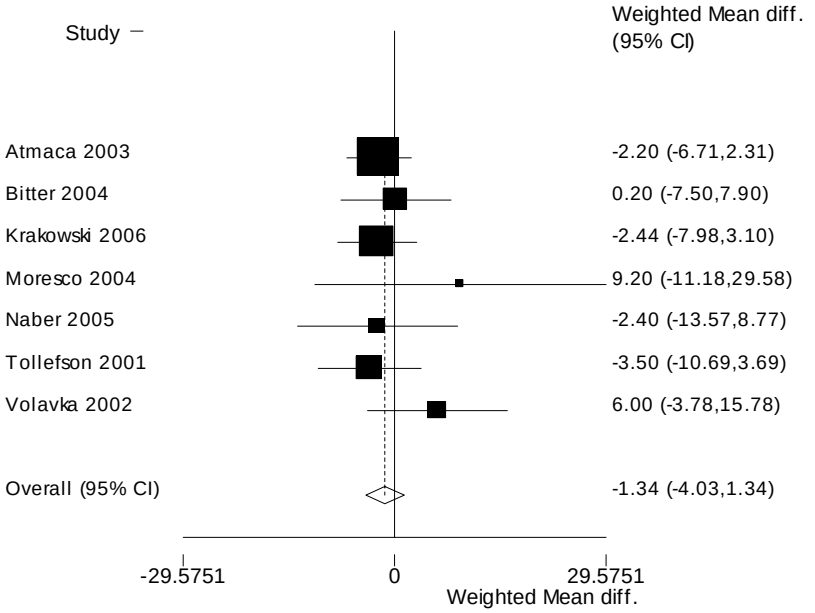
N=701
Heterogeneity chi-squared = 4.78 (d.f. = 3) p = 0.189
Estimate of between-study variance Tau-squared = 7.7295
Test of WMD=0 : z= 0.68 p = 0.494

Figure I. 4. b: PANSS total score - Olanzapine versus Aripiprazole



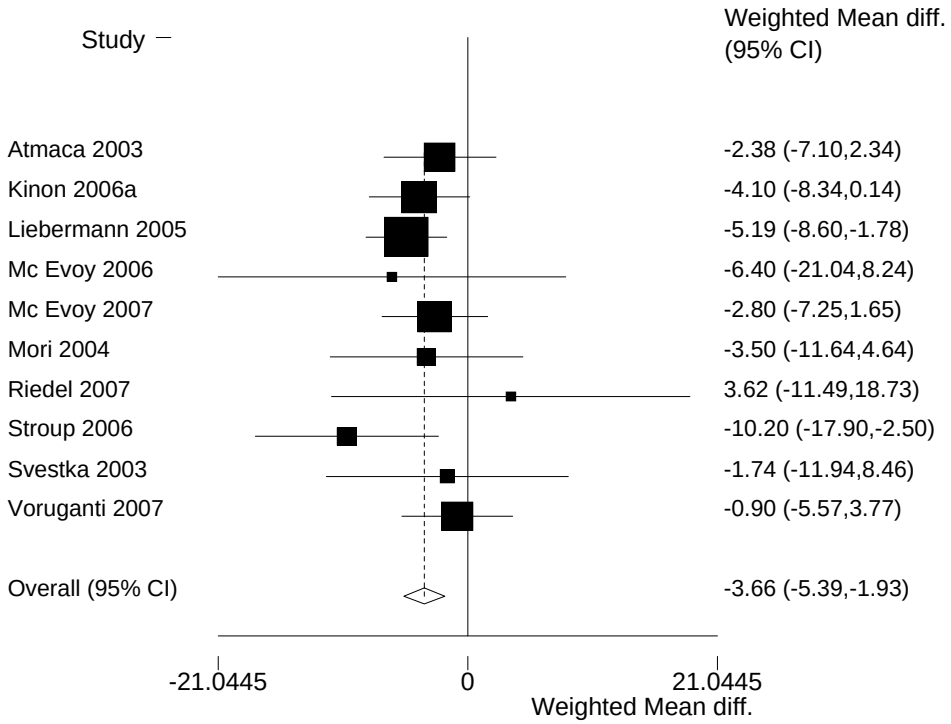
N=794
Heterogeneity chi-squared = 0.20 (d.f. = 1) p = 0.658
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 3.13 p = 0.002

Figure I. 4. c: PANSS total score - Olanzapine versus Clozapine



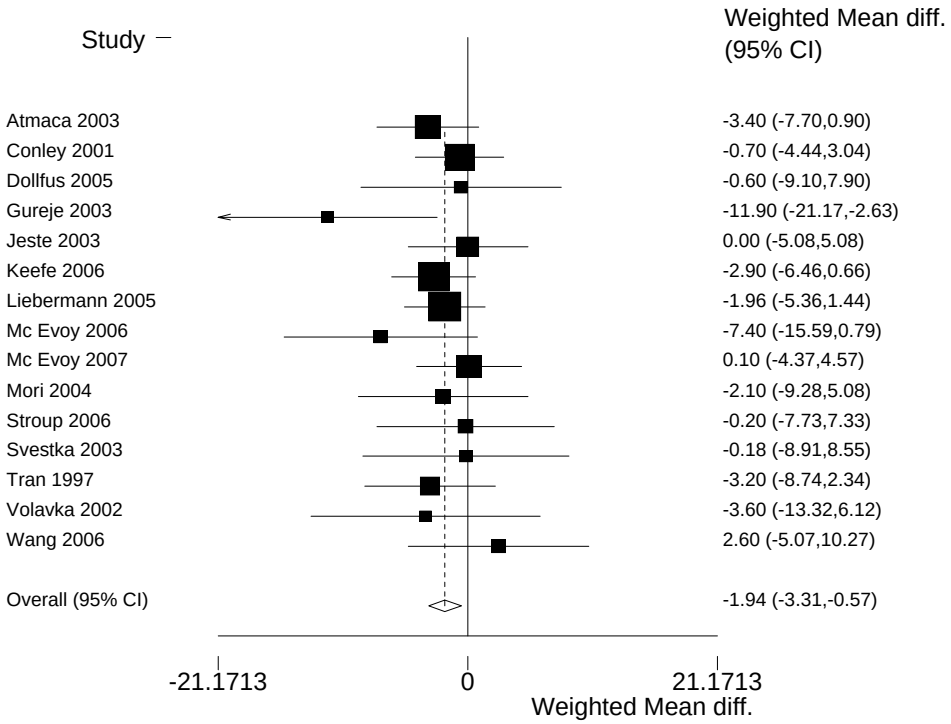
N=619
Heterogeneity chi-squared = 4.02 (d.f. = 6) p = 0.674
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.98 p = 0.327

Figure I. 4. d: PANSS total score - Olanzapine versus Quetiapine



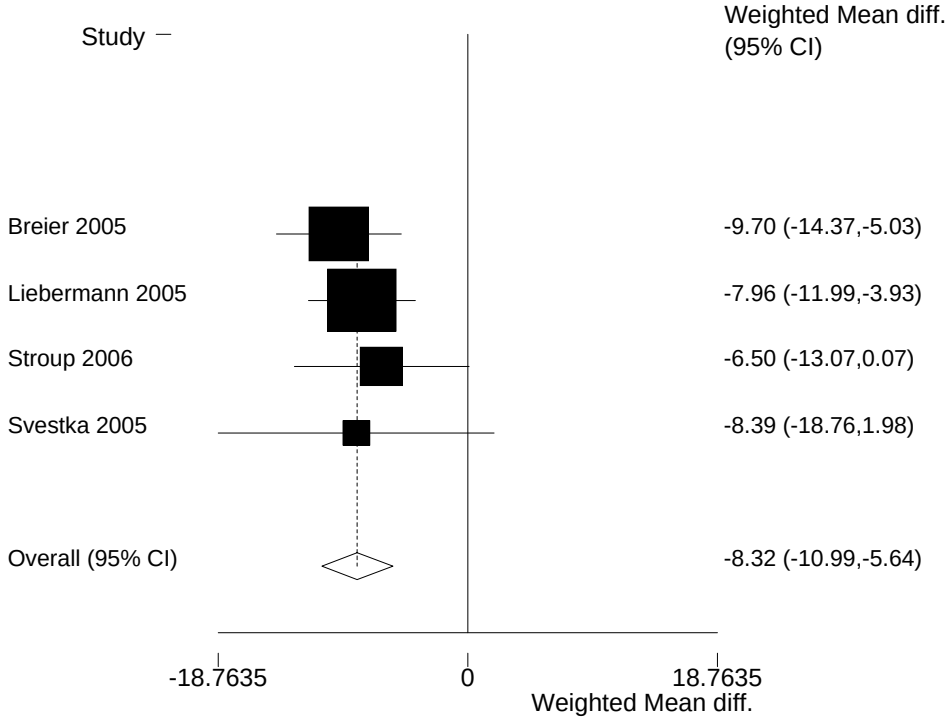
N=1449
Heterogeneity chi-squared = 6.52 (d.f. = 9) p = 0.687
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 4.14 p = 0.000

Figure I. 4. e: PANSS total score - Olanzapine versus Risperidone



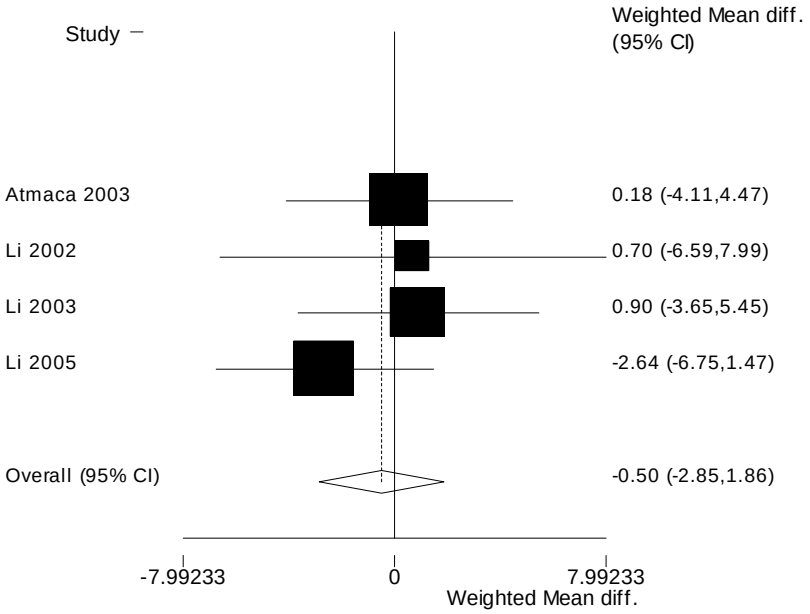
N=2404
Heterogeneity chi-squared = 10.76 (d.f. = 14) p = 0.704
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 2.77 p = 0.006

Figure I. 4. f: PANSS total score - Olanzapine versus Ziprasidone



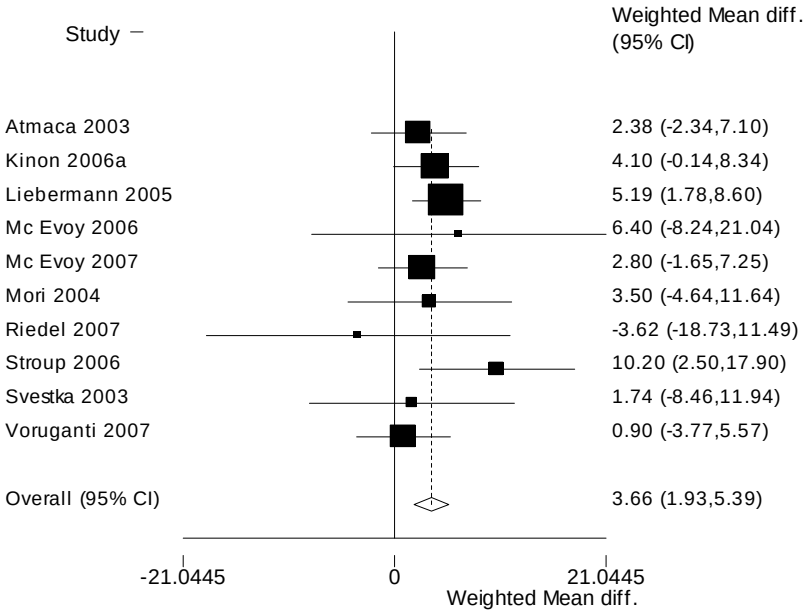

```
N=1291
Heterogeneity chi-squared =   0.66 (d.f. = 3) p = 0.882
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 6.09 p = 0.000
```

Figure I. 5. a: PANSS total score - Quetiapine versus Clozapine



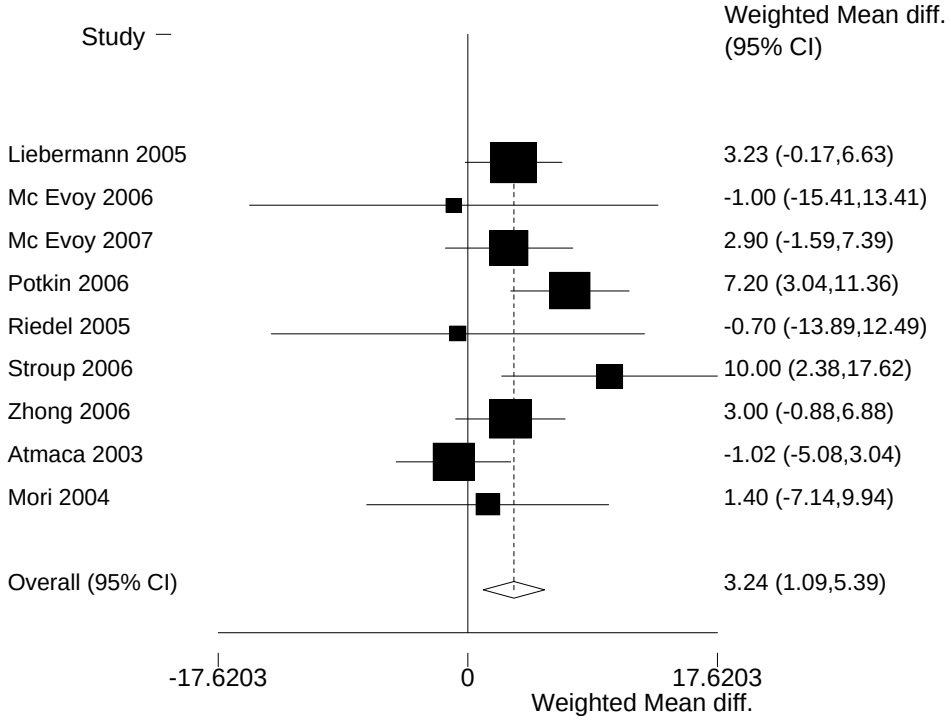
N=232
Heterogeneity chi-squared = 1.61 (d.f. = 3) p = 0.658
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.41 p = 0.679

Figure I. 5. b: PANSS total score - Quetiapine versus Olanzapine



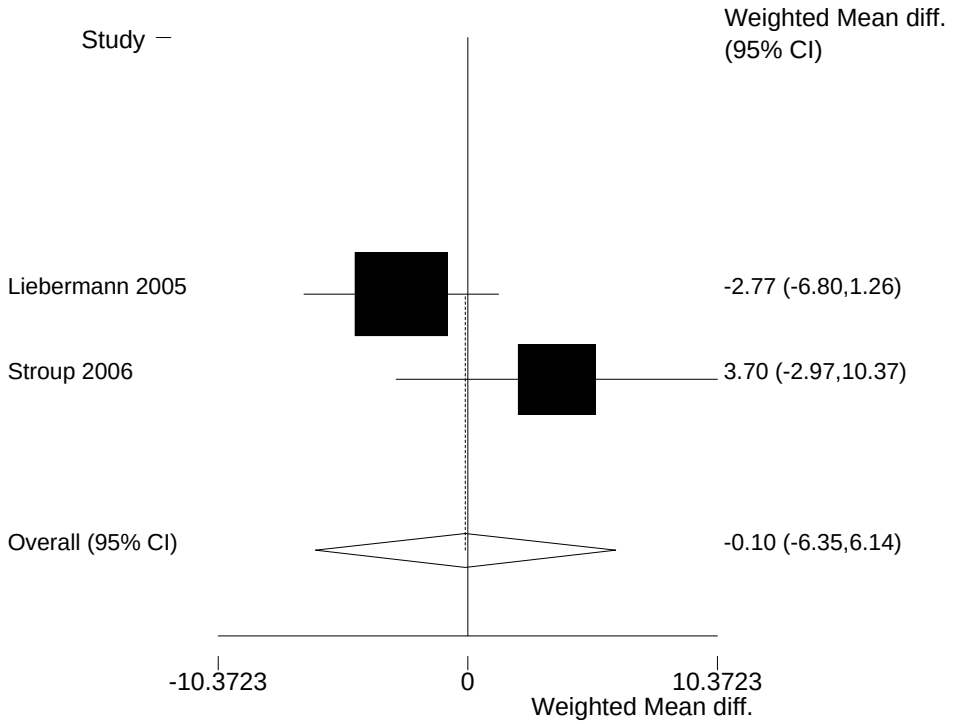
N=1449
Heterogeneity chi-squared = 6.52 (d.f. = 9) p = 0.687
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 4.14 p = 0.000

Figure I. 5. c: PANSS total score - Quetiapine versus Risperidone



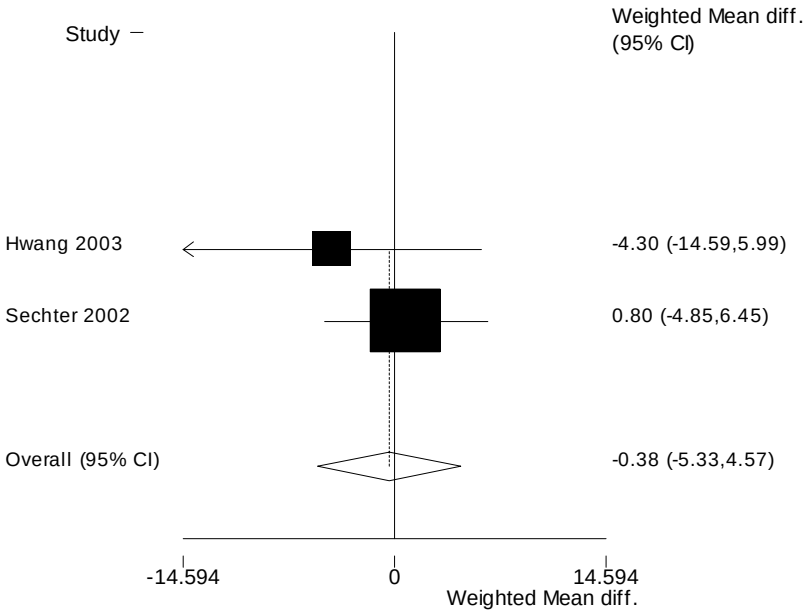

```
N=1953
Heterogeneity chi-squared =  11.64 (d.f. = 8) p = 0.168
Estimate of between-study variance Tau-squared =  3.1314
Test of WMD=0 : z= 2.95 p = 0.003
```

Figure I. 5. d: PANSS total score - Quetiapine versus Ziprasidone



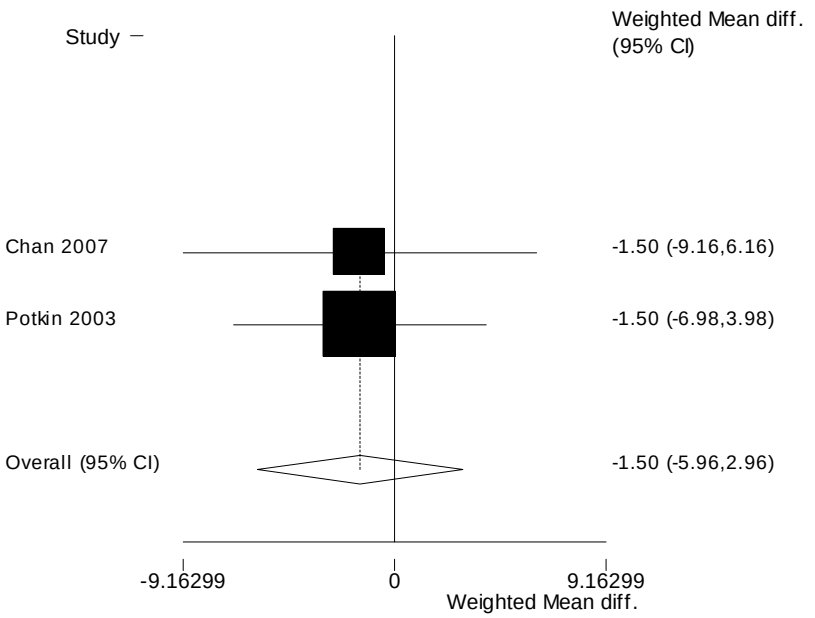
N=710
Heterogeneity chi-squared = 2.65 (d.f. = 1) p = 0.104
Estimate of between-study variance Tau-squared = 13.0191
Test of WMD=0 : z= 0.03 p = 0.974

Figure I. 6. a: PANSS total score - Risperidone versus Amisulpride



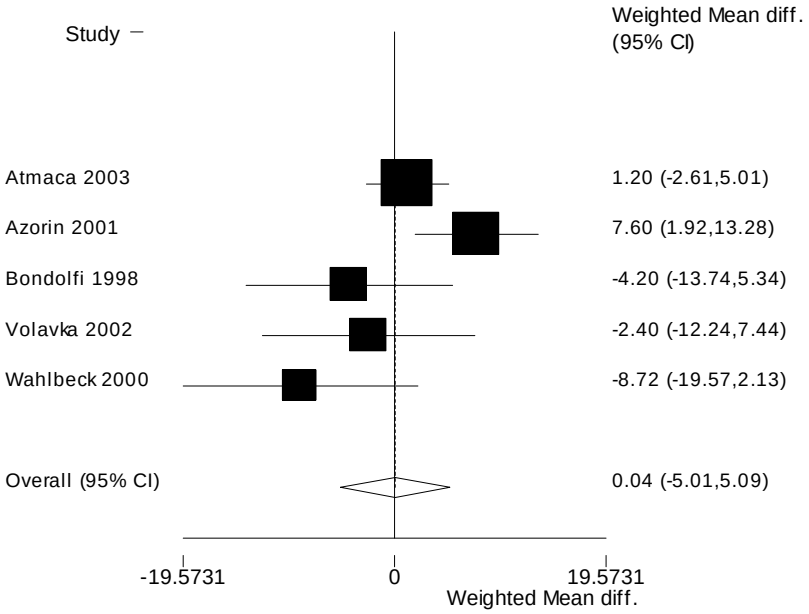
N=291
Heterogeneity chi-squared = 0.72 (d.f. = 1) p = 0.395
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.15 p = 0.880

Figure I. 6. b: PANSS total score - Risperidone versus Aripiprazole



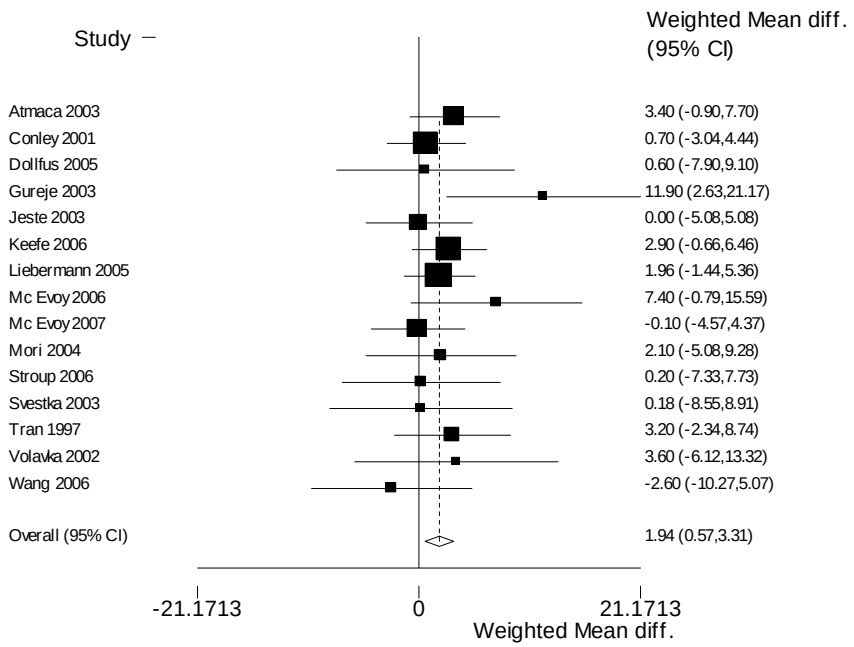
N=372
Heterogeneity chi-squared = 0.00 (d.f. = 1) p = 1.000
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.66 p = 0.509

Figure I. 6. c: PANSS total score - Risperidone versus Clozapine



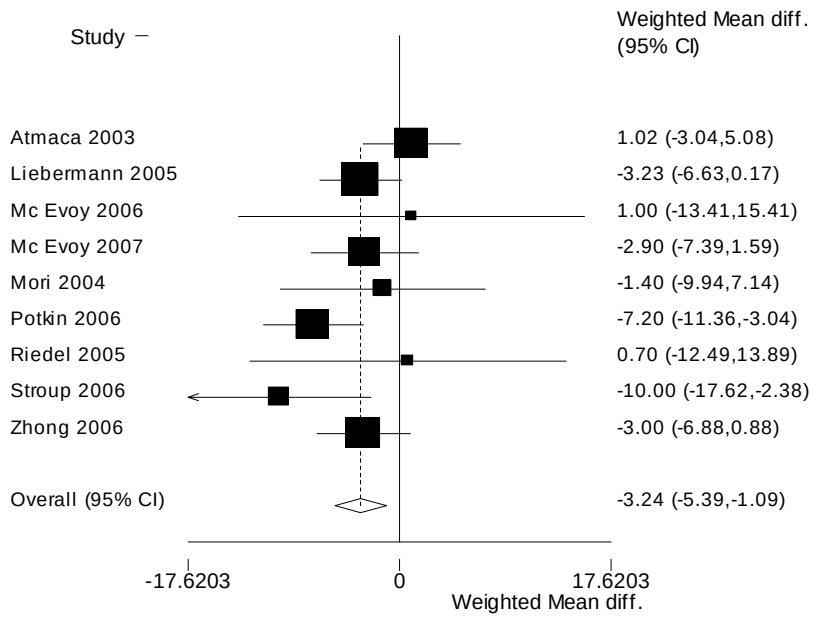
N=466
Heterogeneity chi-squared = 9.81 (d.f. = 4) p = 0.044
Estimate of between-study variance Tau-squared = 18.1717
Test of WMD=0 : z= 0.02 p = 0.987

Figure I. 6. d: PANSS total score - Risperidone versus Olanzapine



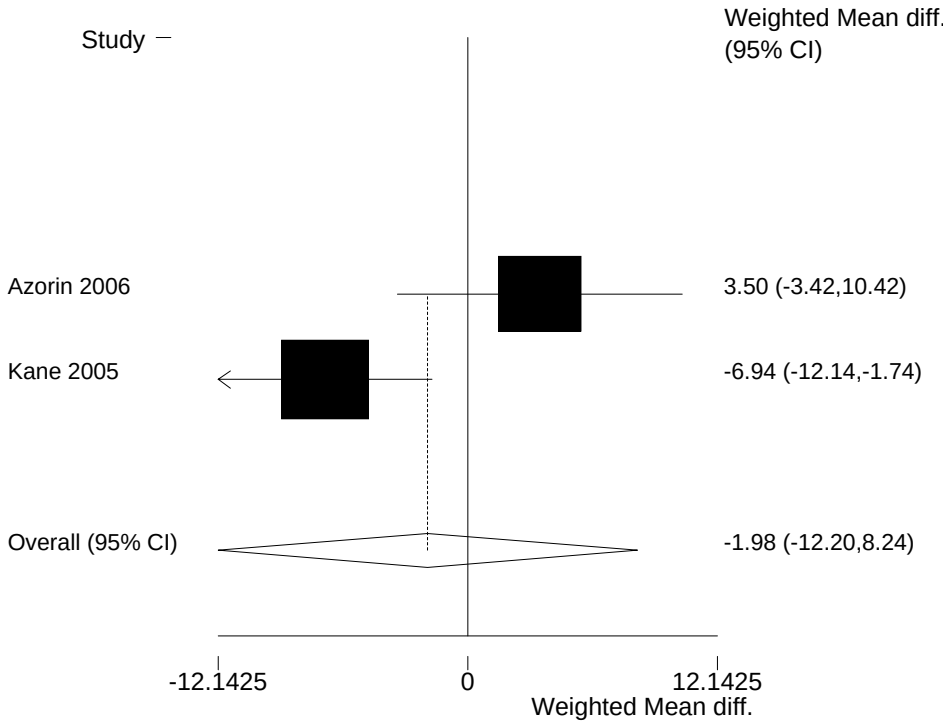
N=2404
Heterogeneity chi-squared = 10.76 (d.f. = 14) p = 0.704
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 2.77 p = 0.006

Figure I. 6. e: PANSS total score - Risperidone versus Quetiapine



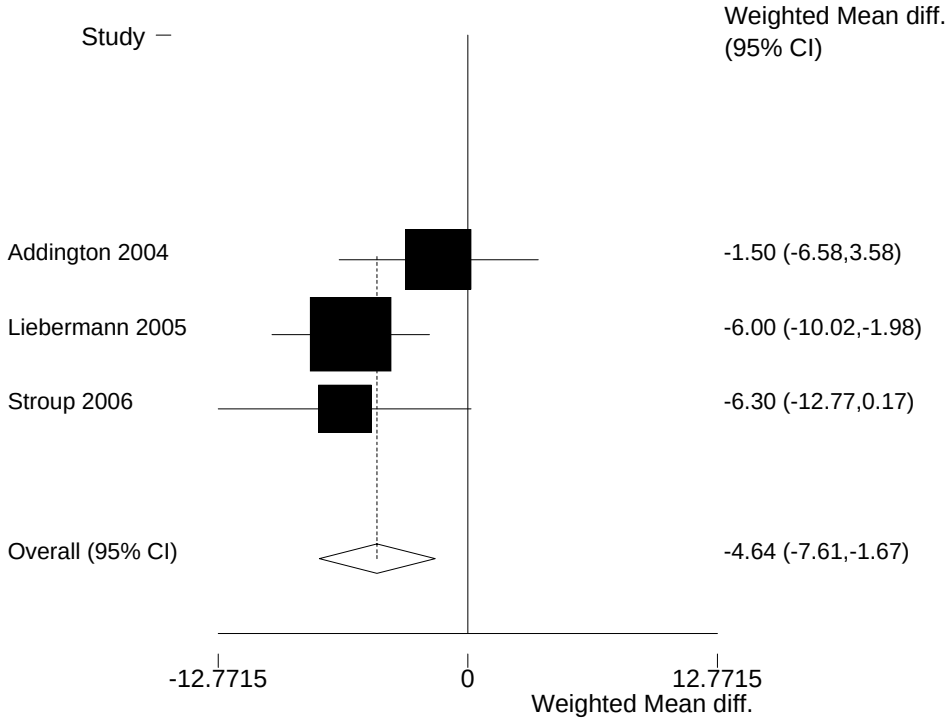
N=1953
Heterogeneity chi-squared = 11.64 (d.f. = 8) p = 0.168
Estimate of between-study variance Tau-squared = 3.1314
Test of WMD=0 : z= 2.95 p = 0.003

Figure I. 6. f: PANSS total score - Risperidone versus Sertindole



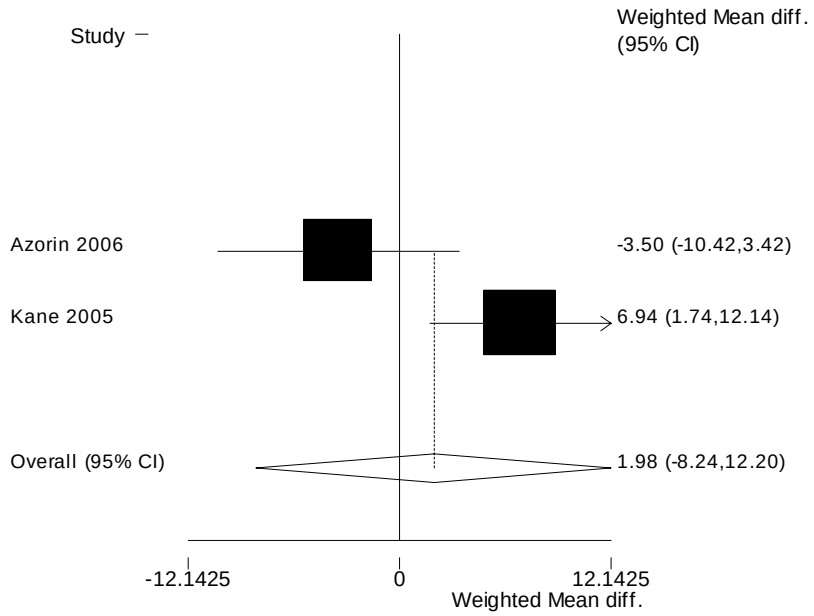
N=493
Heterogeneity chi-squared = 5.59 (d.f. = 1) p = 0.018
Estimate of between-study variance Tau-squared = 44.7410
Test of WMD=0 : z= 0.38 p = 0.704

Figure I. 6. g: PANSS total score - Risperidone versus Ziprasidone



N=1016
Heterogeneity chi-squared = 2.16 (d.f. = 2) p = 0.340
Estimate of between-study variance Tau-squared = 0.5305
Test of WMD=0 : z= 3.06 p = 0.002

Figure I. 7. a: PANSS total score - Sertindole versus Risperidone




```
N=493
Heterogeneity chi-squared =   5.59 (d.f. = 1) p = 0.018
Estimate of between-study variance Tau-squared = 44.7410
Test of WMD=0 : z= 0.38 p = 0.704
```

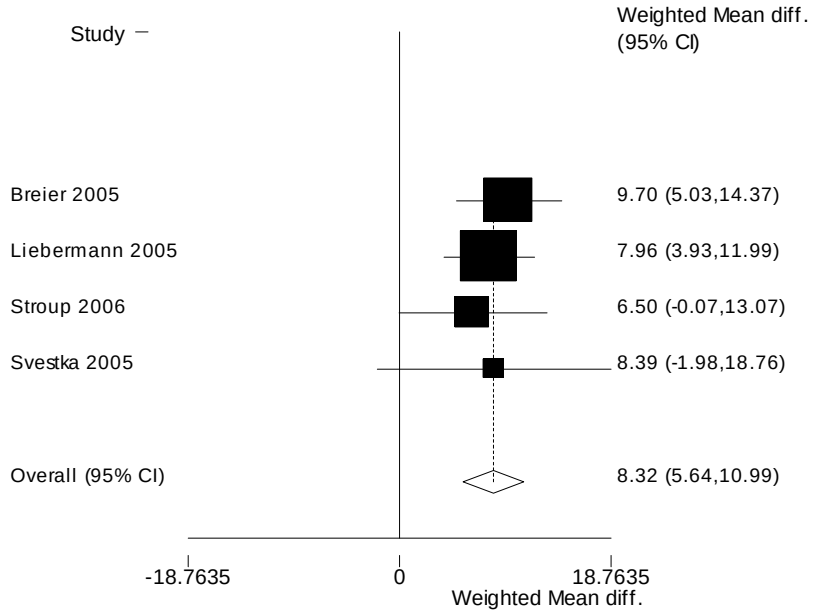
Figure I. 8. a: PANSS total score - Ziprasidone versus Amisulpride

```
           Study |       WMD  [95% Conf. Interval]
-----------------+-------------------------------------
Olie 2006        |      2.7    -3.54949   8.94949
-----------------+-------------------------------------
  I-V pooled WMD |      2.7    -3.54949   8.94949
-----------------+-------------------------------------
N=122
Test of WMD=0 : z= 0.85 p = 0.397
```

Figure I. 8. b: PANSS total score - Ziprasidone versus Clozapine

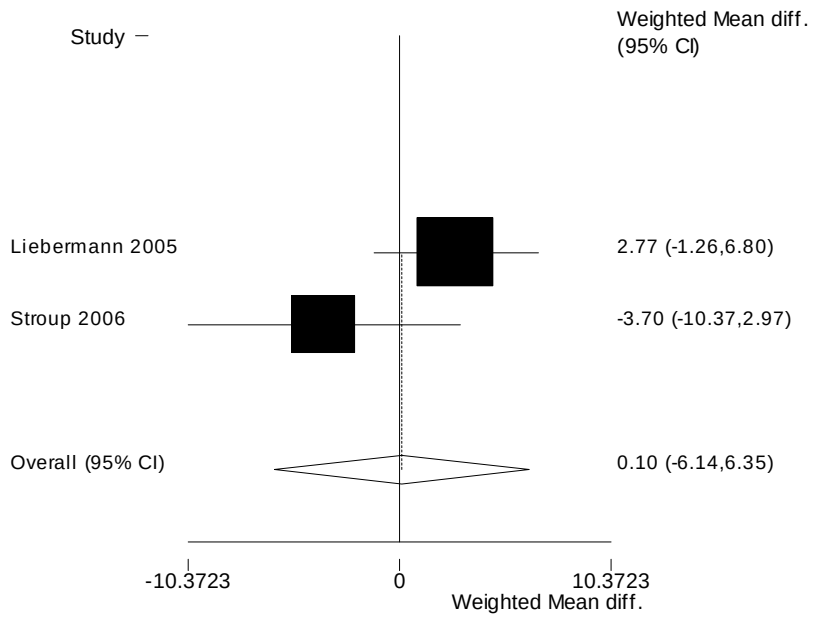
```
           Study |       WMD  [95% Conf. Interval]
-----------------+-------------------------------------
Sacchetti 2006   |      -.5     -7.7187    6.7187
-----------------+-------------------------------------
  I-V pooled WMD |      -.5     -7.7187    6.7187
-----------------+-------------------------------------
N=146
Test of WMD=0 : z= 0.14 p = 0.892
```

Figure I. 8. c: PANSS total score - Ziprasidone versus Olanzapine



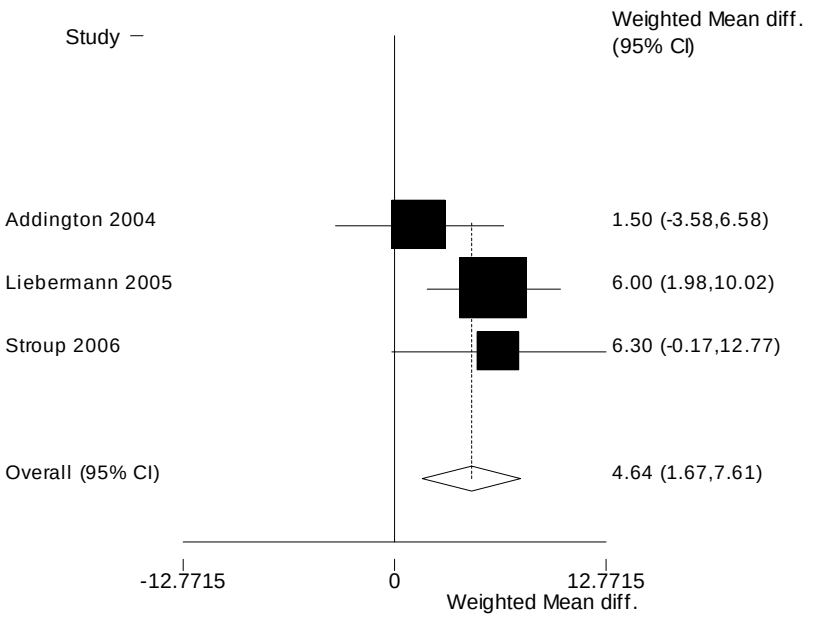
N=1291
Heterogeneity chi-squared = 0.66 (d.f. = 3) p = 0.882
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 6.09 p = 0.000

Figure I. 8. d: PANSS total score - Ziprasidone versus Quetiapine



N=710
Heterogeneity chi-squared = 2.65 (d.f. = 1) p = 0.104
Estimate of between-study variance Tau-squared = 13.0191
Test of WMD=0 : z= 0.03 p = 0.974

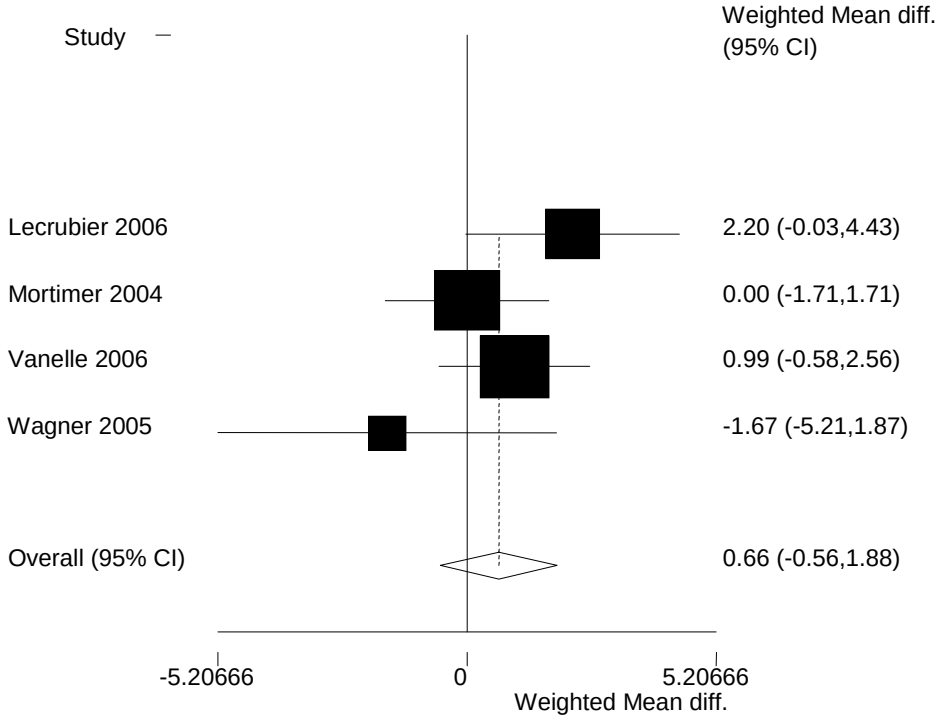
Figure I. 8. e: PANSS total score - Ziprasidone versus Risperidone



N=1016
Heterogeneity chi-squared = 2.16 (d.f. = 2) p = 0.340
Estimate of between-study variance Tau-squared = 0.5305
Test of WMD=0 : z= 3.06 p = 0.002

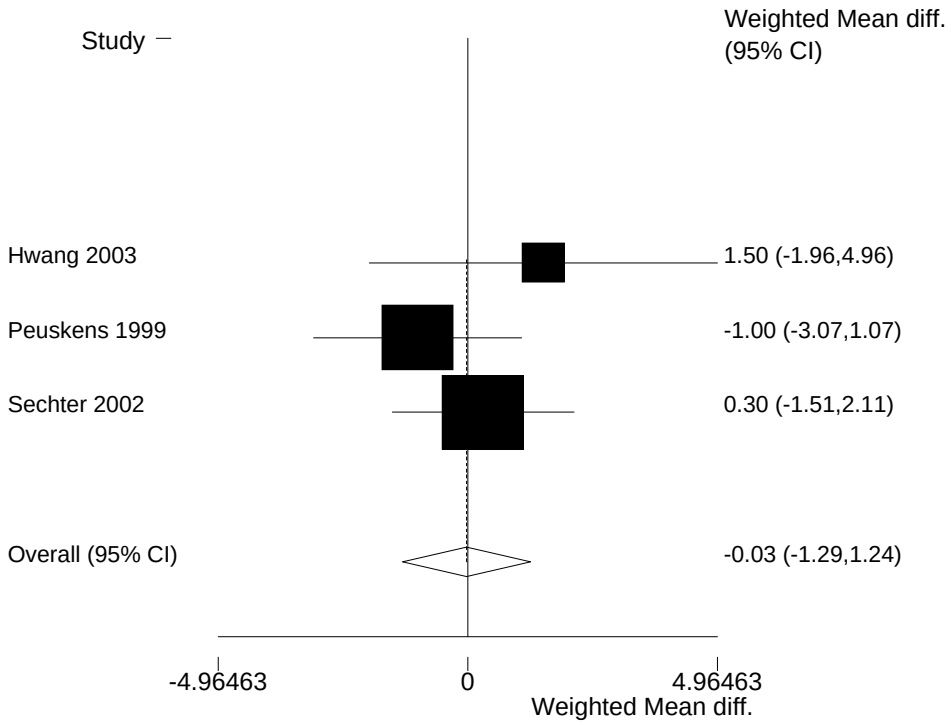
Figures II. 1. a – II. 8. d : PANSS positive subscore (weighted mean difference, WMD)

Figure II. 1. a: PANSS positive subscore - Amisulpride versus Olanzapine



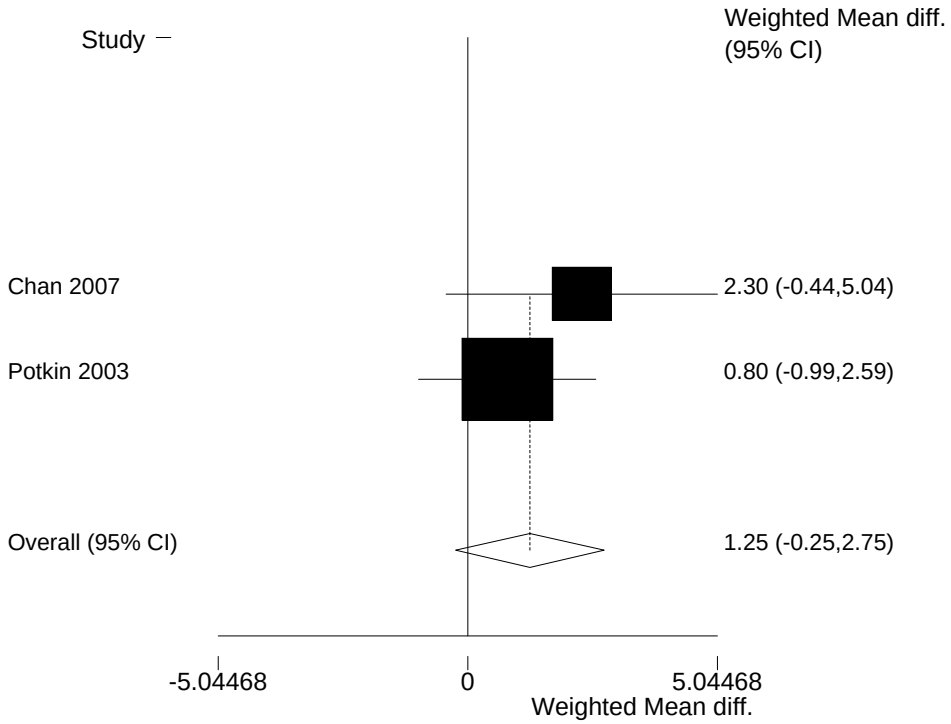

```
N=701
Heterogeneity chi-squared =   4.24 (d.f. = 3) p = 0.237
Estimate of between-study variance Tau-squared =  0.4543
Test of WMD=0 : z= 1.06 p = 0.287
```

Figure II. 1. b: PANSS positive subscore - Amisulpride versus Risperidone



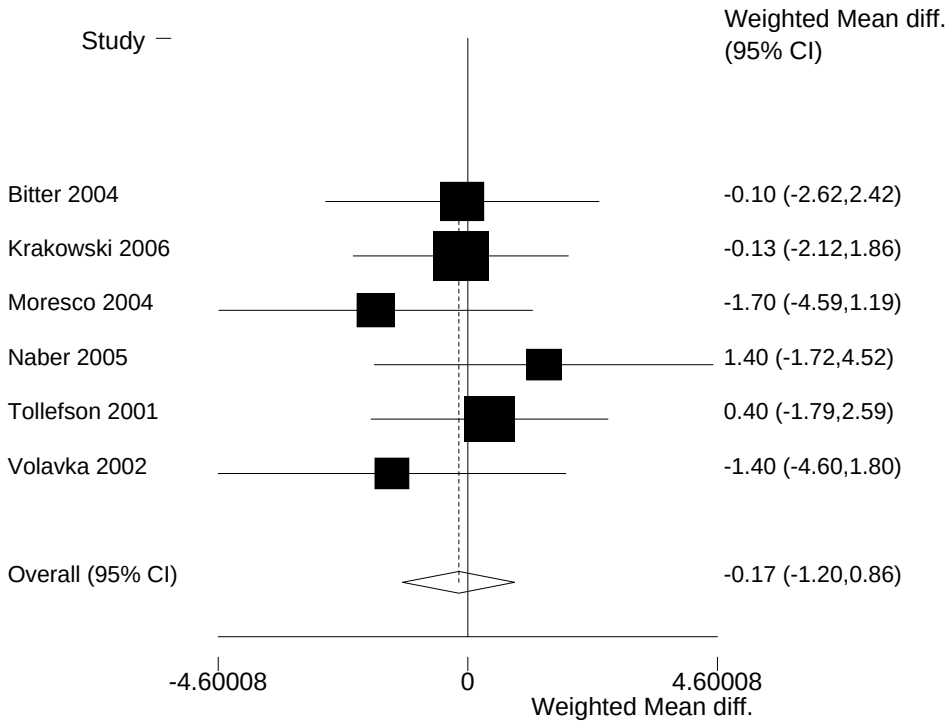
N=519
Heterogeneity chi-squared = 1.72 (d.f. = 2) p = 0.423
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.04 p = 0.966

Figure II. 2. a: PANSS positive subscore - Aripiprazole versus Risperidone



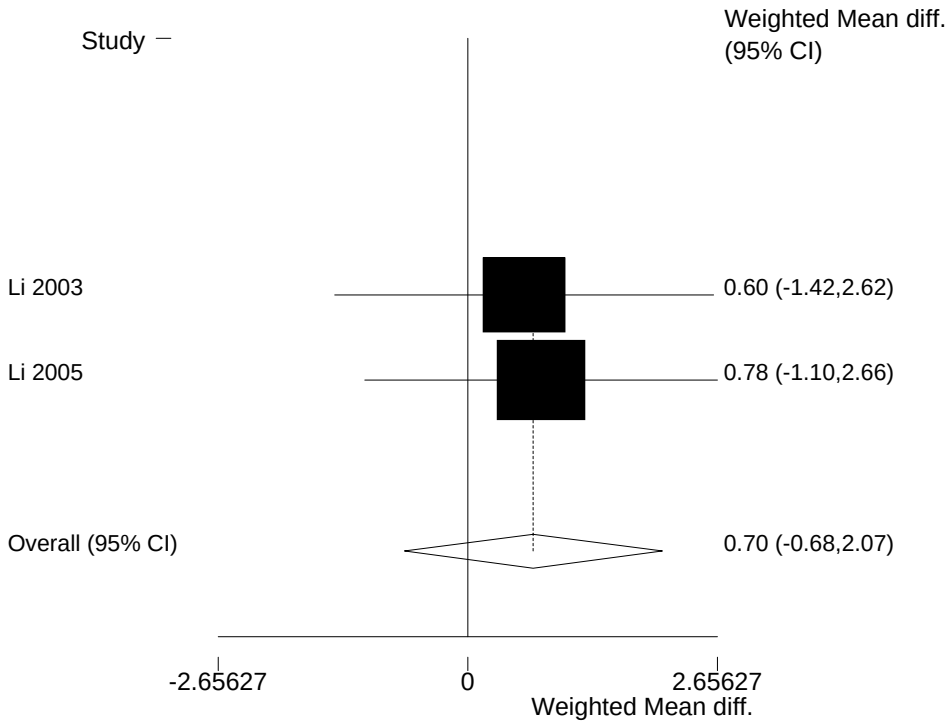
N=372
Heterogeneity chi-squared = 0.80 (d.f. = 1) p = 0.370
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 1.63 p = 0.103

Figure II. 3. a: PANSS positive subscore - Clozapine versus Olanzapine



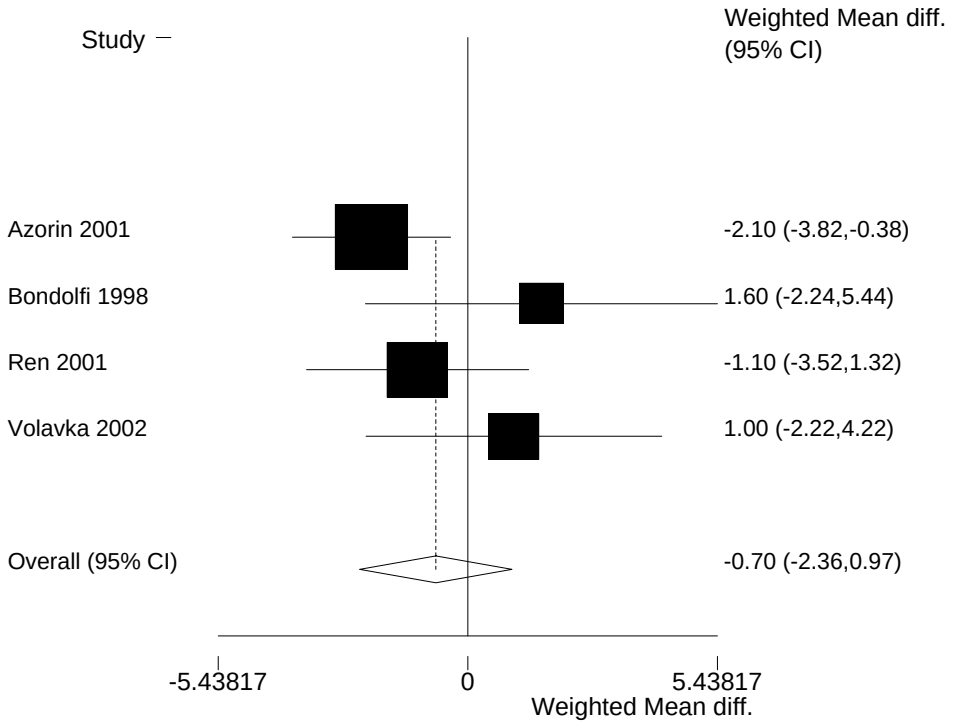

```
N=593
Heterogeneity chi-squared =   2.88 (d.f. = 5) p = 0.718
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.33 p = 0.744
```

Figure II. 3. b: PANSS positive subscore - Clozapine versus Quetiapine



N=142
Heterogeneity chi-squared = 0.02 (d.f. = 1) p = 0.898
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.99 p = 0.320

Figure II. 3. c: PANSS positive subscore - Clozapine versus Risperidone

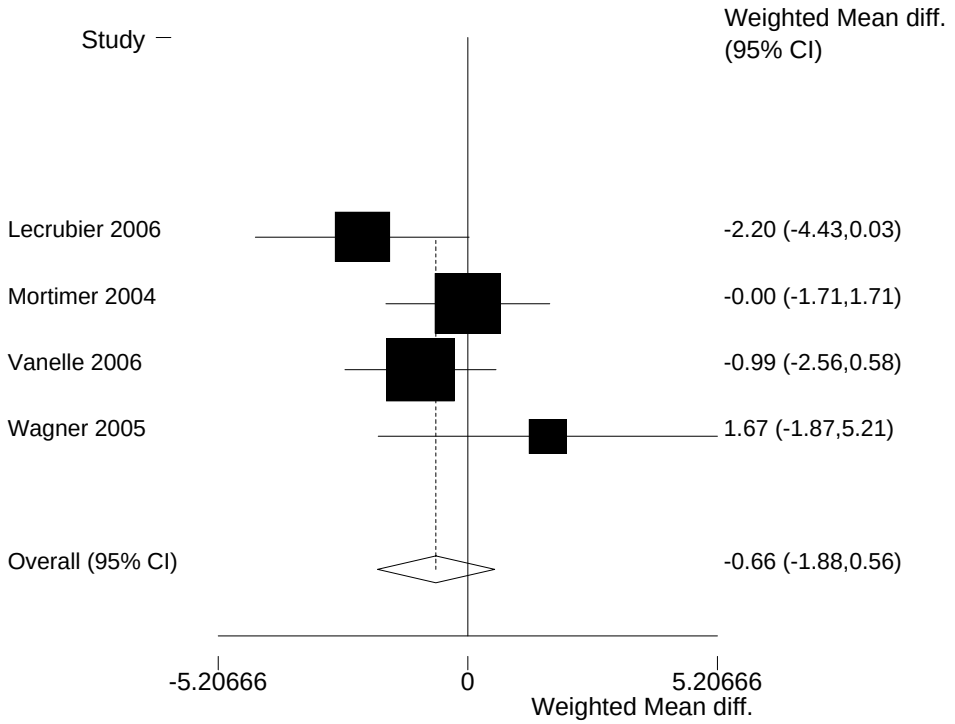



```
N=541
Heterogeneity chi-squared =   4.83 (d.f. = 3) p = 0.185
Estimate of between-study variance Tau-squared =  1.0815
Test of WMD=0 : z= 0.82 p = 0.412
```

Figure II. 3. d: PANSS positive subscore - Clozapine versus Ziprasidone

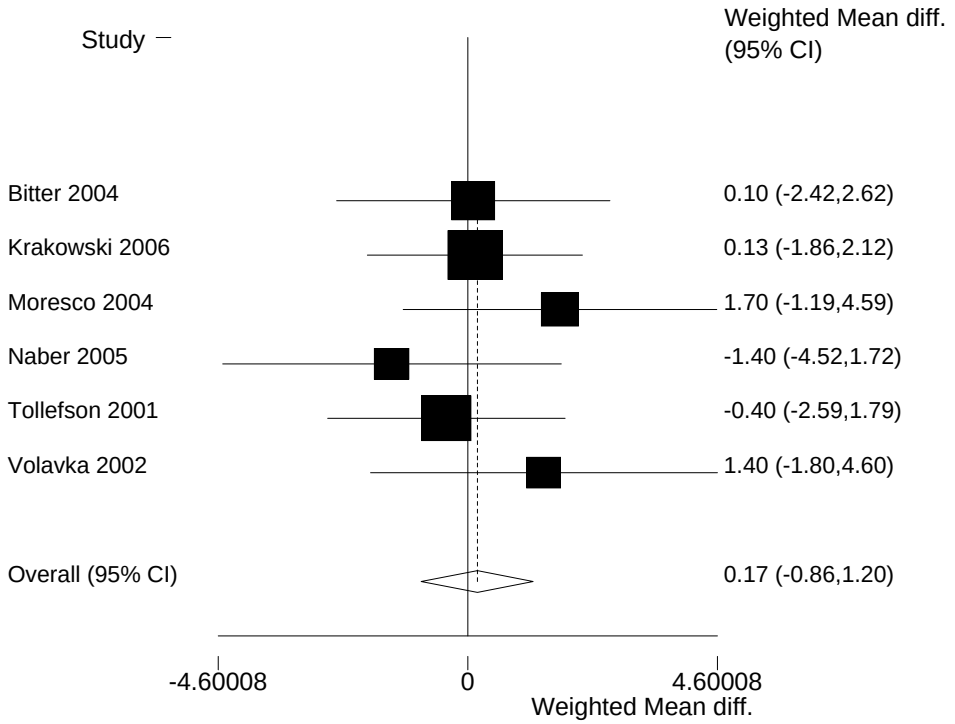
```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Sacchetti 2006   |       -1    -3.38468   1.38468
-----------------+---------------------------------
  I-V pooled WMD |       -1    -3.38468   1.38468
-----------------+---------------------------------
N=144
Test of WMD=0 : z= 0.82 p = 0.411
```

Figure II. 4. a: PANSS positive subscore - Olanzapine versus Amisulpride



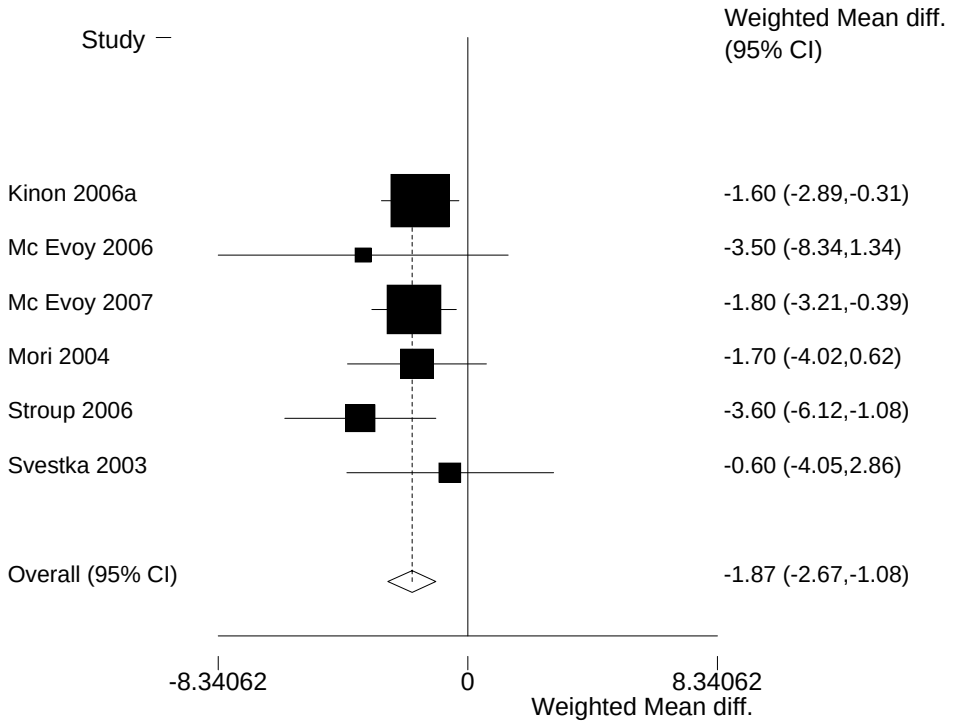
N=701
Heterogeneity chi-squared = 4.24 (d.f. = 3) p = 0.237
Estimate of between-study variance Tau-squared = 0.4543
Test of WMD=0 : z= 1.06 p = 0.287

Figure II. 4. b: PANSS positive subscore - Olanzapine versus Clozapine



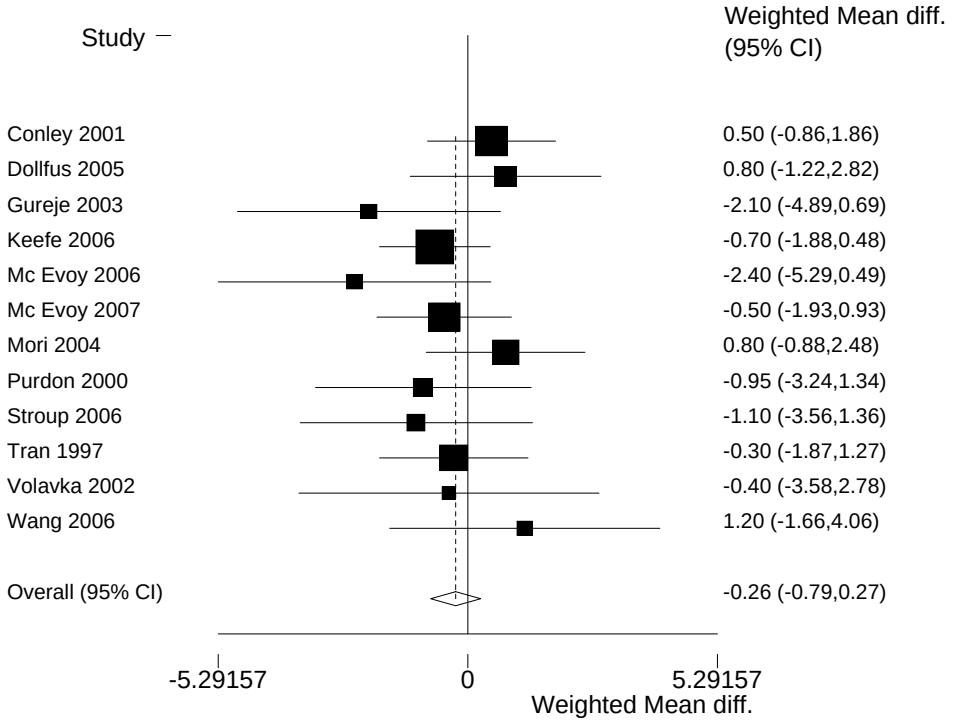
N=593
Heterogeneity chi-squared = 2.88 (d.f. = 5) p = 0.718
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.33 p = 0.744

Figure II. 4. c: PANSS positive subscore - Olanzapine versus Quetiapine



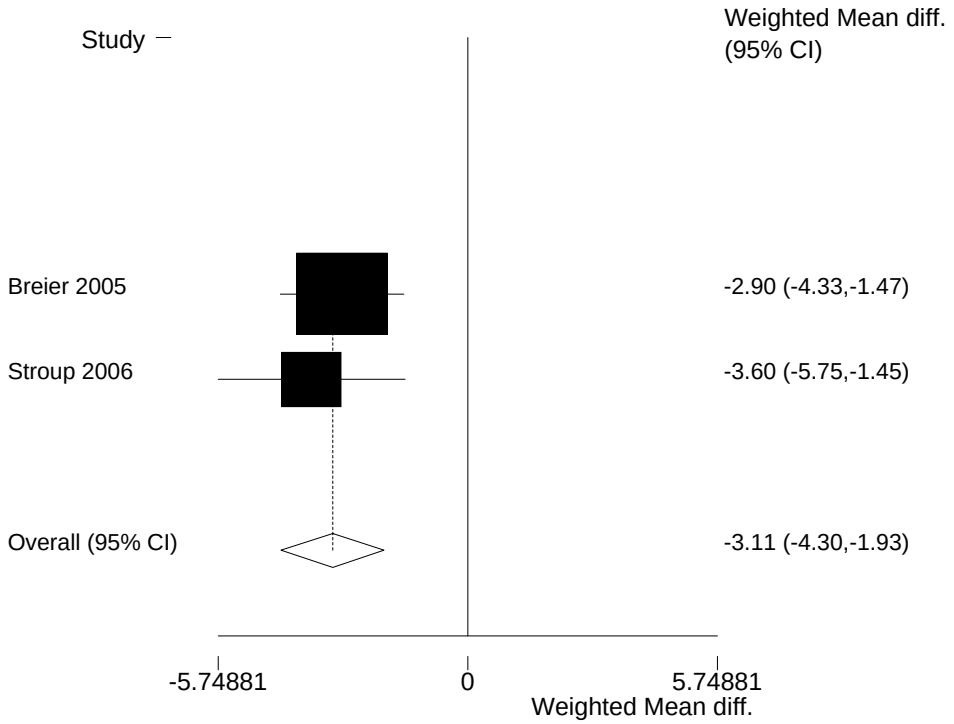
N=646
Heterogeneity chi-squared = 2.97 (d.f. = 5) p = 0.705
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 4.61 p = 0.000

Figure II. 4. d: PANSS positive subscore - Olanzapine versus Risperidone



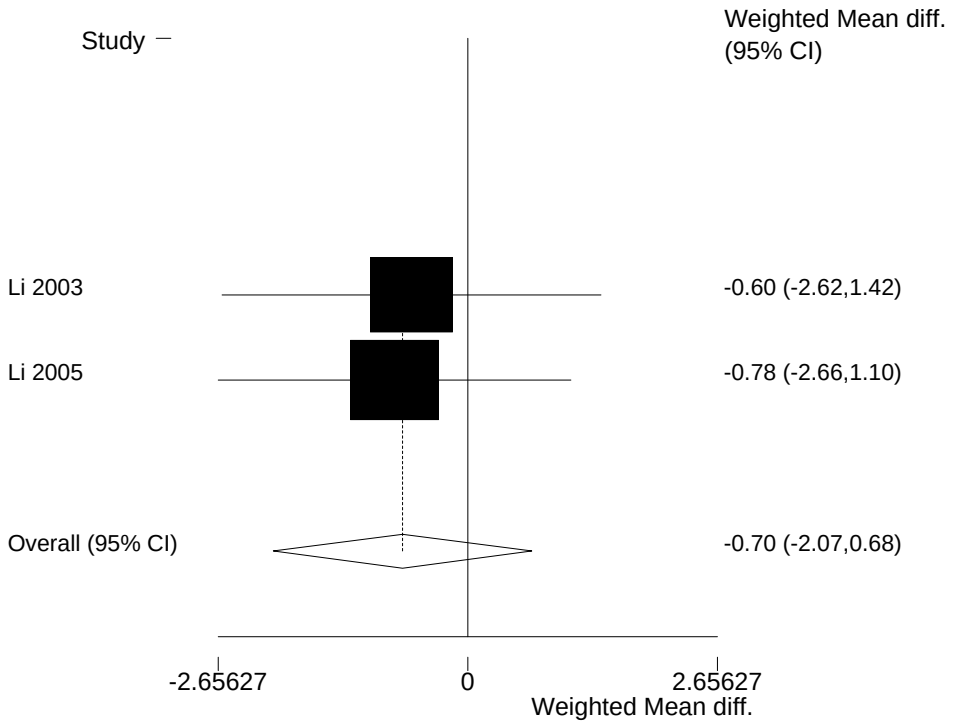

```
N=1545
Heterogeneity chi-squared =  10.01 (d.f. = 11) p = 0.529
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.97 p = 0.332
```

Figure II. 4. e: PANSS positive subscore - Olanzapine versus Ziprasidone



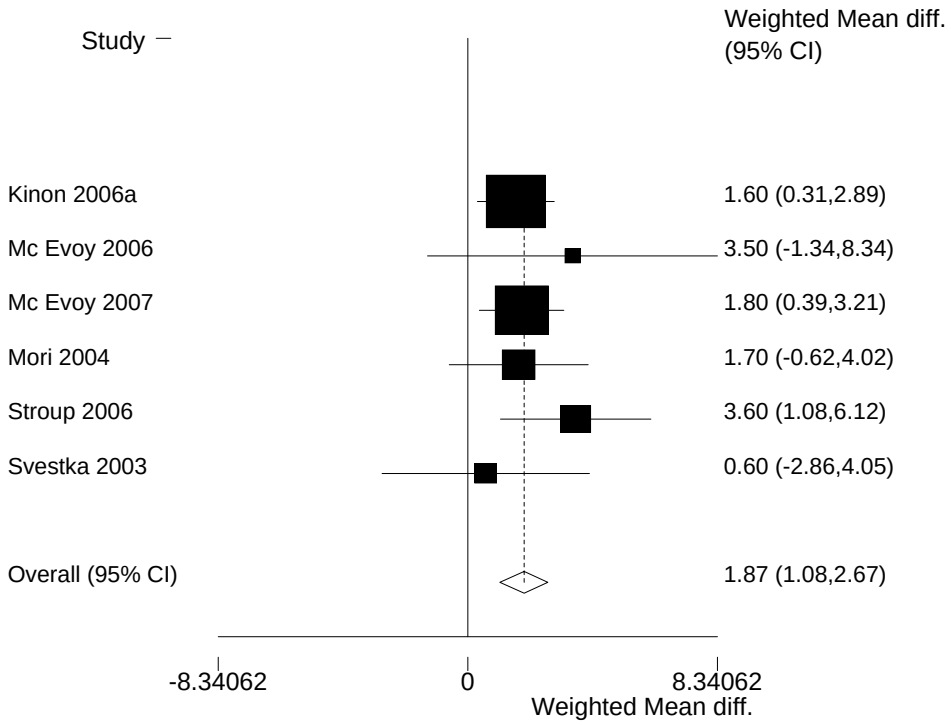
N=730
Heterogeneity chi-squared = 0.28 (d.f. = 1) p = 0.595
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 5.14 p = 0.000

Figure II. 5. a: PANSS positive subscore - Quetiapine versus Clozapine



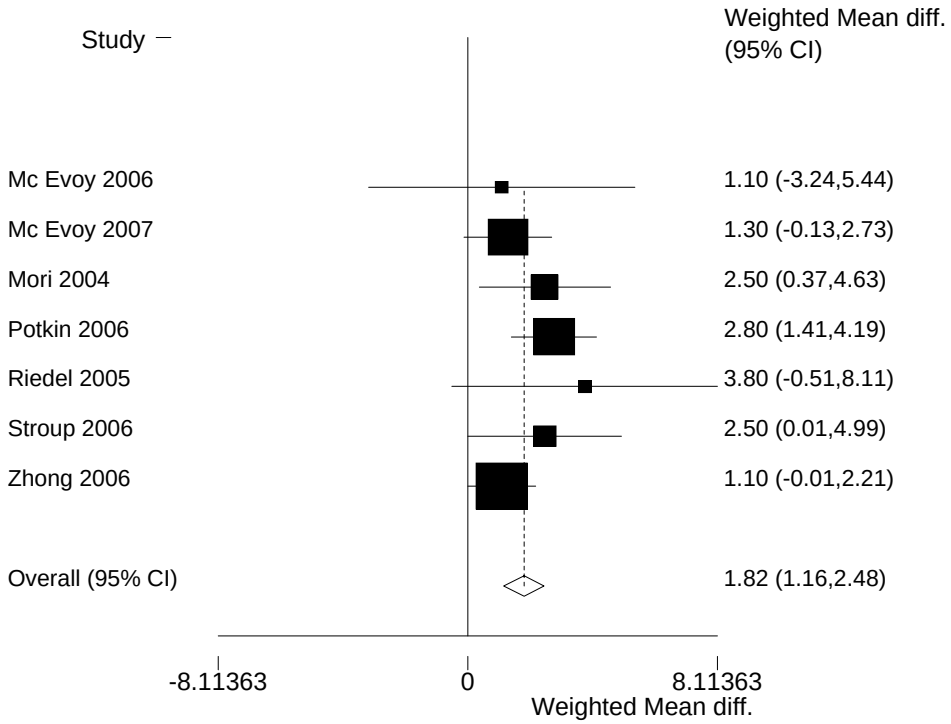

```
N=142
Heterogeneity chi-squared =   0.02 (d.f. = 1) p = 0.898
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.99 p = 0.320
```

Figure II. 5. b: PANSS positive subscore - Quetiapine versus Olanzapine



N=646
Heterogeneity chi-squared = 2.97 (d.f. = 5) p = 0.705
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 4.61 p = 0.000

Figure II. 5. c: PANSS positive subscore - Quetiapine versus Risperidone

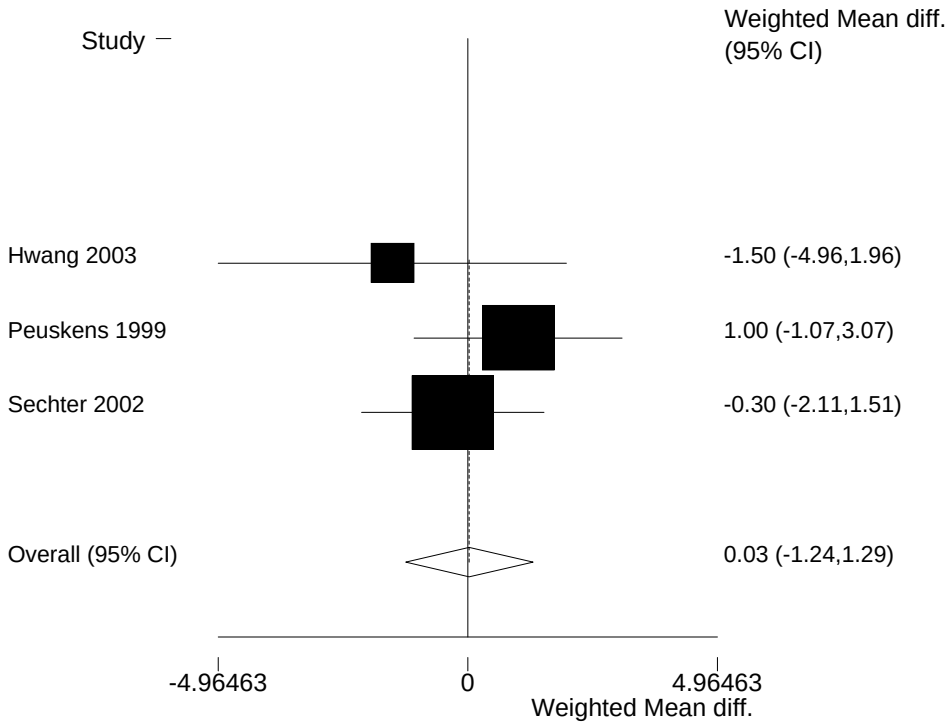



```
N=1264
Heterogeneity chi-squared =   5.65 (d.f. = 6) p = 0.464
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 5.42 p = 0.000
```

Figure II. 5. d: PANSS positive subscore - Quetiapine versus Ziprasidone

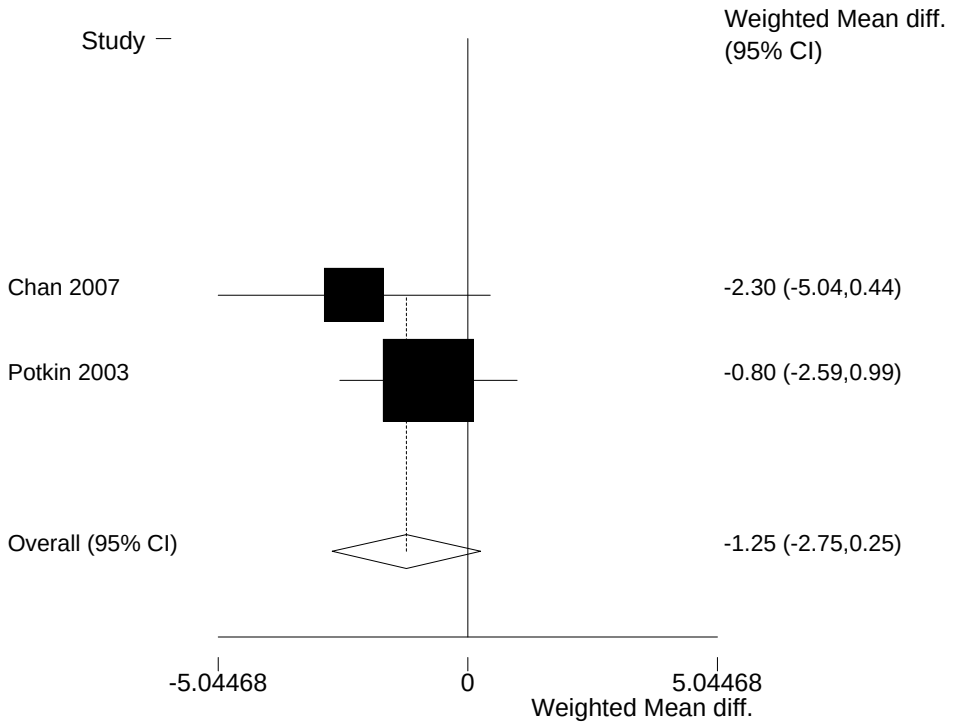
```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Stroup 2006      |         0    -2.18291   2.18291
-----------------+---------------------------------
  I-V pooled WMD |         0    -2.18291   2.18291
-----------------+---------------------------------
N=198
Test of WMD=0 : z= 0.00 p = 1.000
```

Figure II. 6. a: PANSS positive subscore - Risperidone versus Amisulpride



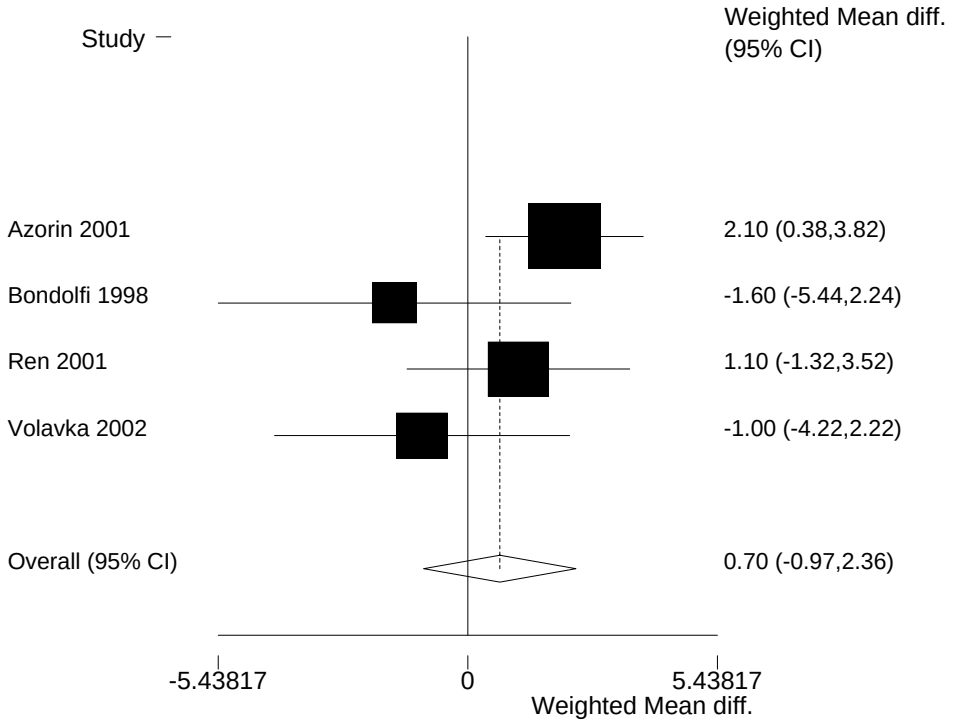
N=519
Heterogeneity chi-squared = 1.72 (d.f. = 2) p = 0.423
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.04 p = 0.966

Figure II. 6. b: PANSS positive subscore - Risperidone versus Aripiprazole



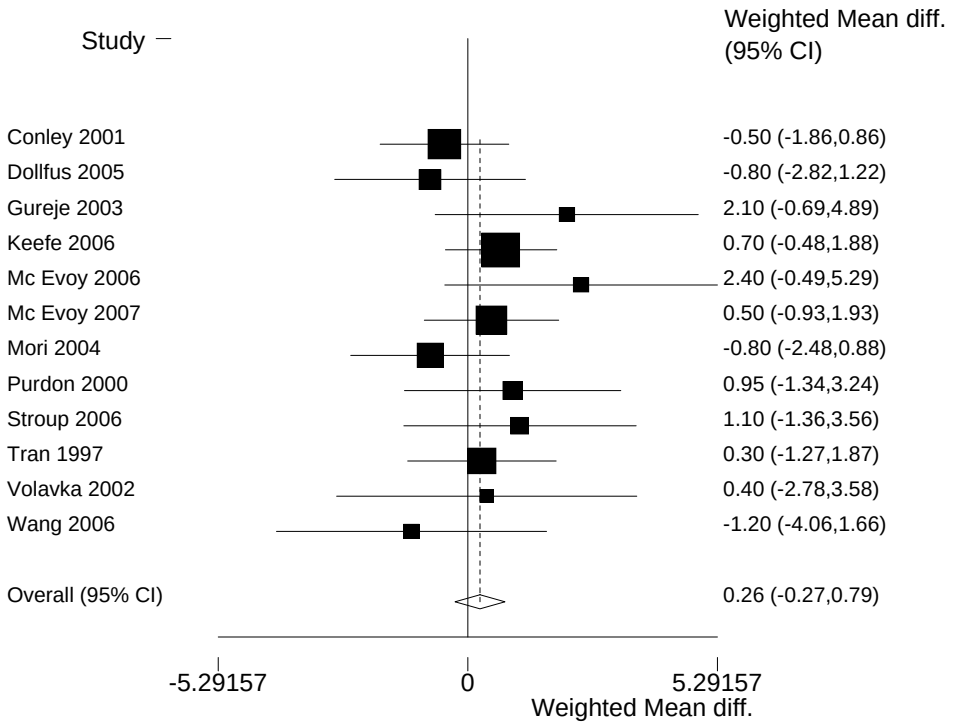

```
N=372
Heterogeneity chi-squared =   0.80 (d.f. = 1) p = 0.370
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 1.63 p = 0.103
```

Figure II. 6. b: PANSS positive subscore - Risperidone versus Clozapine



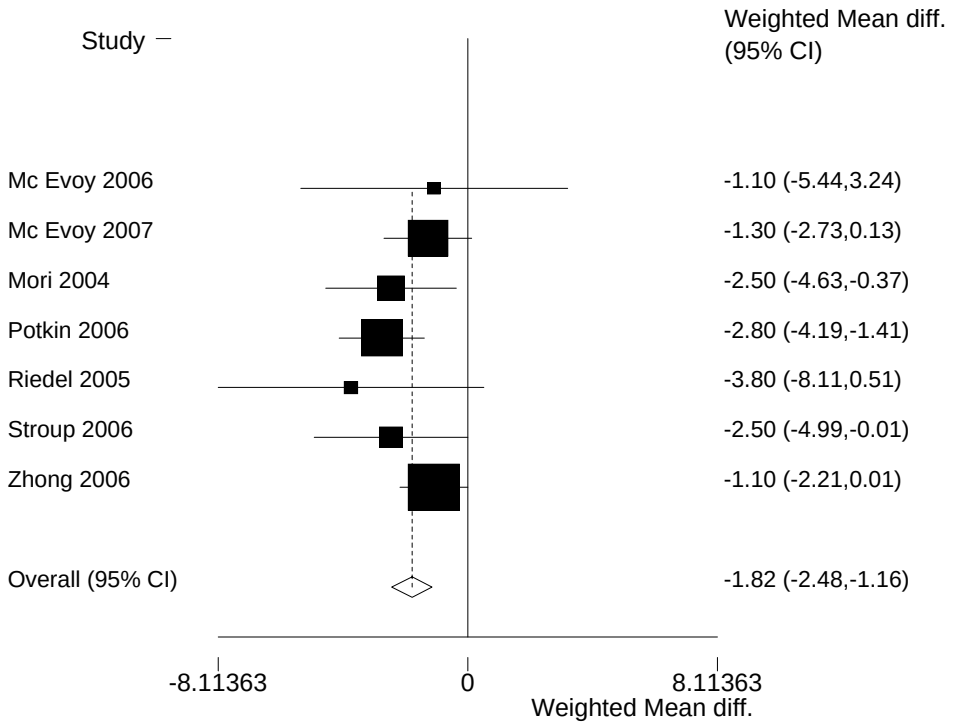
N=541
Heterogeneity chi-squared = 4.83 (d.f. = 3) p = 0.185
Estimate of between-study variance Tau-squared = 1.0815
Test of WMD=0 : z= 0.82 p = 0.412

Figure II. 6. c: PANSS positive subscore - Risperidone versus Olanzapine



N=1545
Heterogeneity chi-squared = 10.01 (d.f. = 11) p = 0.529
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.97 p = 0.332

Figure II. 6. d: PANSS positive subscore - Risperidone versus Quetiapine




```
N=1264
Heterogeneity chi-squared =   5.65 (d.f. = 6) p = 0.464
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 5.42 p = 0.000
```

Figure II. 6. e: PANSS positive subscore - Risperidone versus Sertindole

```
          Study |       WMD  [95% Conf. Interval]
----------------+---------------------------------
Azorin 2006     |       .8    -1.35479   2.95479
----------------+---------------------------------
  I-V pooled WMD |       .8    -1.35479   2.95479
----------------+---------------------------------
N=172
Test of WMD=0 : z= 0.73 p = 0.467
```

Figure II. 6. f: PANSS positive subscore - Risperidone versus Ziprasidone

```
          Study |       WMD  [95% Conf. Interval]
----------------+---------------------------------
Stroup 2006     |     -2.5    -4.61721  -.382794
----------------+---------------------------------
  I-V pooled WMD |     -2.5    -4.61721  -.382794
----------------+---------------------------------
N=204
Test of WMD=0 : z= 2.31 p = 0.021
```

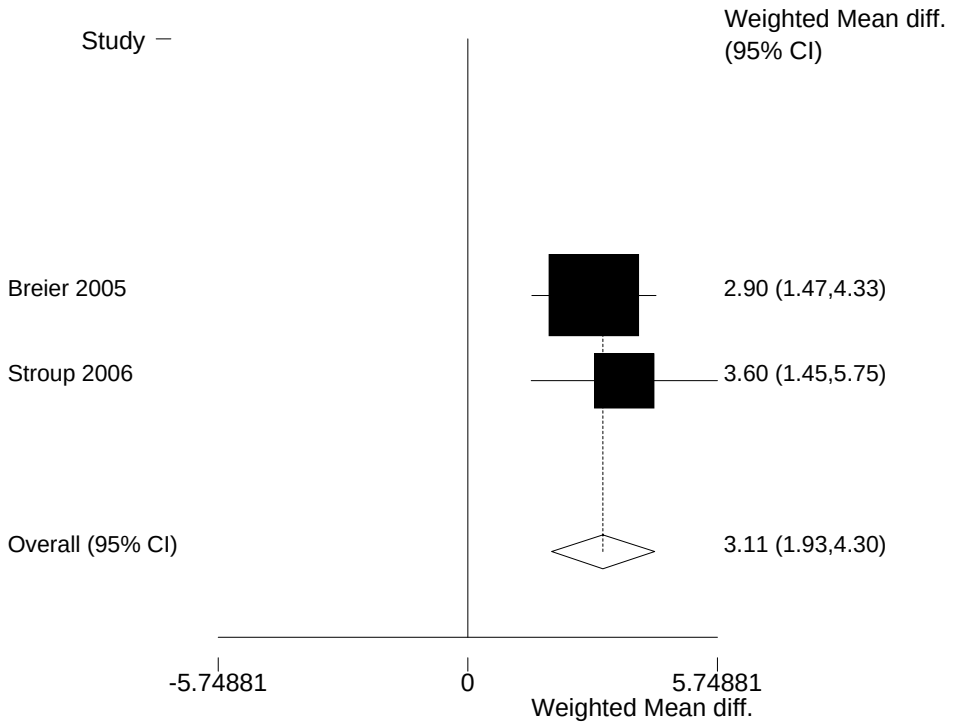
Figure II. 7. a: PANSS positive subscore - Sertindole versus Risperidone

```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Azorin 2006      |      -.8    -2.95479   1.35479
-----------------+---------------------------------
  I-V pooled WMD |      -.8    -2.95479   1.35479
-----------------+---------------------------------
N=172
Test of WMD=0 : z= 0.73 p = 0.467
```

Figure II. 8. a: PANSS positive subscore - Ziprasidone versus Clozapine

```
      Study |       WMD  [95% Conf. Interval]
------------+---------------------------------
Sacchetti 2006   |        1    -1.38468   3.38468
-----------------+---------------------------------
  I-V pooled WMD |        1    -1.38468   3.38468
-----------------+---------------------------------
N=144
Test of WMD=0 : z= 0.82 p = 0.411
```

Figure II. 8. b: PANSS positive subscore - Ziprasidone versus Olanzapine




```
N=730
Heterogeneity chi-squared =   0.28 (d.f. = 1) p = 0.595
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 5.14 p = 0.000
```

Figure II. 8. c: PANSS positive subscore - Ziprasidone versus Quetiapine

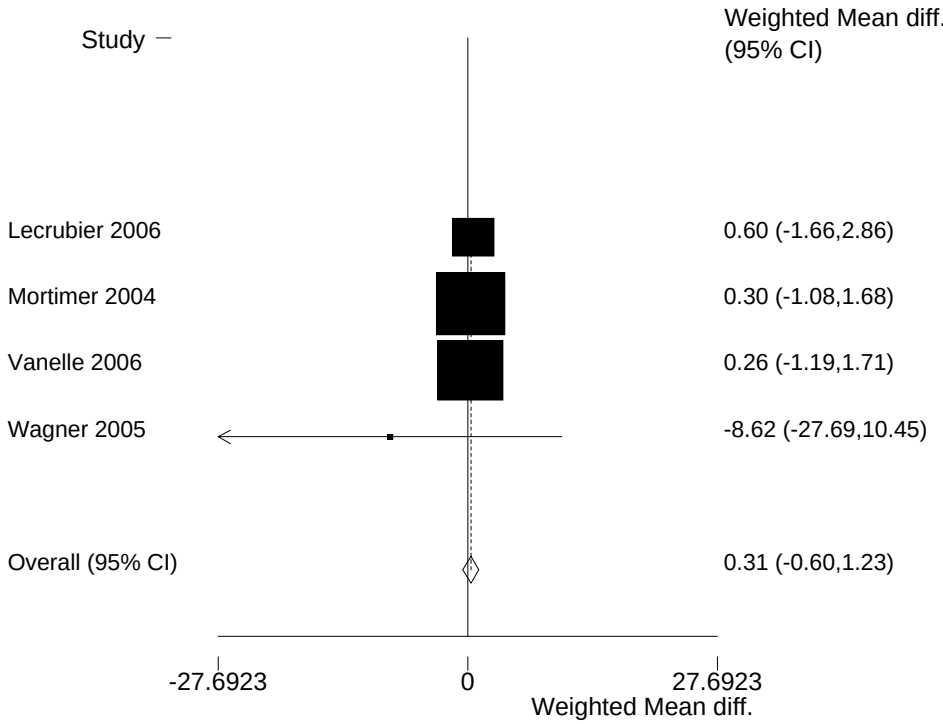
```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Stroup 2006      | -3.0e-09    -2.18291   2.18291
-----------------+---------------------------------
  I-V pooled WMD | -3.0e-09    -2.18291   2.18291
-----------------+---------------------------------
N=198
Test of WMD=0 : z= 0.00 p = 1.000
```

Figure II. 8. d: PANSS positive subscore - Ziprasidone versus Risperidone

```
          Study |       WMD  [95% Conf. Interval]
----------------+---------------------------------
Stroup 2006     |      2.5     .382793   4.61721
----------------+---------------------------------
  I-V pooled WMD |      2.5     .382794   4.61721
----------------+---------------------------------
N=204
Test of WMD=0 : z= 2.31 p = 0.021
```

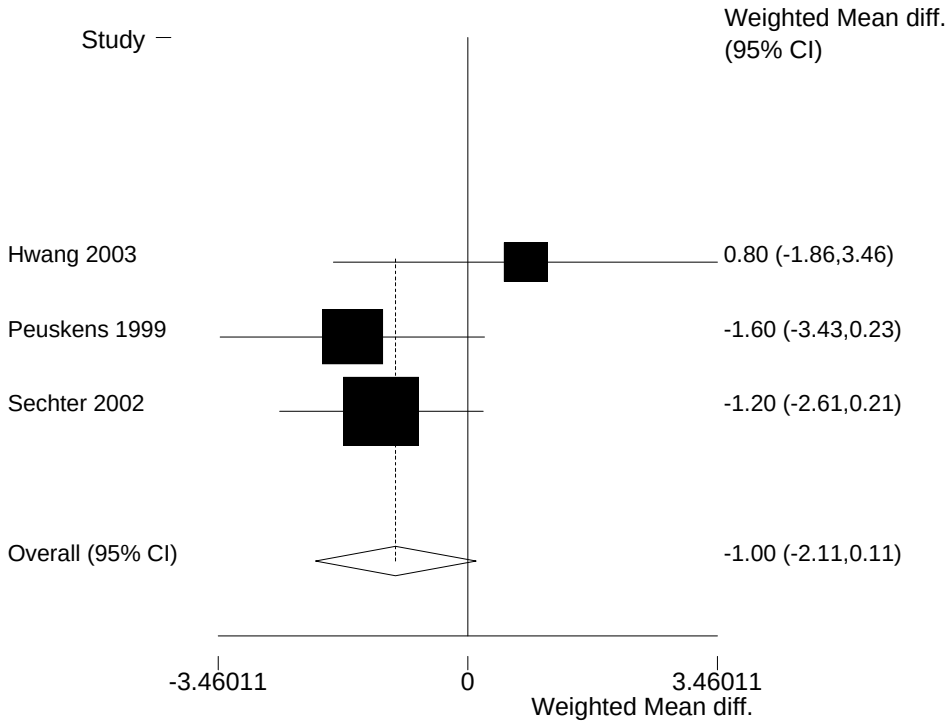
Figures III. 1. a – III. 8. d : PANSS negative subscore (weighted mean difference, WMD)

Figure III. 1. a: PANSS negative subscore - Amisulpride versus Olanzapine




```
N=698
Heterogeneity chi-squared =   0.91 (d.f. = 3) p = 0.823
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.67 p = 0.502
```

Figure III. 1. b: PANSS negative subscore - Amisulpride versus Risperidone

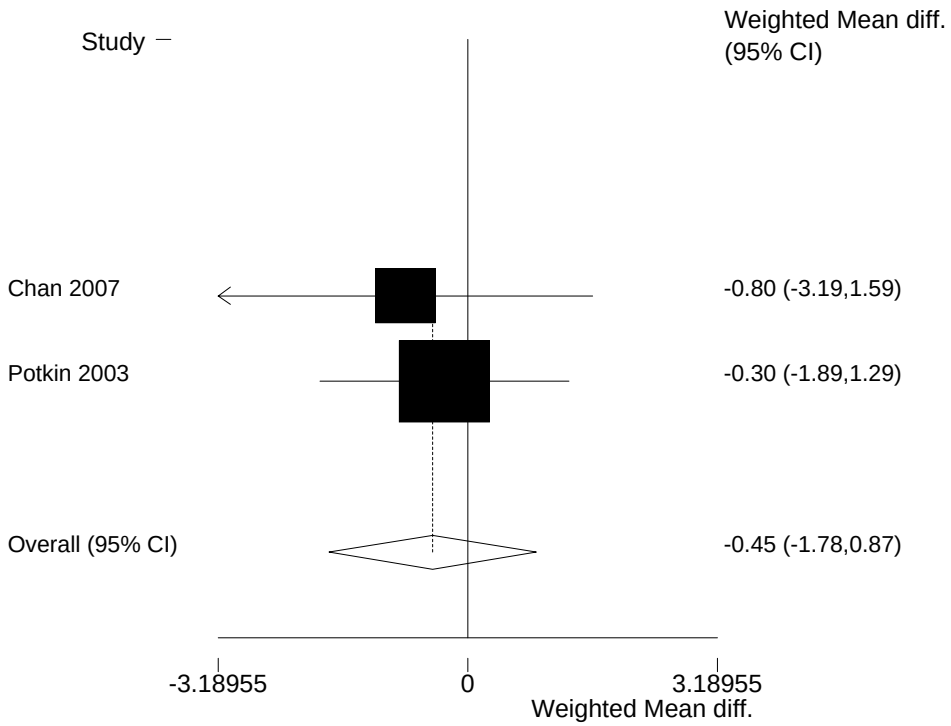



```
  N=519
  Heterogeneity chi-squared =   2.25 (d.f. = 2) p = 0.325
  Estimate of between-study variance Tau-squared =  0.1144
  Test of WMD=0 : z= 1.76 p = 0.078
```

Figure III. 1. c: PANSS negative subscore - Amisulpride versus Ziprasidone

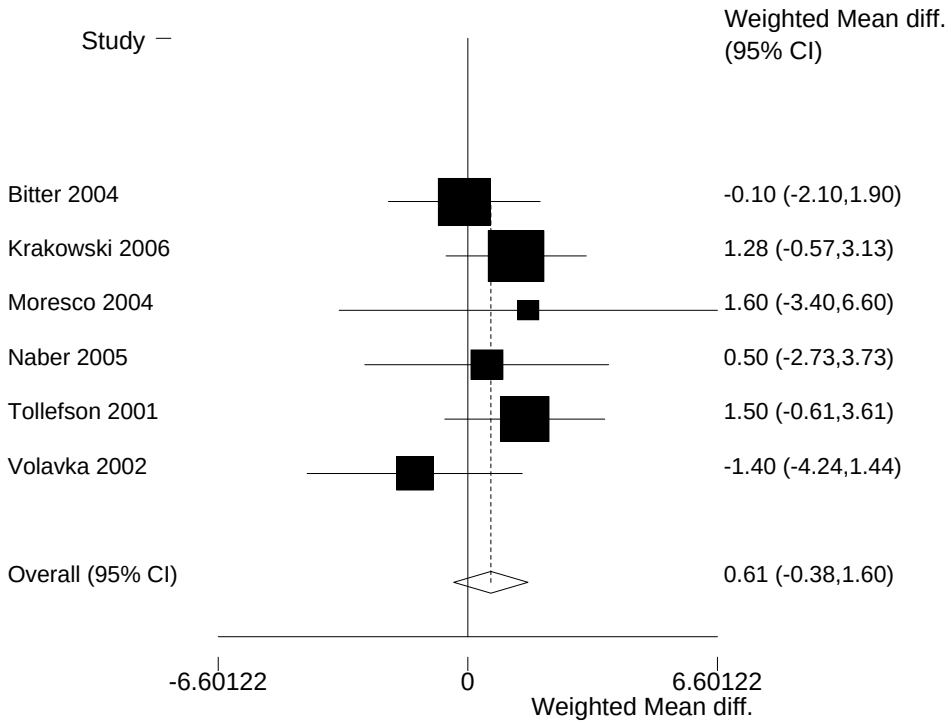
```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Olie 2006        |      -.8    -3.01218   1.41218
-----------------+---------------------------------
  I-V pooled WMD |      -.8    -3.01218   1.41218
-----------------+---------------------------------
N=122
Test of WMD=0 : z= 0.71 p = 0.478
```

Figure III. 2. a: PANSS negative subscore - Aripiprazole versus Risperidone



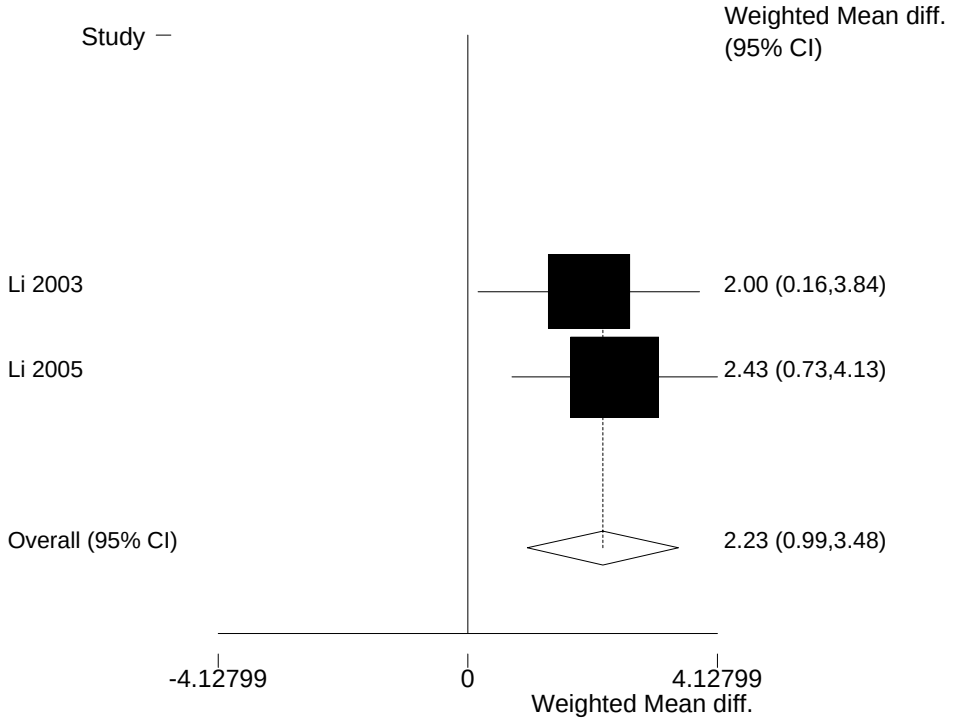
N=372
Heterogeneity chi-squared = 0.12 (d.f. = 1) p = 0.733
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.67 p = 0.502

Figure III. 3. a: PANSS negative subscore - Clozapine versus Olanzapine



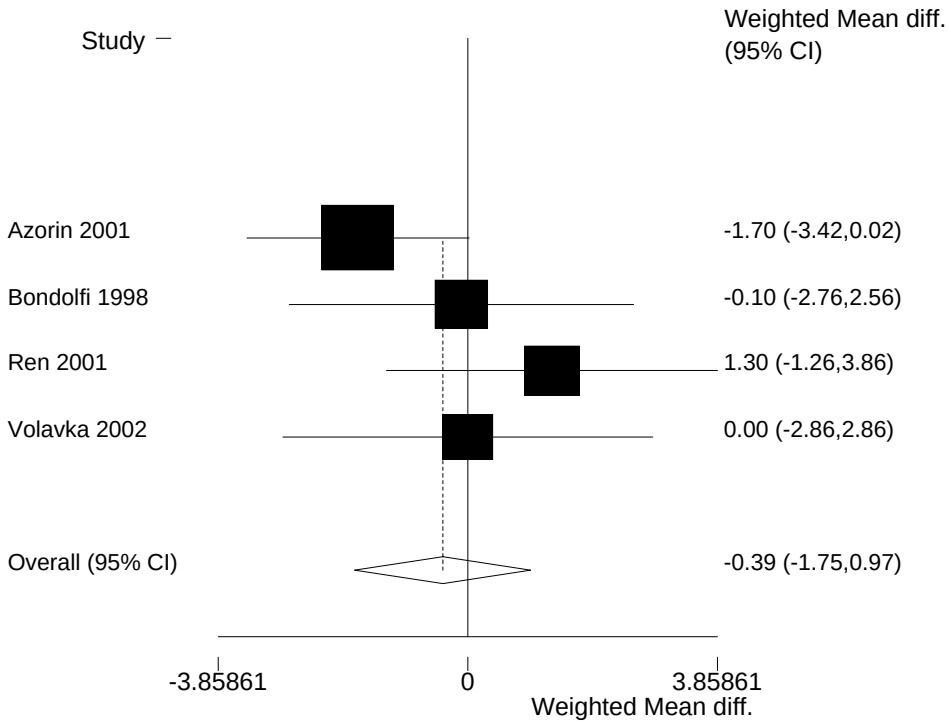

```
N=593
Heterogeneity chi-squared =   3.74 (d.f. = 5) p = 0.587
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 1.21 p = 0.227
```

Figure III. 3. b: PANSS negative subscore - Clozapine versus Quetiapine



N=142
Heterogeneity chi-squared = 0.11 (d.f. = 1) p = 0.736
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 3.51 p = 0.000

Figure III. 3. c: PANSS negative subscore - Clozapine versus Risperidone

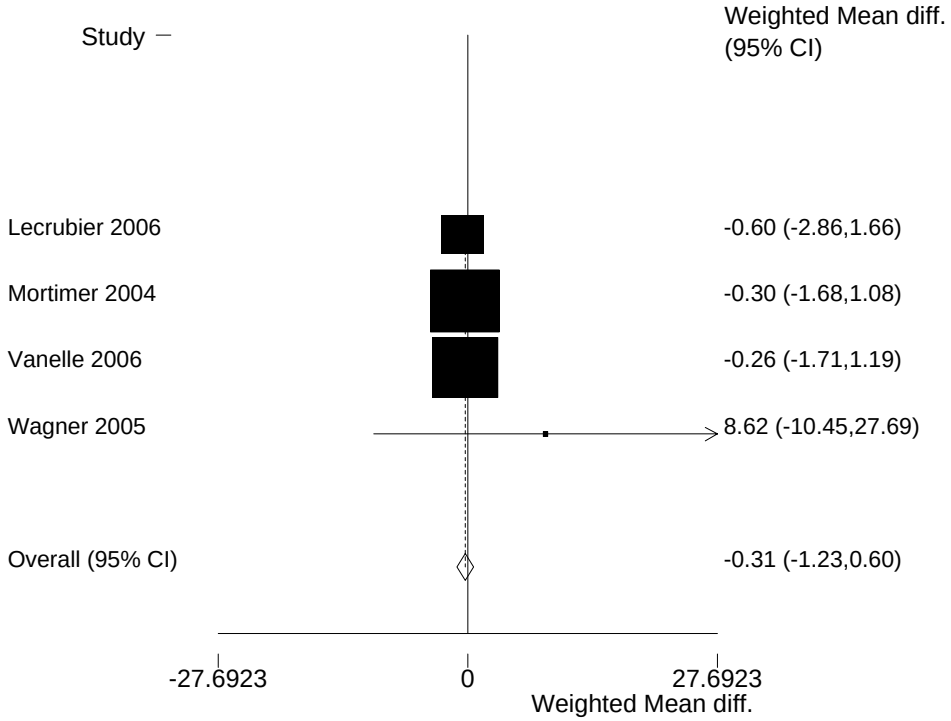



```
N=541
Heterogeneity chi-squared =   3.98 (d.f. = 3) p = 0.263
Estimate of between-study variance Tau-squared =  0.4872
Test of WMD=0 : z= 0.56 p = 0.575
```

Figure III. 3. d: PANSS negative subscore - Clozapine versus Ziprasidone

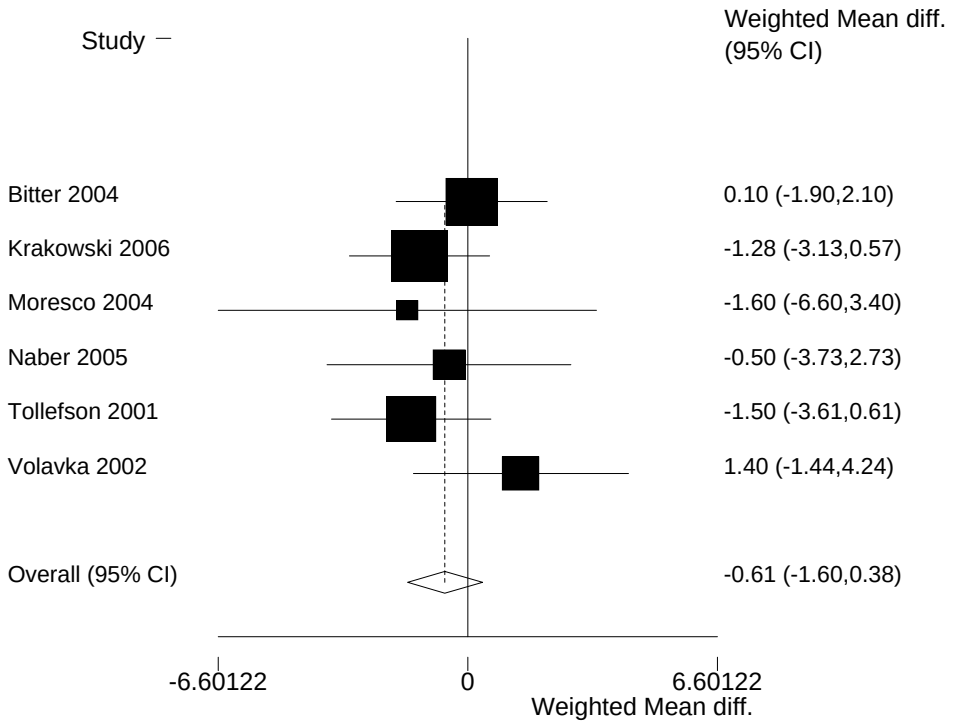
```
          Study |       WMD  [95% Conf. Interval]
----------------+---------------------------------
Sacchetti 2006  |      1.5    -.618468   3.61847
----------------+---------------------------------
  I-V pooled WMD |      1.5    -.618468   3.61847
----------------+---------------------------------
N=144
Test of WMD=0 : z= 1.39 p = 0.165
```

Figure III. 4. a: PANSS negative subscore - Olanzapine versus Amisulpride



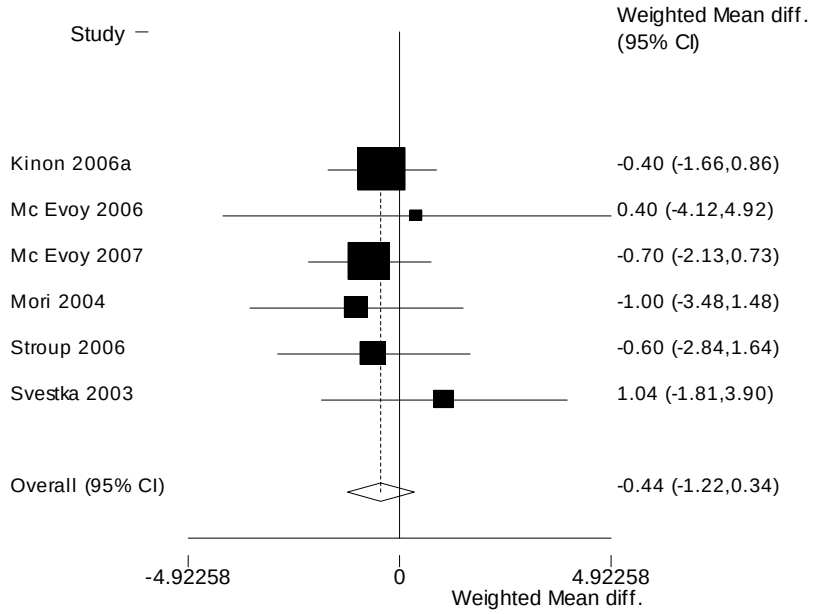
N=698
Heterogeneity chi-squared = 0.91 (d.f. = 3) p = 0.823
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.67 p = 0.502

Figure III. 4. b: PANSS negative subscore - Olanzapine versus Clozapine



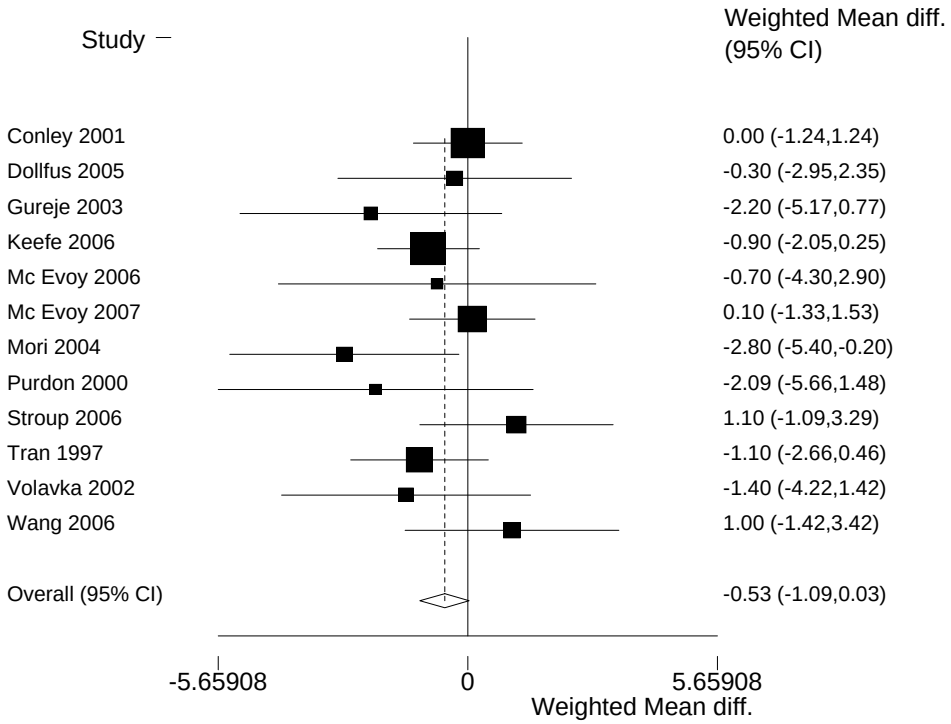
N=593
Heterogeneity chi-squared = 3.74 (d.f. = 5) p = 0.587
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 1.21 p = 0.227

Figure III. 4. c: PANSS negative subscore - Olanzapine versus Quetiapine



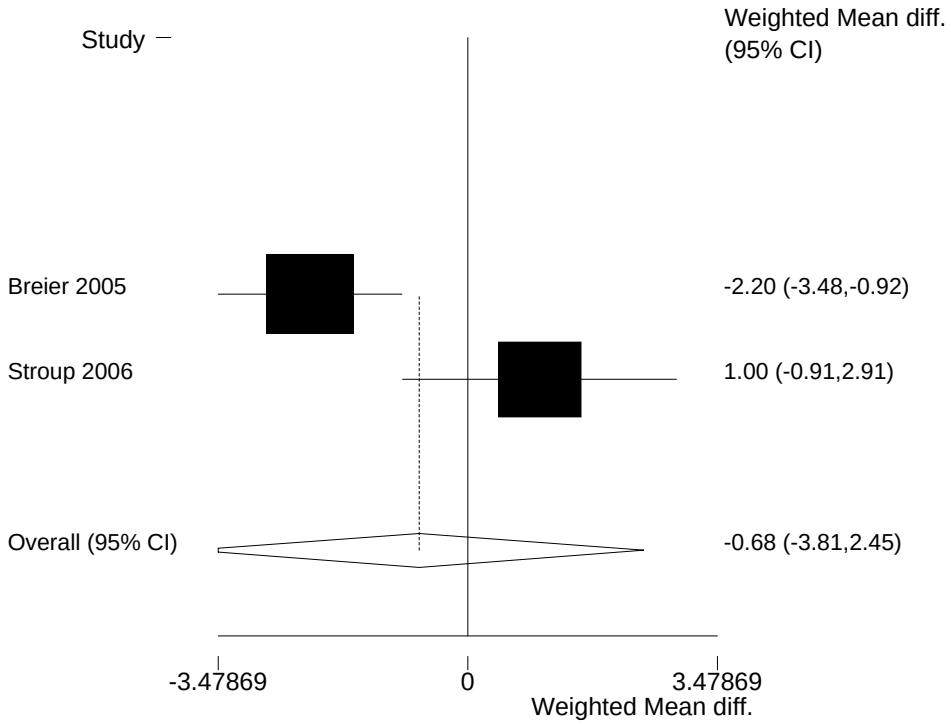
N=646
Heterogeneity chi-squared = 1.51 (d.f. = 5) p = 0.912
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 1.11 p = 0.266

Figure III. 4. d: PANSS negative subscore - Olanzapine versus Risperidone



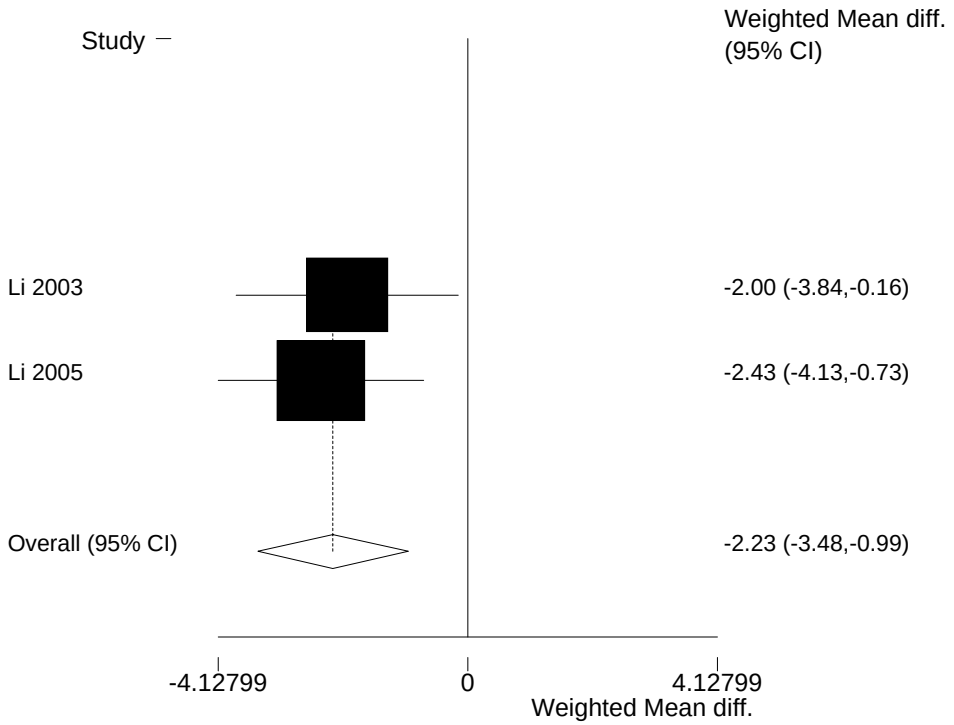

```
N=1545
Heterogeneity chi-squared =  11.31 (d.f. = 11) p = 0.417
Estimate of between-study variance Tau-squared =  0.0281
Test of WMD=0 : z= 1.87 p = 0.062
```

Figure III. 4. e: PANSS negative subscore - Olanzapine versus Ziprasidone



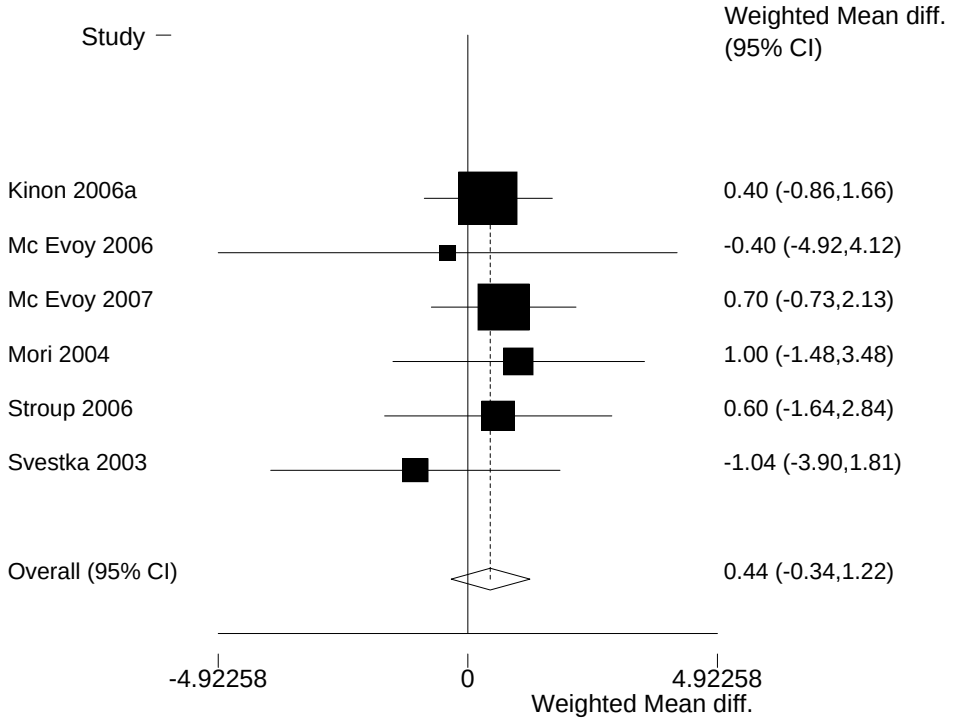
N=730
Heterogeneity chi-squared = 7.45 (d.f. = 1) p = 0.006
Estimate of between-study variance Tau-squared = 4.4329
Test of WMD=0 : z= 0.43 p = 0.670

Figure III. 5. a: PANSS negative subscore - Quetiapine versus Clozapine



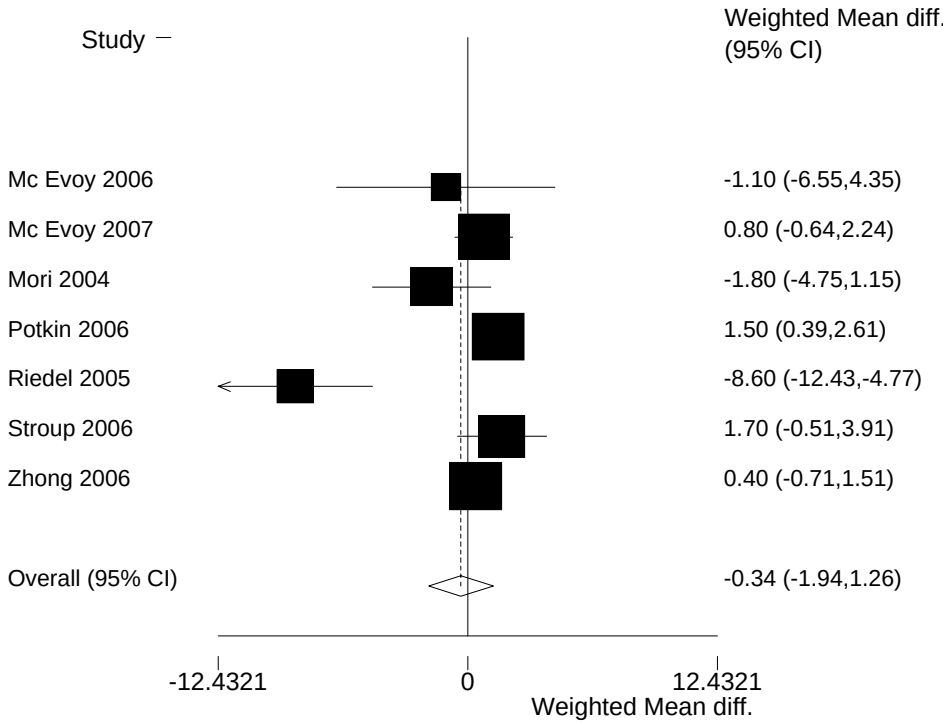
N=142
Heterogeneity chi-squared = 0.11 (d.f. = 1) p = 0.736
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 3.51 p = 0.000

Figure III. 5. b: PANSS negative subscore - Quetiapine versus Olanzapine



N=646
Heterogeneity chi-squared = 1.51 (d.f. = 5) p = 0.912
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 1.11 p = 0.266

Figure III. 5. c: PANSS negative subscore - Quetiapine versus Risperidone

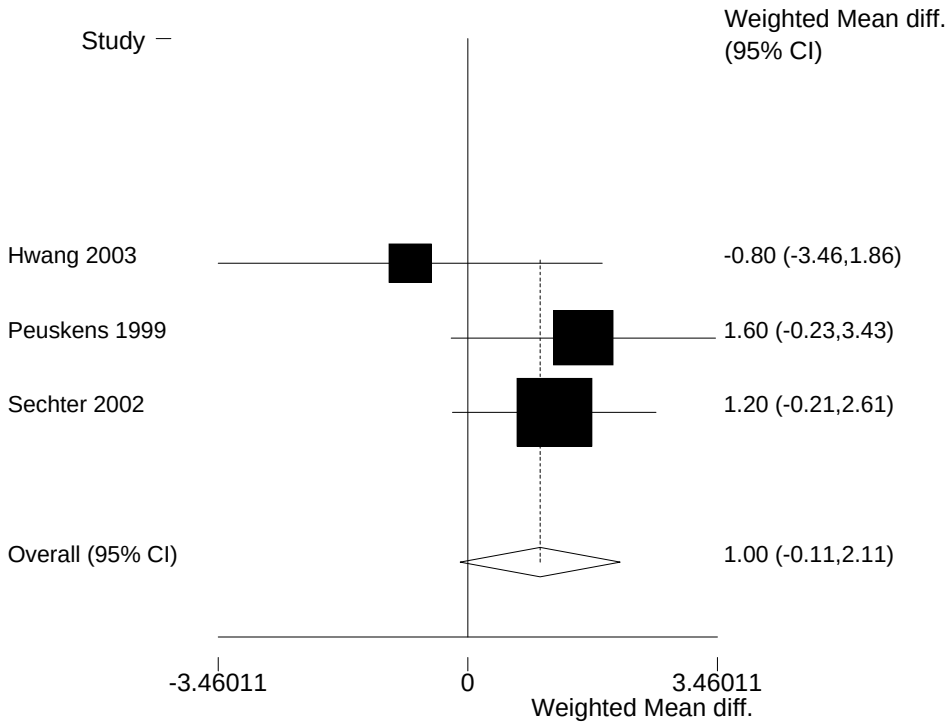



```
N=1264
Heterogeneity chi-squared =  28.72 (d.f. = 6) p = 0.000
Estimate of between-study variance Tau-squared =  3.1291
Test of WMD=0 : z= 0.42 p = 0.673
```

Figure III. 5. d: PANSS negative subscore - Quetiapine versus Ziprasidone

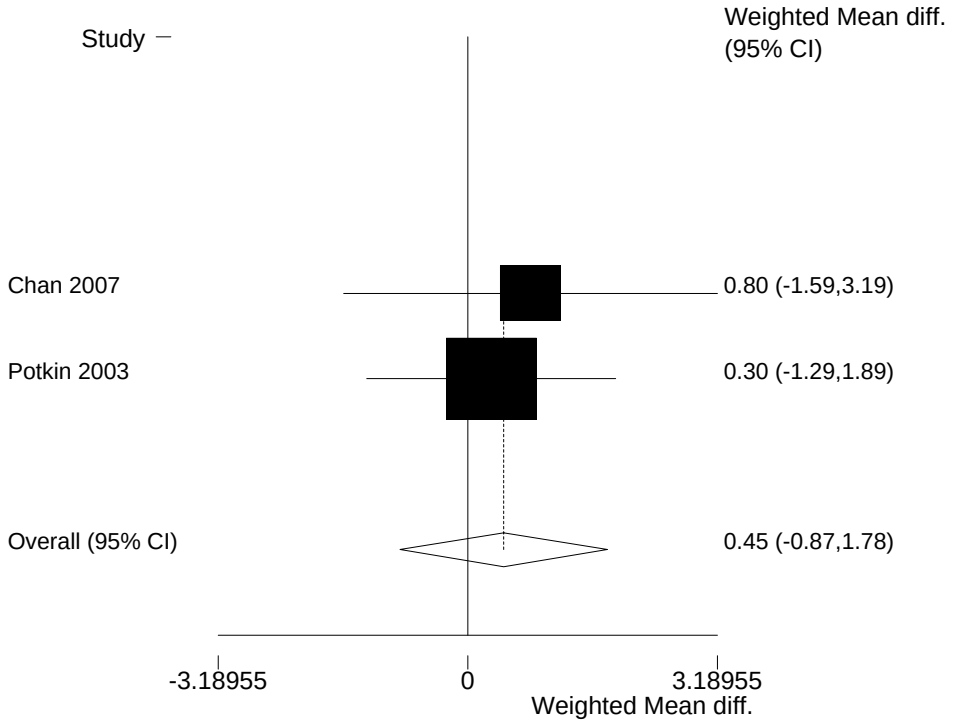
```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Stroup 2006      |      1.6    -.339218   3.53922
-----------------+---------------------------------
  I-V pooled WMD |      1.6    -.339218   3.53922
-----------------+---------------------------------
N=198
Test of WMD=0 : z= 1.62 p = 0.106
```

Figure III. 6. a: PANSS negative subscore - Risperidone versus Amisulpride



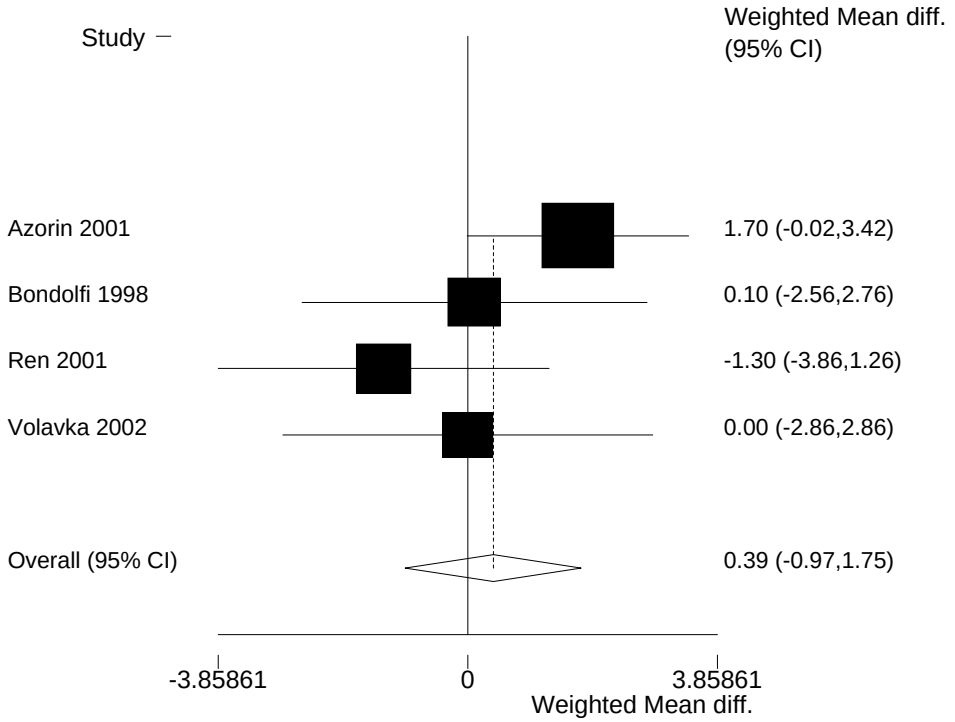

```
N=519
Heterogeneity chi-squared =   2.25 (d.f. = 2) p = 0.325
Estimate of between-study variance Tau-squared =  0.1144
Test of WMD=0 : z= 1.76 p = 0.078
```

Figure III. 6. b: PANSS negative subscore - Risperidone versus Aripiprazole



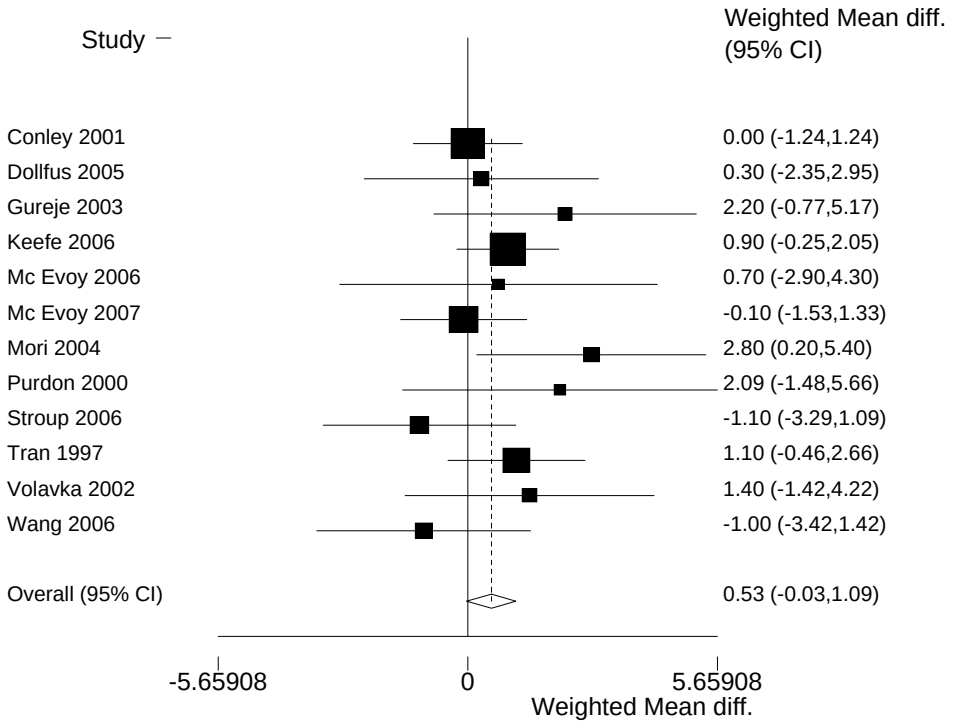
N=372
Heterogeneity chi-squared = 0.12 (d.f. = 1) p = 0.733
Estimate of between-study variance Tau-squared = 0.0000
Test of WMD=0 : z= 0.67 p = 0.502

Figure III. 6. c: PANSS negative subscore - Risperidone versus Clozapine



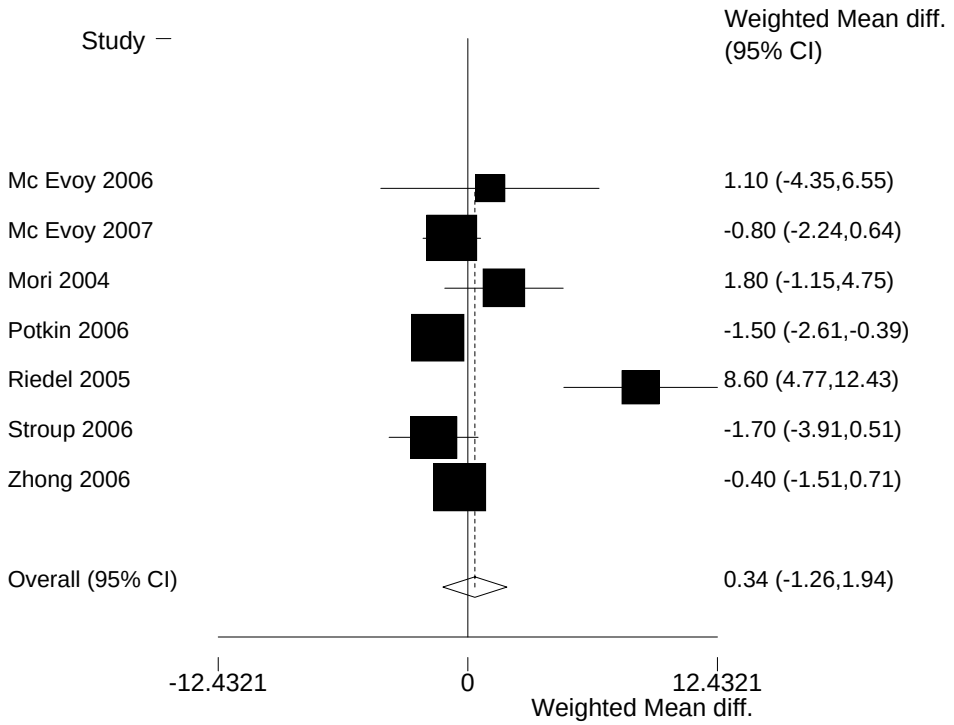
N=541
Heterogeneity chi-squared = 3.98 (d.f. = 3) p = 0.263
Estimate of between-study variance Tau-squared = 0.4872
Test of WMD=0 : z= 0.56 p = 0.575

Figure III. 6. d: PANSS negative subscore - Risperidone versus Olanzapine



N=1545
Heterogeneity chi-squared = 11.31 (d.f. = 11) p = 0.417
Estimate of between-study variance Tau-squared = 0.0281
Test of WMD=0 : z= 1.87 p = 0.062

Figure III. 6. e: PANSS negative subscore - Risperidone versus Quetiapine

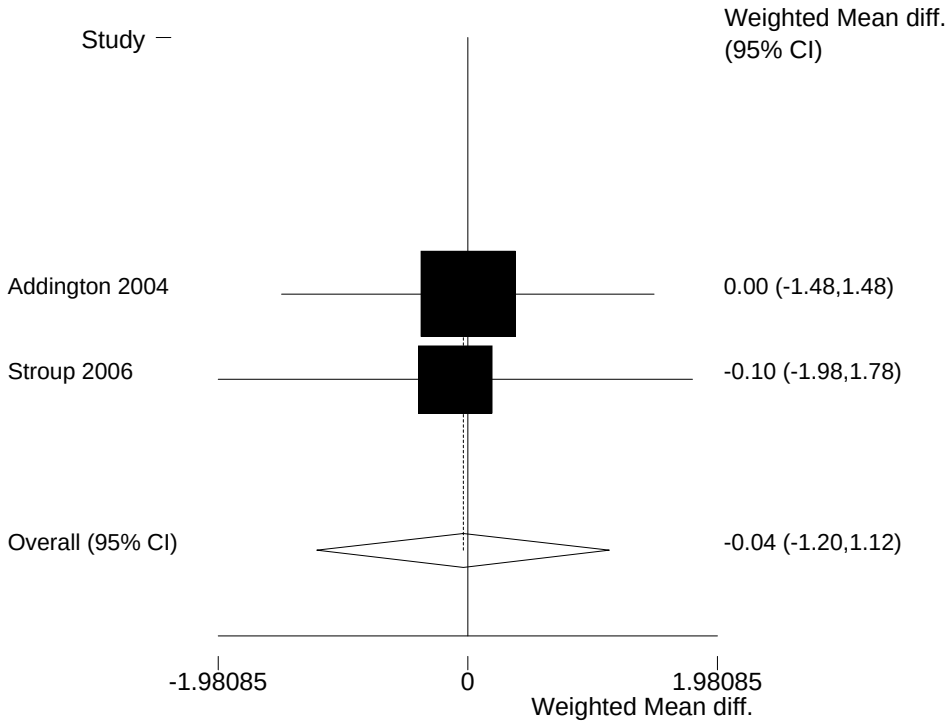



```
N=1264
Heterogeneity chi-squared =  28.72 (d.f. = 6) p = 0.000
Estimate of between-study variance Tau-squared =  3.1291
Test of WMD=0 : z= 0.42 p = 0.673
```

Figure III. 6. f: PANSS negative subscore - Risperidone versus Sertindole

```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Azorin 2006      |      1.3    -.531586   3.13159
-----------------+---------------------------------
  I-V pooled WMD |      1.3    -.531586   3.13159
-----------------+---------------------------------
N=172
Test of WMD=0 : z= 1.39 p = 0.164
```

Figure III. f. g: PANSS negative subscore - Risperidone versus Ziprasidone




```
N=500
Heterogeneity chi-squared =   0.01 (d.f. = 1) p = 0.935
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.06 p = 0.949
```

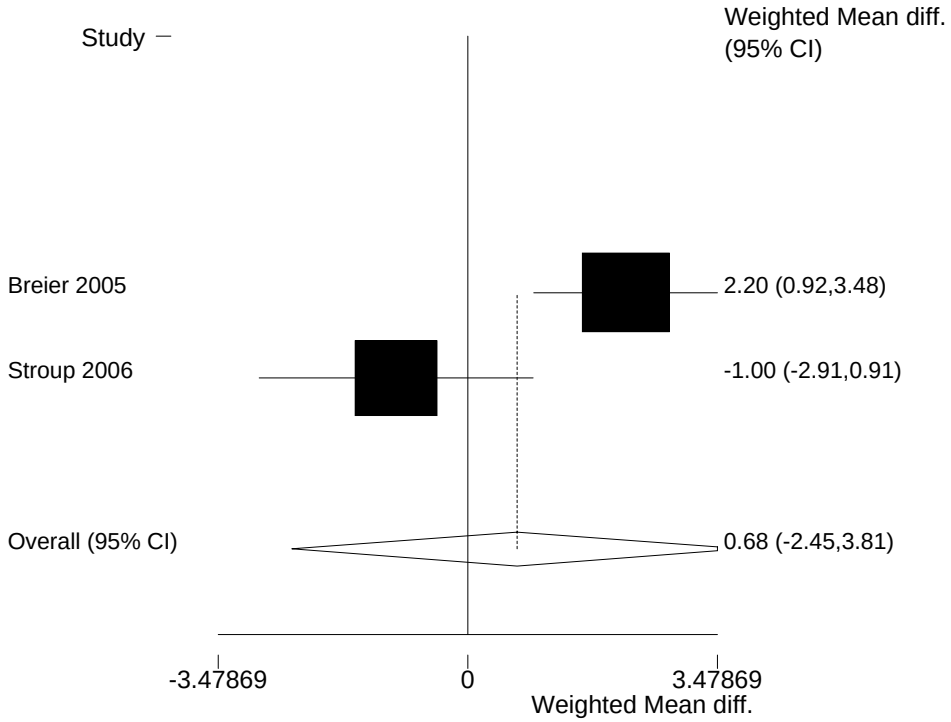
Figure III. 7. a: PANSS negative subscore - Sertindole versus Risperidone

```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Azorin 2006      |     -1.3    -3.13159   .531586
-----------------+---------------------------------
  I-V pooled WMD |     -1.3    -3.13159   .531586
-----------------+---------------------------------
N=172
Test of WMD=0 : z= 1.39 p = 0.164
```

Figure III. 8. a: PANSS negative subscore - Ziprasidone versus Amisulpride

```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Olie 2006        |       .8    -1.41218   3.01218
-----------------+---------------------------------
  I-V pooled WMD |       .8    -1.41218   3.01218
-----------------+---------------------------------
N=122
Test of WMD=0 : z= 0.71 p = 0.478
```

Figure III. 8. b: PANSS negative subscore - Ziprasidone versus Olanzapine

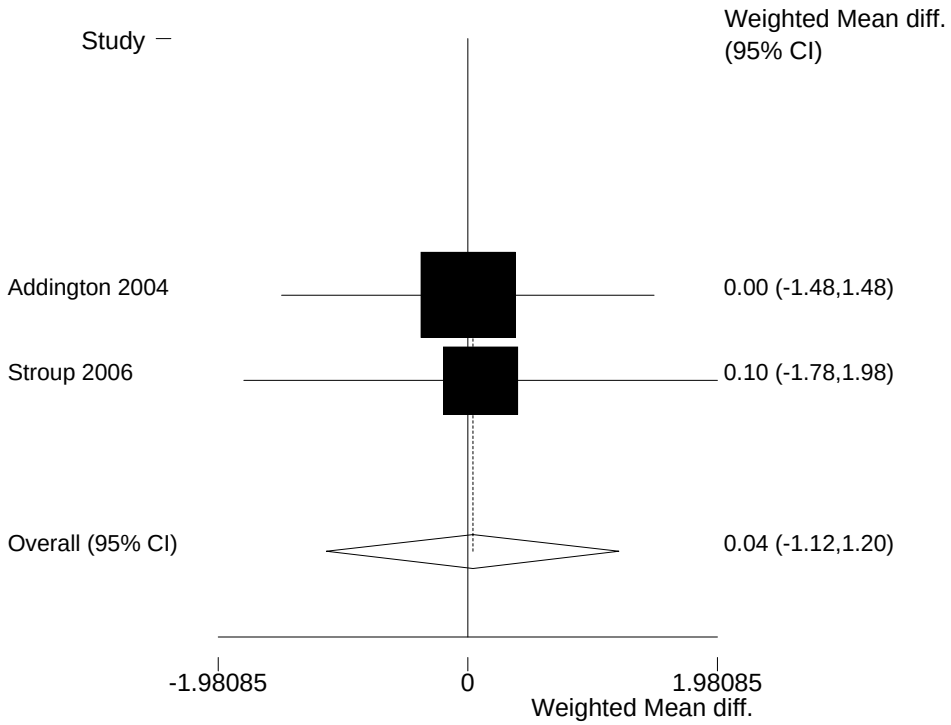



```
N=730
Heterogeneity chi-squared =   7.45 (d.f. = 1) p = 0.006
Estimate of between-study variance Tau-squared =  4.4329
Test of WMD=0 : z= 0.43 p = 0.670
```

Figure III. 8. c: PANSS negative subscore - Ziprasidone versus Quetiapine

```
           Study |       WMD  [95% Conf. Interval]
-----------------+---------------------------------
Stroup 2006      |     -1.6    -3.53922   .339218
-----------------+---------------------------------
  I-V pooled WMD |     -1.6    -3.53922   .339218
-----------------+---------------------------------
N=198
Test of WMD=0 : z= 1.62 p = 0.106
```

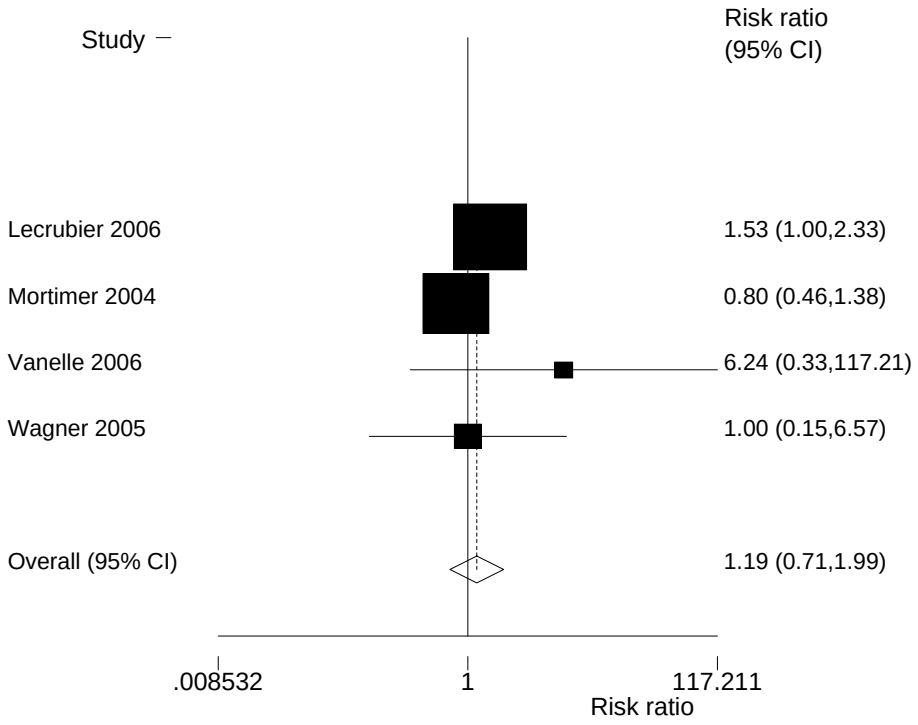
Figure III. 8. d: PANSS negative subscore - Ziprasidone versus Risperidone




```
N=500
Heterogeneity chi-squared =   0.01 (d.f. = 1) p = 0.935
Estimate of between-study variance Tau-squared =  0.0000
Test of WMD=0 : z= 0.06 p = 0.949
```

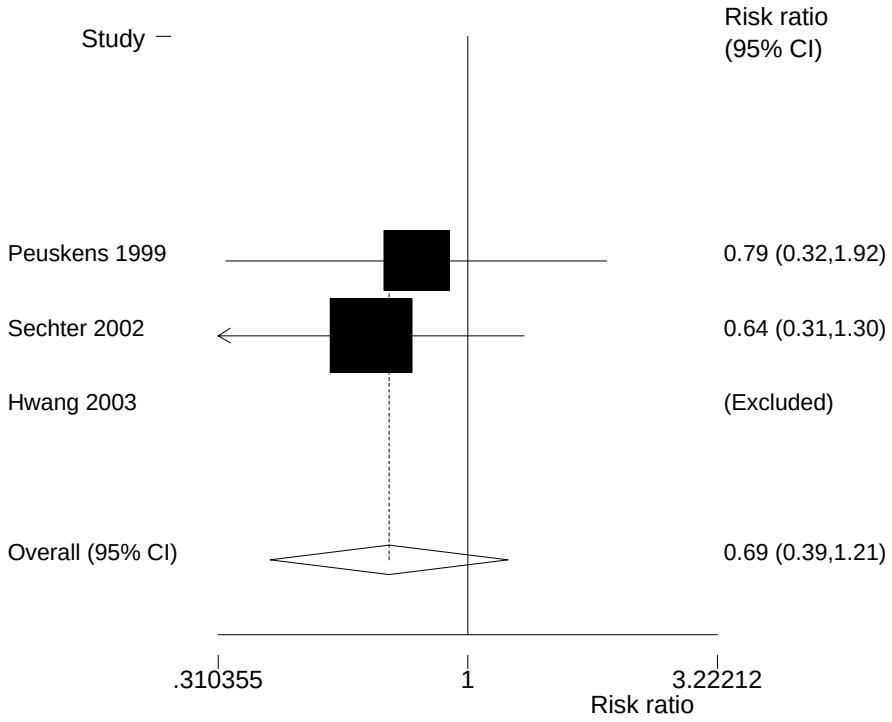
Figures IV. 1. a – IV. 9. a. : Dropout due to inefficacy (risk ratio)

Figure IV. 1. a: Dropout due to inefficacy - Amisulpride versus Olanzapine



N=724
Heterogeneity chi-squared = 4.65 (d.f. = 3) p = 0.199
Estimate of between-study variance Tau-squared = 0.0909
Test of RR=1 : z= 0.66 p = 0.506

Figure IV. 1. b: Dropout due to inefficacy - Amisulpride versus Risperidone




```
N=538
Heterogeneity chi-squared =   0.13 (d.f. = 1) p = 0.715
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 1.30 p = 0.194
```

Figure IV. 1. c: Dropout due to inefficacy – Amisulpride versus Ziprasidone

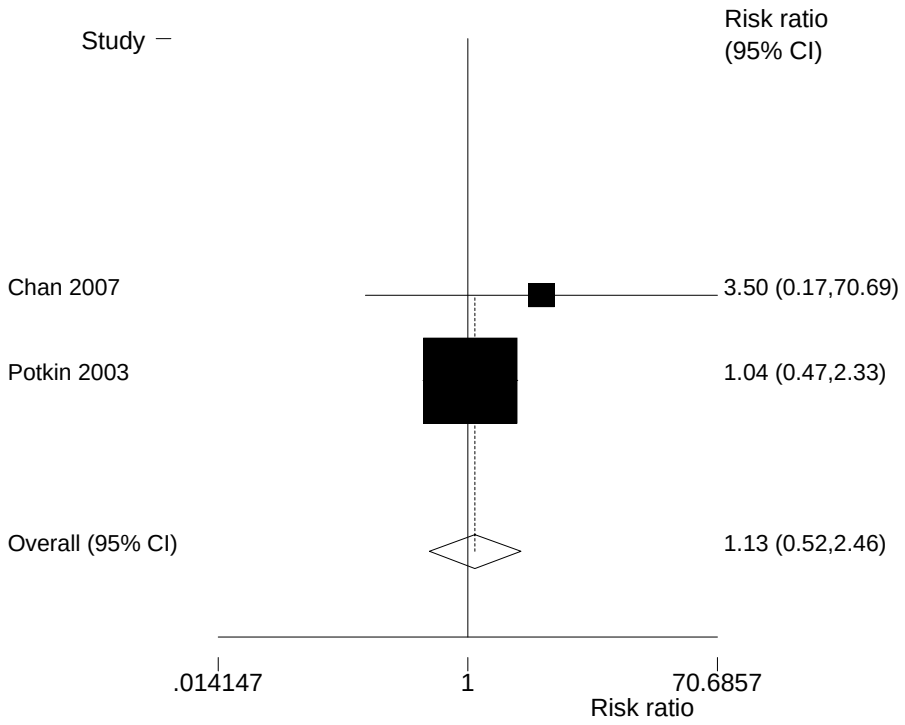
```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Olie 2006        |   0.21        .05      0.94          100
-----------------+-------------------------------------------------------
  M-H pooled RR  |   0.21        .05      0.94          100

  N=123
  Test of RR=1 : z= 2.04 p = 0.04
```

Figure IV. 2. a: Dropout due to inefficacy - Aripiprazole versus Olanzapine

Study	RR	[95% Conf.	Interval]	% Weight
McQuade 2004	1.69551	.905877	3.17346	100
M-H pooled RR	1.69551	.905877	3.17346	

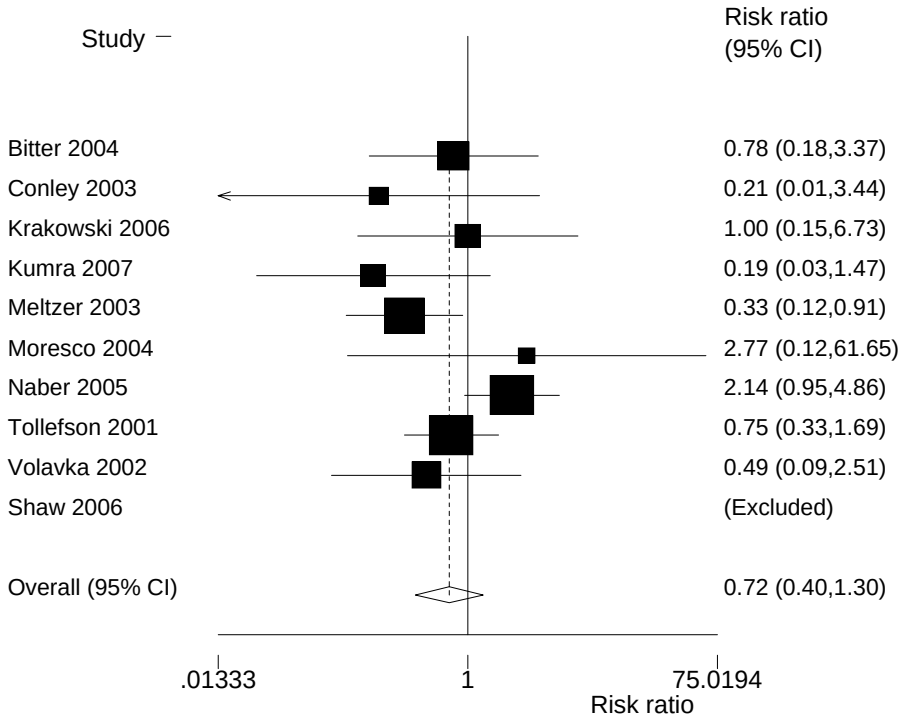
N=317
Test of RR=1 : z= 1.65 p = 0.099

Figure IV. 2. b: Dropout due to inefficacy - Aripiprazole versus Risperidone



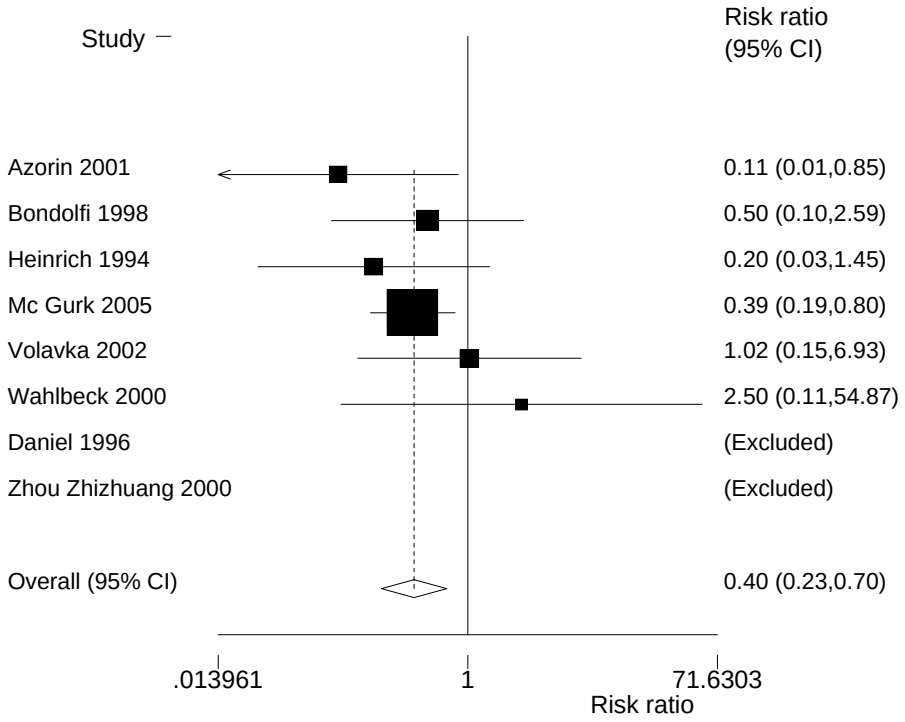
N=384
Heterogeneity chi-squared = 0.59 (d.f. = 1) p = 0.442
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 0.31 p = 0.759

Figure IV. 3. a: Dropout due to inefficacy - Clozapine versus Olanzapine




```
N=1649
Heterogeneity chi-squared =  12.39 (d.f. = 8) p = 0.135
Estimate of between-study variance Tau-squared =  0.2532
Test of RR=1 : z= 1.08 p = 0.279
```

Figure IV. 3. b: Dropout due to inefficacy - Clozapine versus Risperidone

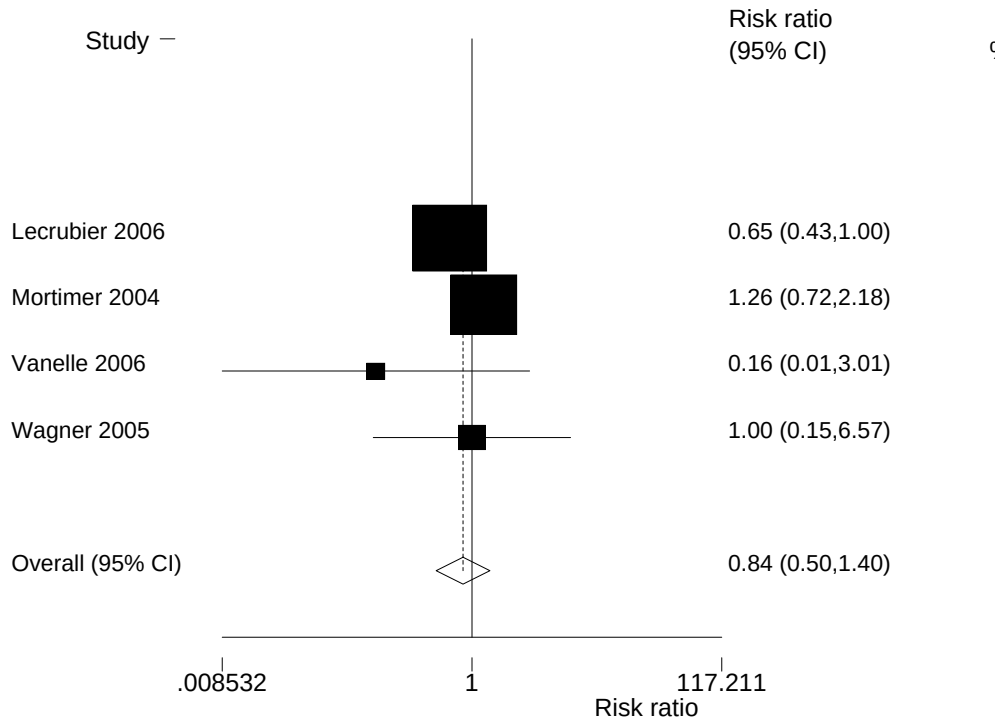



```
N=627
Heterogeneity chi-squared =   4.46 (d.f. = 5) p = 0.485
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 3.21 p = 0.001
```

Figure IV. 3. c: Dropout due to inefficacy - Clozapine versus Ziprasidone

```
          Study |       RR   [95% Conf. Interval]    % Weight
----------------+-------------------------------------------------------
Sacchetti 2006  |  .657658     .113176    3.8216          100
----------------+-------------------------------------------------------
  M-H pooled RR |  .657658     .113176    3.8216
----------------+-------------------------------------------------------
  N=147
  Heterogeneity chi-squared =   0.00 (d.f. = 0) p =    .
  Test of RR=1 : z= 0.47 p = 0.641
```

Figure IV. 4. a: Dropout due to inefficacy - Olanzapine versus Amisulpride

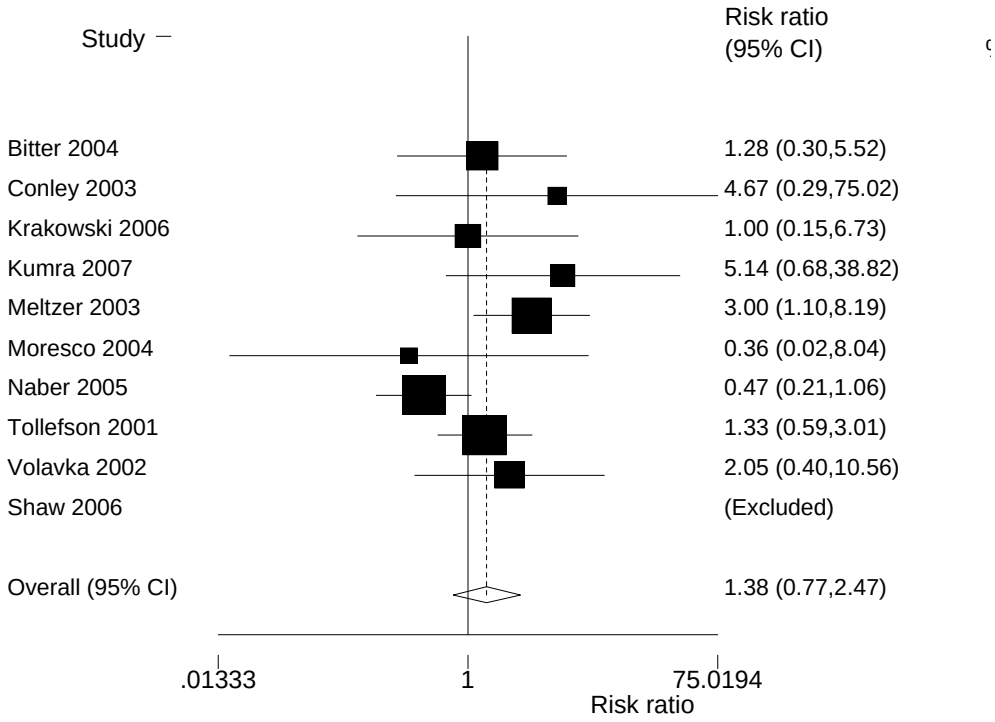



```
  N=724
  Heterogeneity chi-squared =   4.65 (d.f. = 3) p = 0.199
  Estimate of between-study variance Tau-squared =  0.0909
  Test of RR=1 : z= 0.66 p = 0.506
```

Figure IV. 4. b: Dropout due to inefficacy - Olanzapine versus Aripiprazole

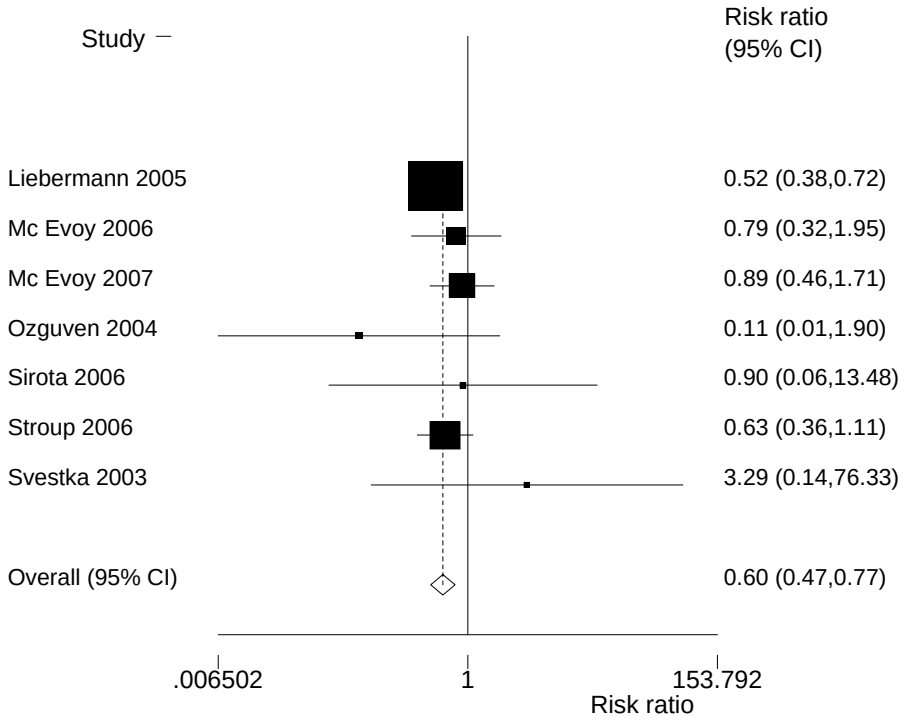
```
          Study |       RR   [95% Conf. Interval]    % Weight
----------------+-------------------------------------------------
McQuade 2004    |  .589792     .315113    1.1039          100
----------------+-------------------------------------------------
  M-H pooled RR |  .589792     .315113    1.1039
----------------+-------------------------------------------------
  N=317
  Test of RR=1 : z= 1.65 p = 0.099
```

Figure IV. 4. c: Dropout due to inefficacy - Olanzapine versus Clozapine



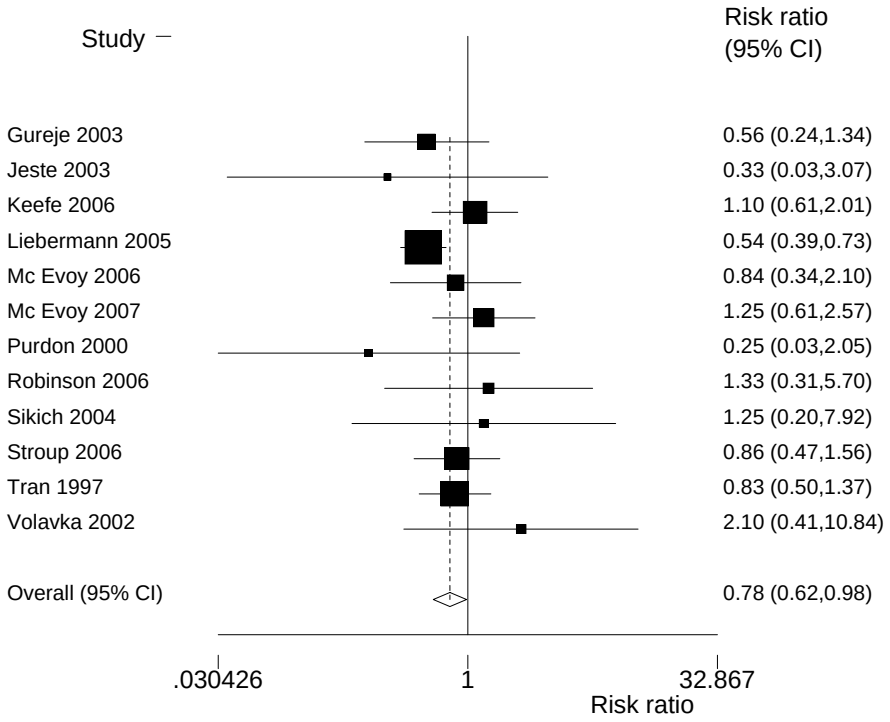

```
N=1649
Heterogeneity chi-squared =  12.39 (d.f. = 8) p = 0.135
Estimate of between-study variance Tau-squared =  0.2532
Test of RR=1 : z= 1.08 p = 0.279
```

Figure IV. 4. d: Dropout due to inefficacy - Olanzapine versus Quetiapine



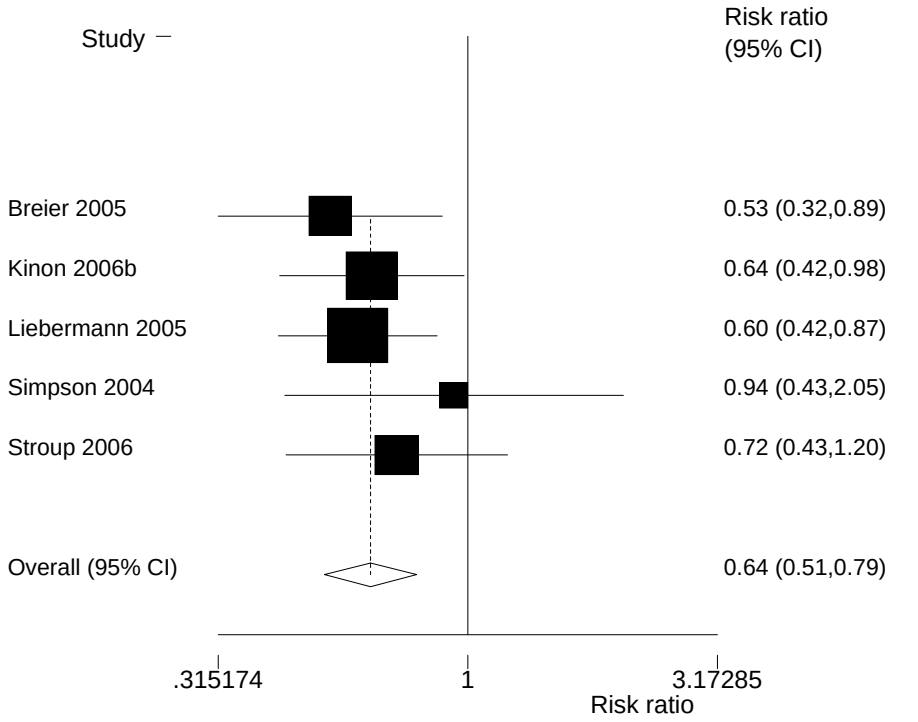

```
N=1217
Heterogeneity chi-squared =   5.09 (d.f. = 6) p = 0.533
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 4.13 p = 0.000
```

Figure IV. 4. e: Dropout due to inefficacy - Olanzapine versus Risperidone



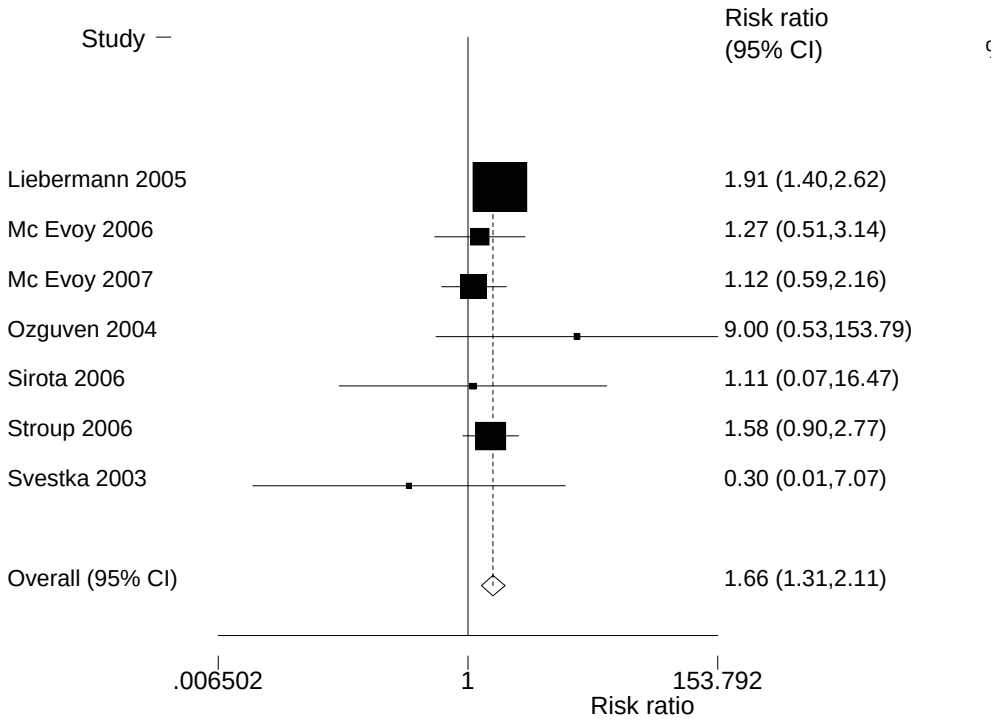

```
N=2291
Heterogeneity chi-squared =  12.74 (d.f. = 11) p = 0.311
Estimate of between-study variance Tau-squared =  0.0225
Test of RR=1 : z= 2.10 p = 0.035
```

Figure IV. 4. f: Dropout due to inefficacy - Olanzapine versus Ziprasidone



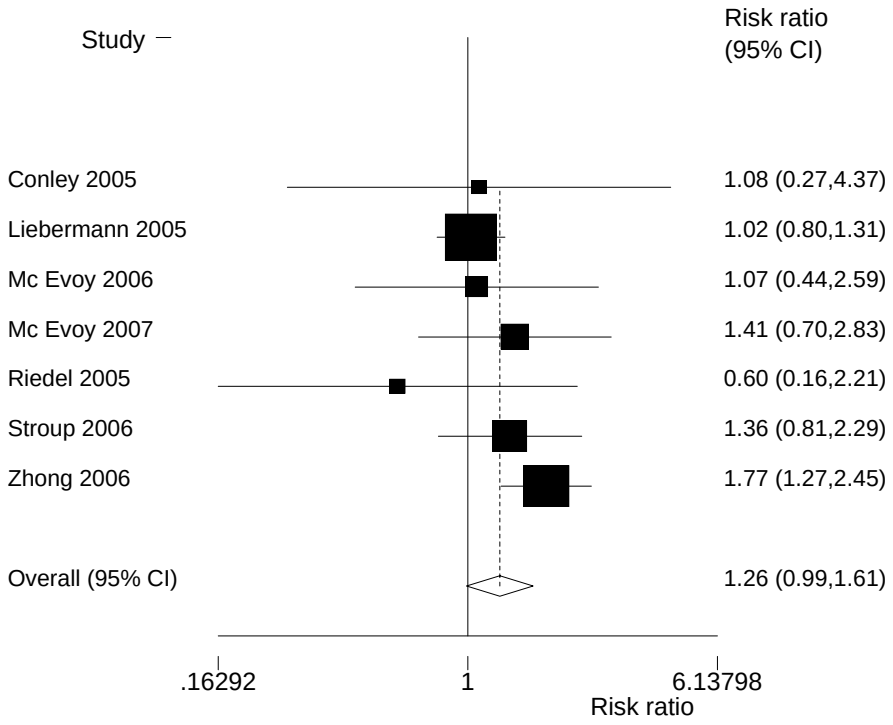
N=1937
Heterogeneity chi-squared = 1.75 (d.f. = 4) p = 0.782
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 4.15 p = 0.000

Figure IV. 5. a: Dropout due to inefficacy - Quetiapine versus Olanzapine



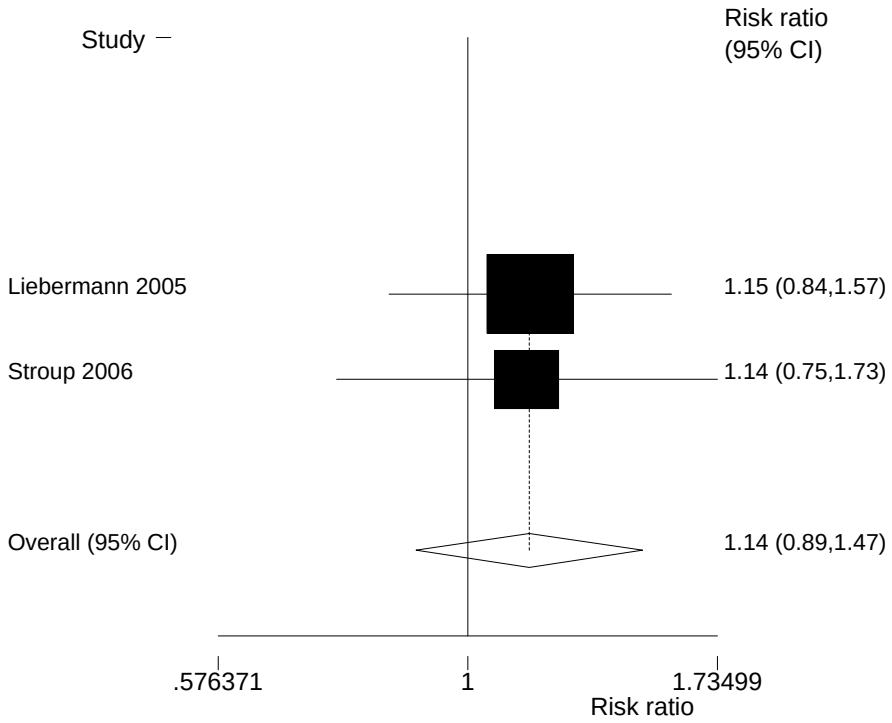
N=1217
Heterogeneity chi-squared = 5.09 (d.f. = 6) p = 0.533
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 4.13 p = 0.000

Figure IV. 5. b: Dropout due to inefficacy - Quetiapine versus Risperidone



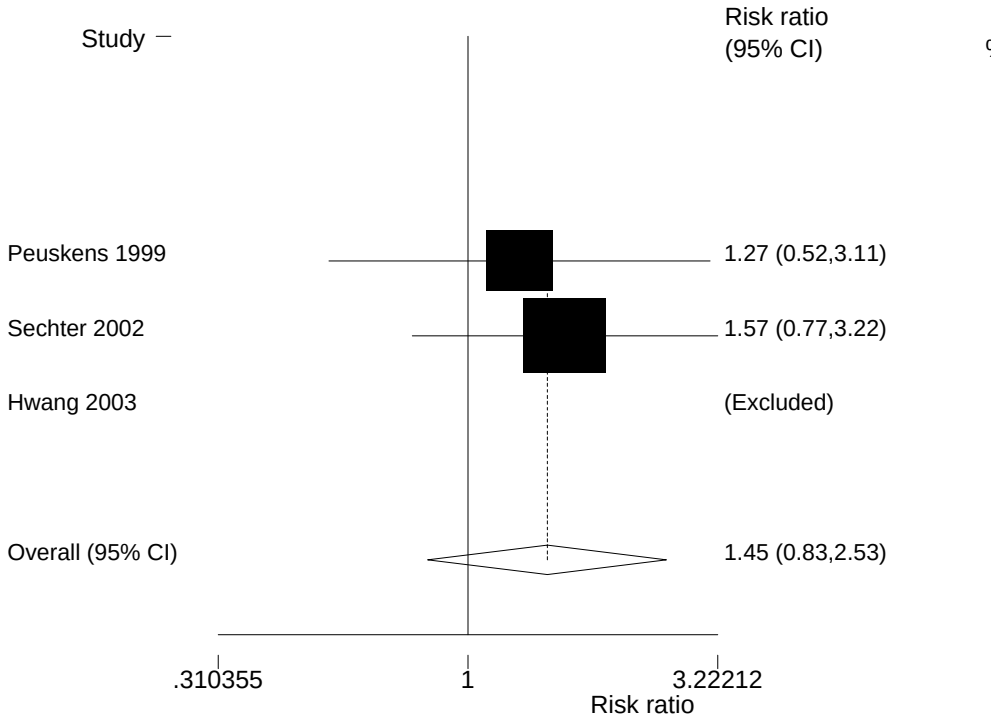
N=1851
Heterogeneity chi-squared = 8.41 (d.f. = 6) p = 0.210
Estimate of between-study variance Tau-squared = 0.0277
Test of RR=1 : z= 1.90 p = 0.058

Figure IV. 5. c: Dropout due to inefficacy - Quetiapine versus Ziprasidone



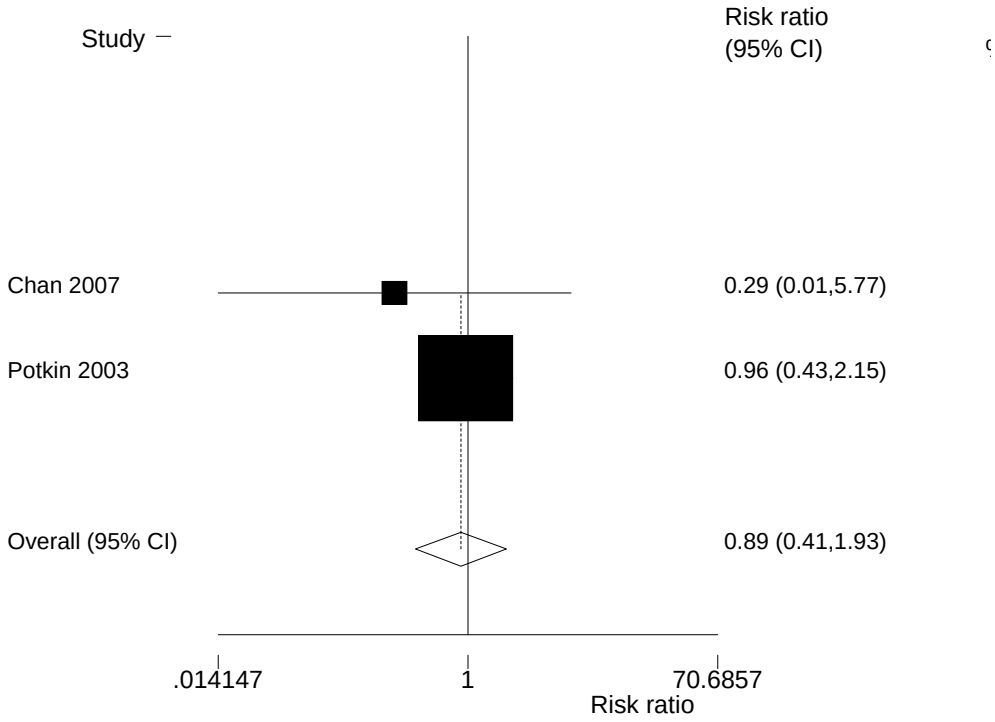
N=722
Heterogeneity chi-squared = 0.00 (d.f. = 1) p = 0.977
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 1.06 p = 0.290

Figure IV. 6. a: Dropout due to inefficacy - Risperidone versus Amisulpride



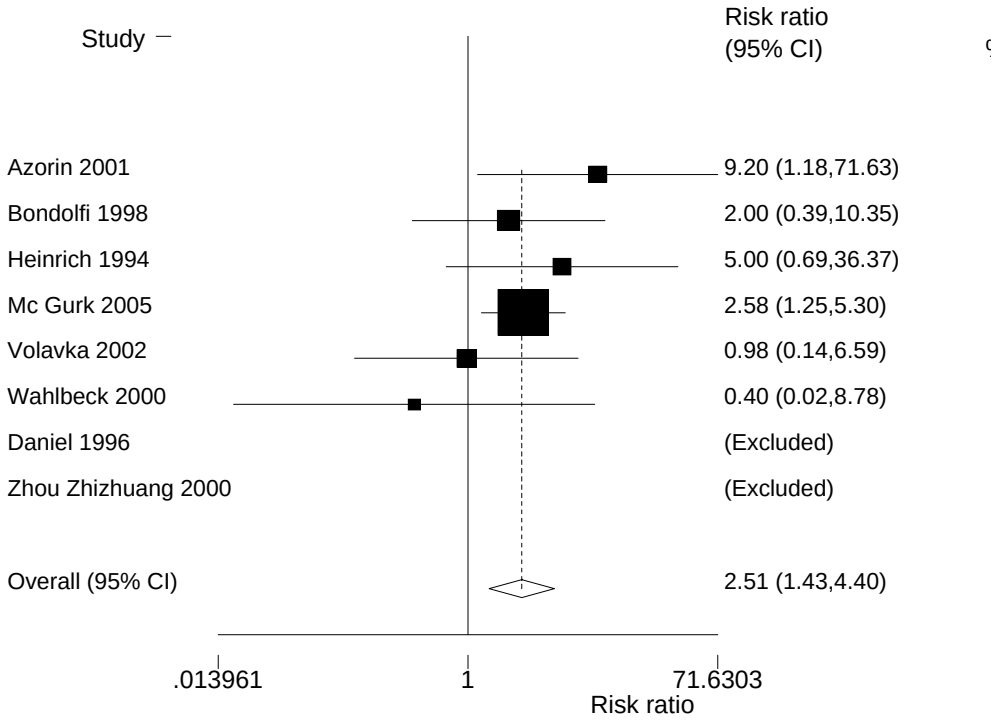

```
N=538
Heterogeneity chi-squared =   0.13 (d.f. = 1) p = 0.715
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 1.30 p = 0.194
```

Figure IV. 6. b: Dropout due to inefficacy - Risperidone versus Aripiprazole



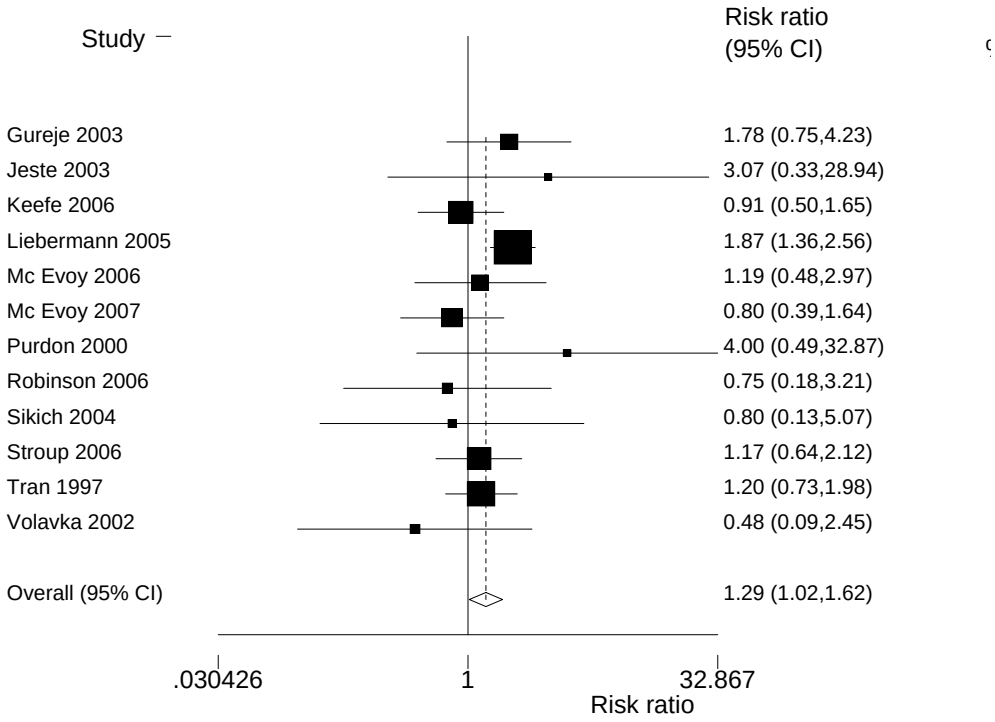

```
N=384
Heterogeneity chi-squared =   0.59 (d.f. = 1) p = 0.442
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 0.31 p = 0.759
```

Figure IV. 6. c: Dropout due to inefficacy - Risperidone versus Clozapine



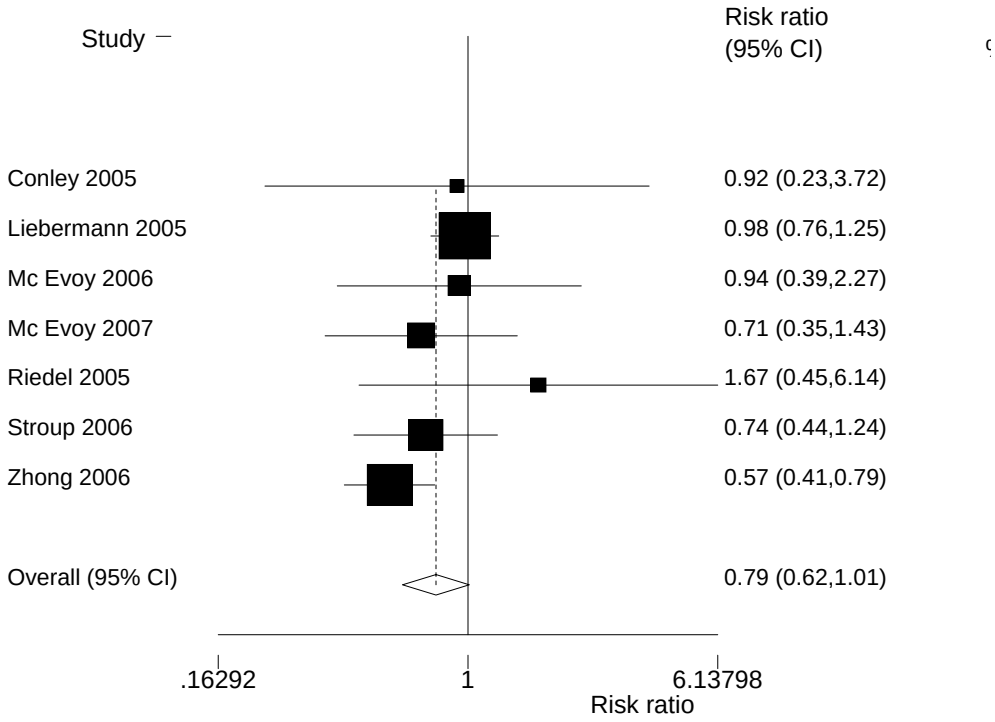

```
N=627
Heterogeneity chi-squared =   4.46 (d.f. = 5) p = 0.485
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 3.21 p = 0.001
```

Figure IV. 6. d: Dropout due to inefficacy - Risperidone versus Olanzapine



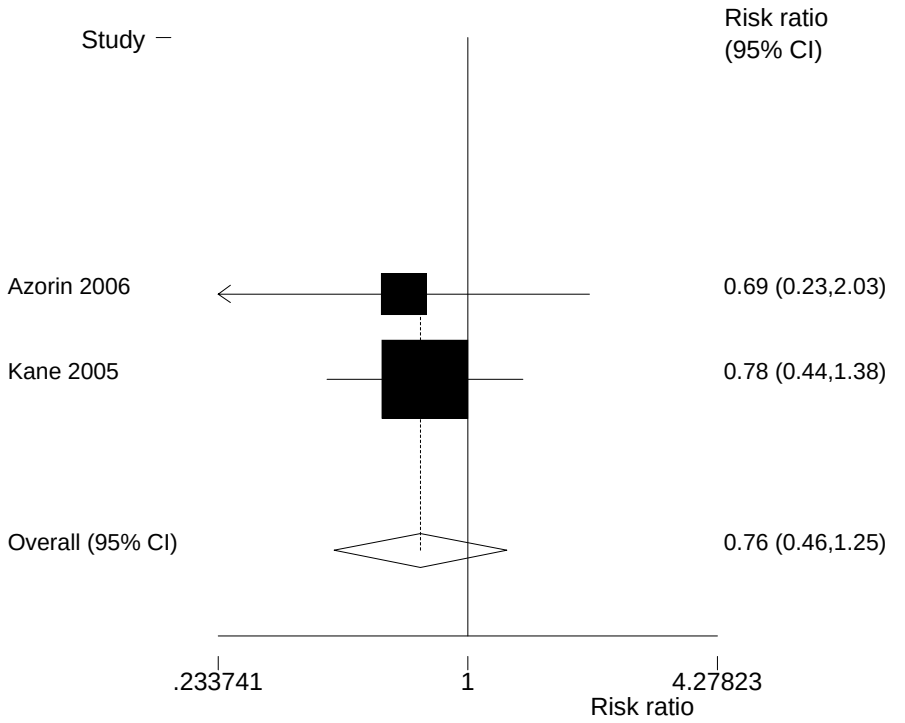

```
N=2291
Heterogeneity chi-squared =  12.74 (d.f. = 11) p = 0.311
Estimate of between-study variance Tau-squared =  0.0225
Test of RR=1 : z= 2.10 p = 0.035
```

Figure IV. 6. e: Dropout due to inefficacy - Risperidone versus Quetiapine



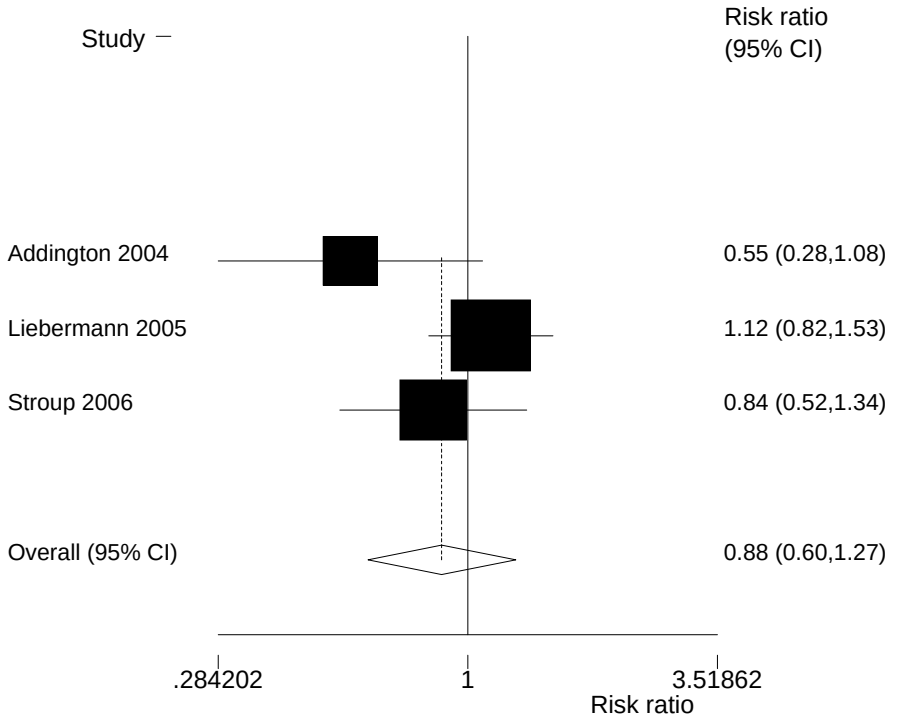
N=1851
Heterogeneity chi-squared = 8.41 (d.f. = 6) p = 0.210
Estimate of between-study variance Tau-squared = 0.0277
Test of RR=1 : z= 1.90 p = 0.058

Figure IV. 6. f: Dropout due to inefficacy - Risperidone versus Sertindole



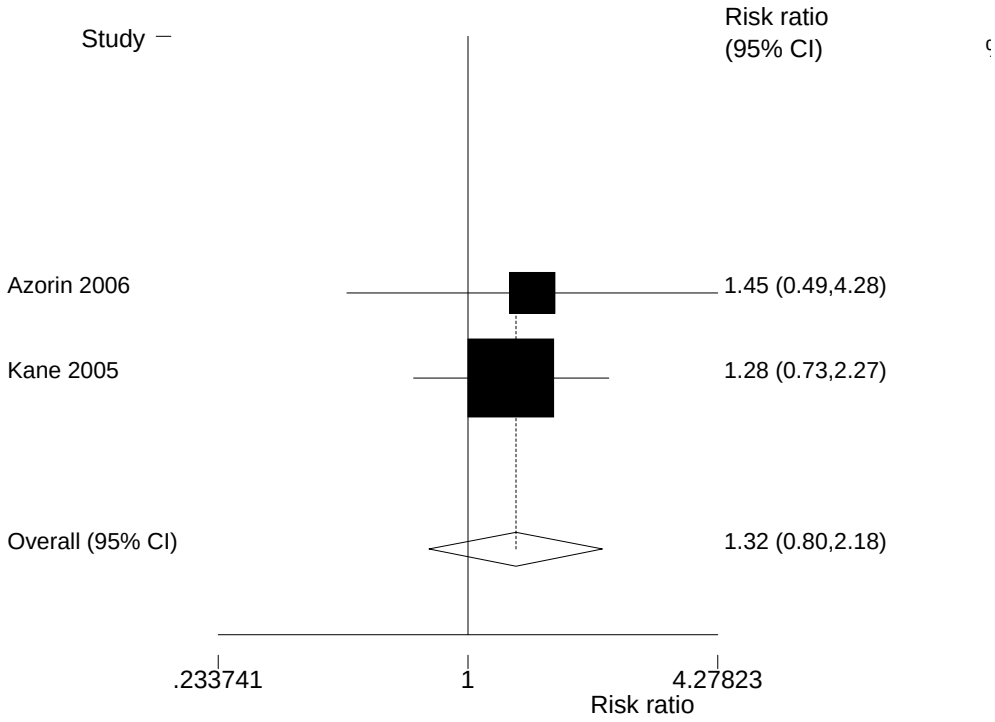

```
N=508
Heterogeneity chi-squared =   0.04 (d.f. = 1) p = 0.843
Estimate of between-study variance Tau-squared =  0.0000


Test of RR=1 : z= 1.08 p = 0.280
```

Figure IV. 6. g: Dropout due to inefficacy - Risperidone versus Ziprasidone




```
N=1029
Heterogeneity chi-squared =   3.92 (d.f. = 2) p = 0.141
Estimate of between-study variance Tau-squared =  0.0534
Test of RR=1 : z= 0.69 p = 0.489
```

Figure IV. 7. a: Dropout due to inefficacy - Sertindole versus Risperidone




```
N=508
Heterogeneity chi-squared =   0.04 (d.f. = 1) p = 0.843
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 1.08 p = 0.280
```

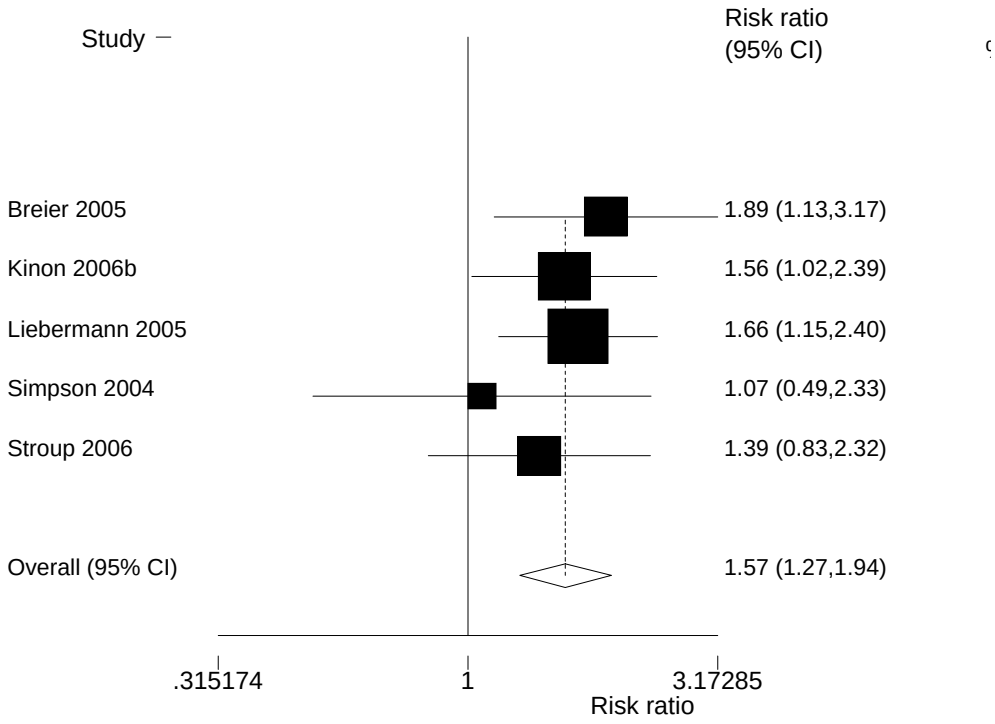
Figure IV. 8. a: Dropout due to inefficacy – Ziprasidone versus Amisulpride

```
           Study |       RR   [95% Conf. Interval]    % Weight
-----------------+-------------------------------------------------------
Olie 2006        |   4.73        1.06      20.98        100
-----------------+-------------------------------------------------------
  M-H pooled RR  |   4.73        1.06      20.98        100

  N=123
  Test of RR=1 : z= 2.04 p = 0.04
```

Figure IV. 8. b: Dropout due to inefficacy - Ziprasidone versus Clozapine

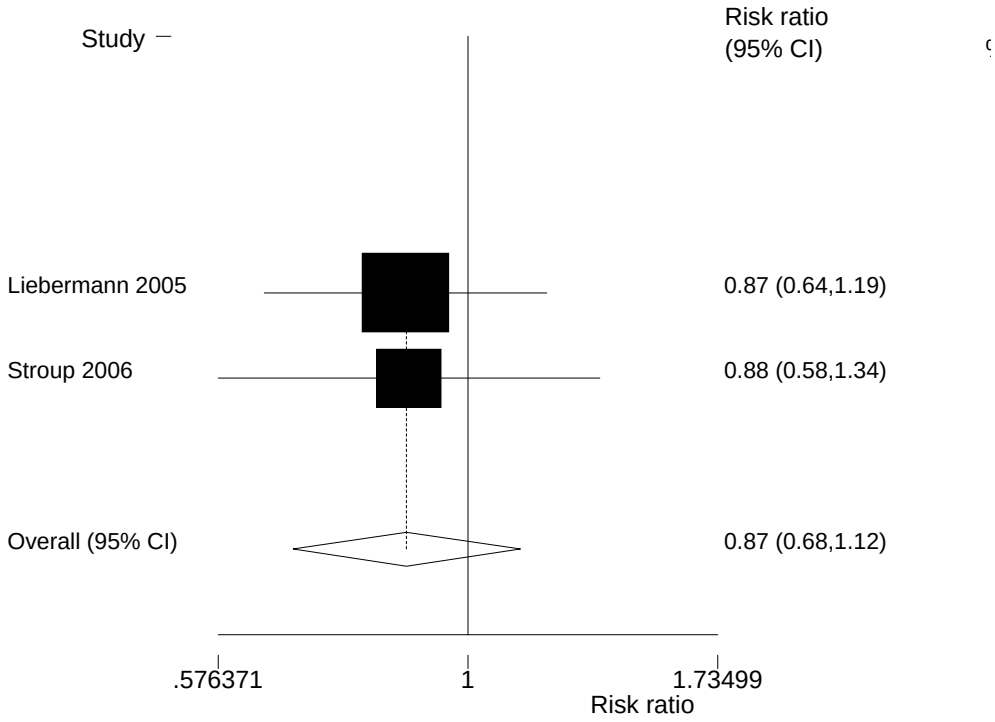
```
-----------------+-------------------------------------------------------
Sacchetti 2006   |  1.52055     .261671   8.83578          100
-----------------+-------------------------------------------------------
  M-H pooled RR  |  1.52055     .261671   8.83578
-----------------+-------------------------------------------------------
  N=147
  Test of RR=1 : z= 0.47 p = 0.641
```

Figure IV. 8. c: Dropout due to inefficacy - Ziprasidone versus Olanzapine



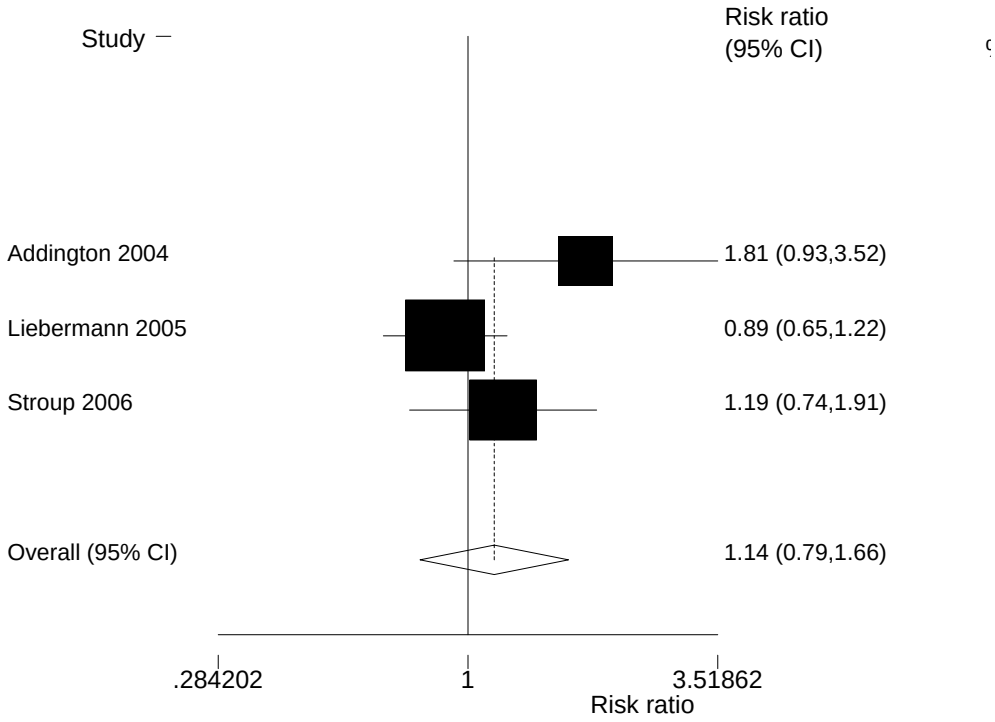
N=1937
Heterogeneity chi-squared = 1.75 (d.f. = 4) p = 0.782
Estimate of between-study variance Tau-squared = 0.0000
Test of RR=1 : z= 4.15 p = 0.000

Figure IV. 8. d: Dropout due to inefficacy - Ziprasidone versus Quetiapine




```
N=722
Heterogeneity chi-squared =   0.00 (d.f. = 1) p = 0.977
Estimate of between-study variance Tau-squared =  0.0000
Test of RR=1 : z= 1.06 p = 0.290
```

Figure IV. 8. e: Dropout due to inefficacy - Ziprasidone versus Risperidone



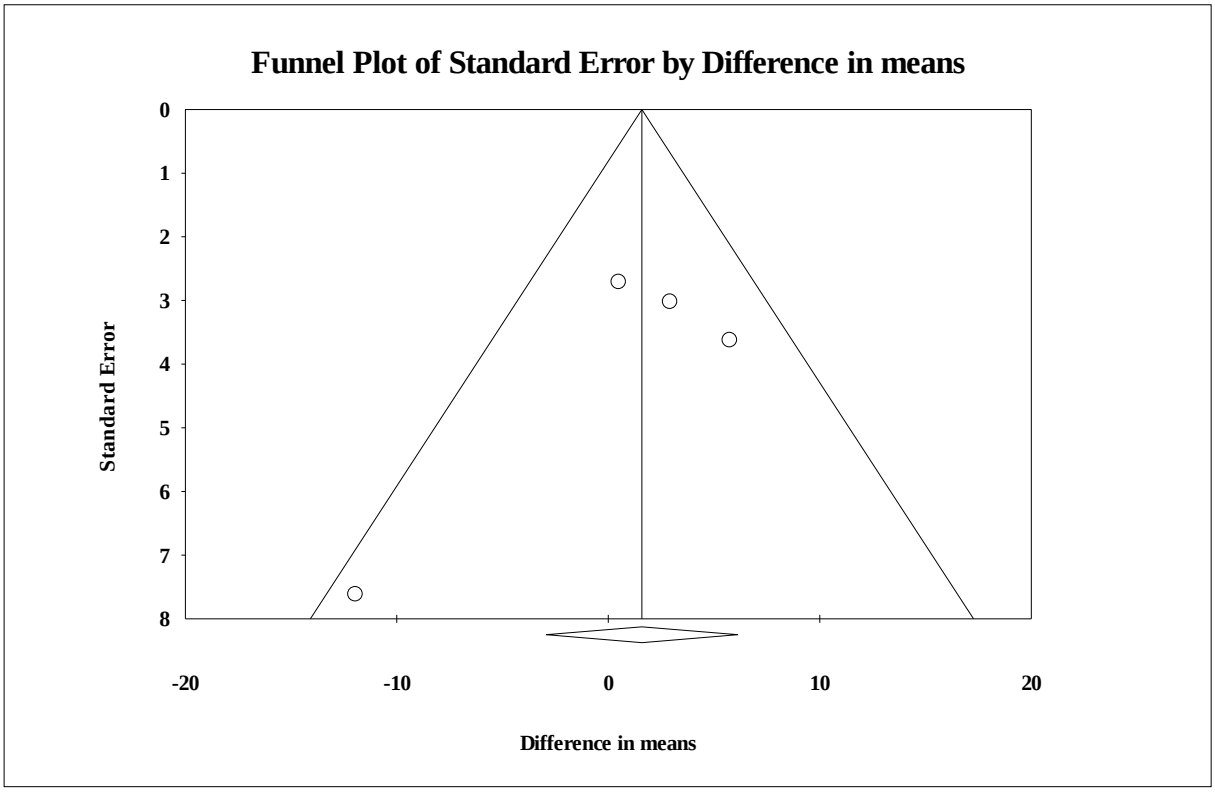

```
N=1029
Heterogeneity chi-squared =   3.92 (d.f. = 2) p = 0.141
Estimate of between-study variance Tau-squared =  0.0534
Test of RR=1 : z= 0.69 p = 0.489
```

Figure V.a to V.i: Publication bias assessed by funnel plots, fail-safe estimates and Egger's tests:

Note that comparisons with less than three published studies could not be assessed by these methods.

Results are shown only once, for example amisulpride versus olanzapine, but not again olanzapine versus amisulpride

Figure V.a: Amisulpride versus olanzapine

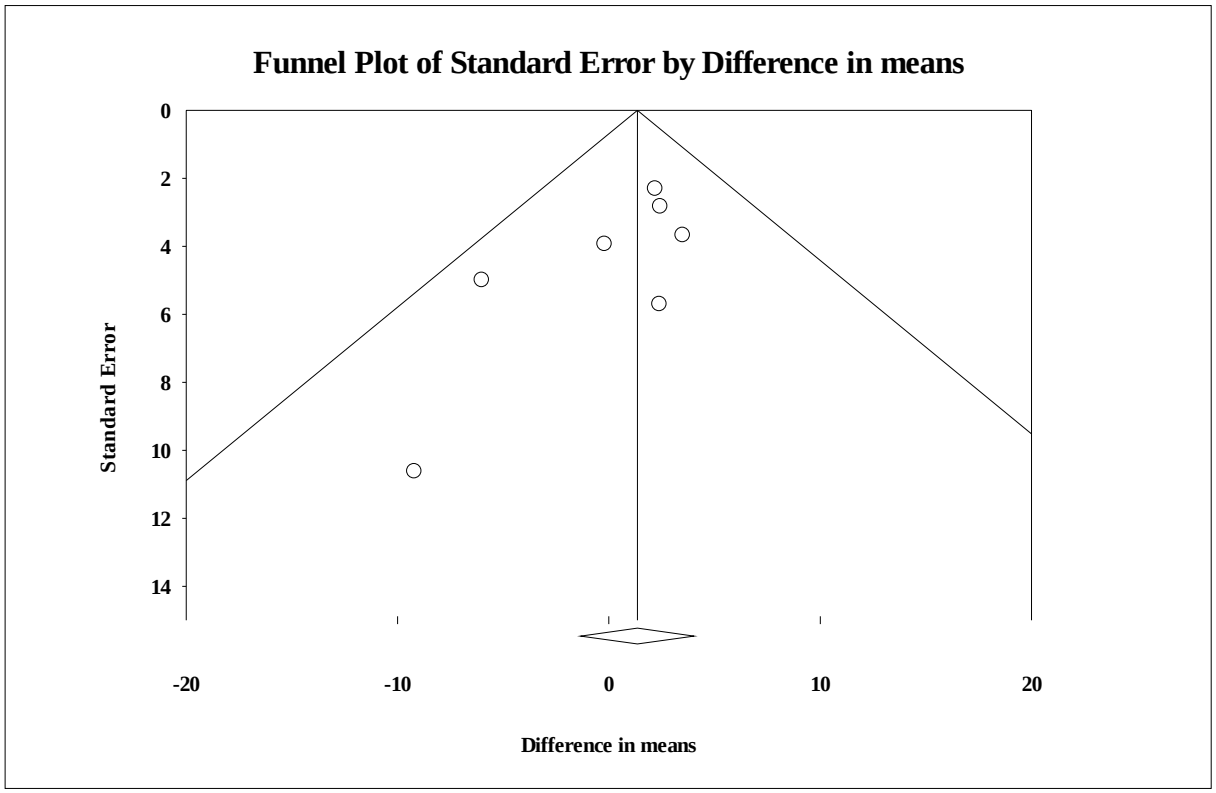


Fail-safe calculation: does not apply, because the difference was not statistically significant.

Egger's regression intercept

Intercept	-2,225
Standard error	1,946
95% lower limit (2-tailed)	-10,600
95% upper limit (2-tailed)	6,149
t-value	1,143
df	2,000
P-value (1-tailed)	0,186
P-value (2-tailed)	0,371

Figure V.b: Clozapine versus olanzapine

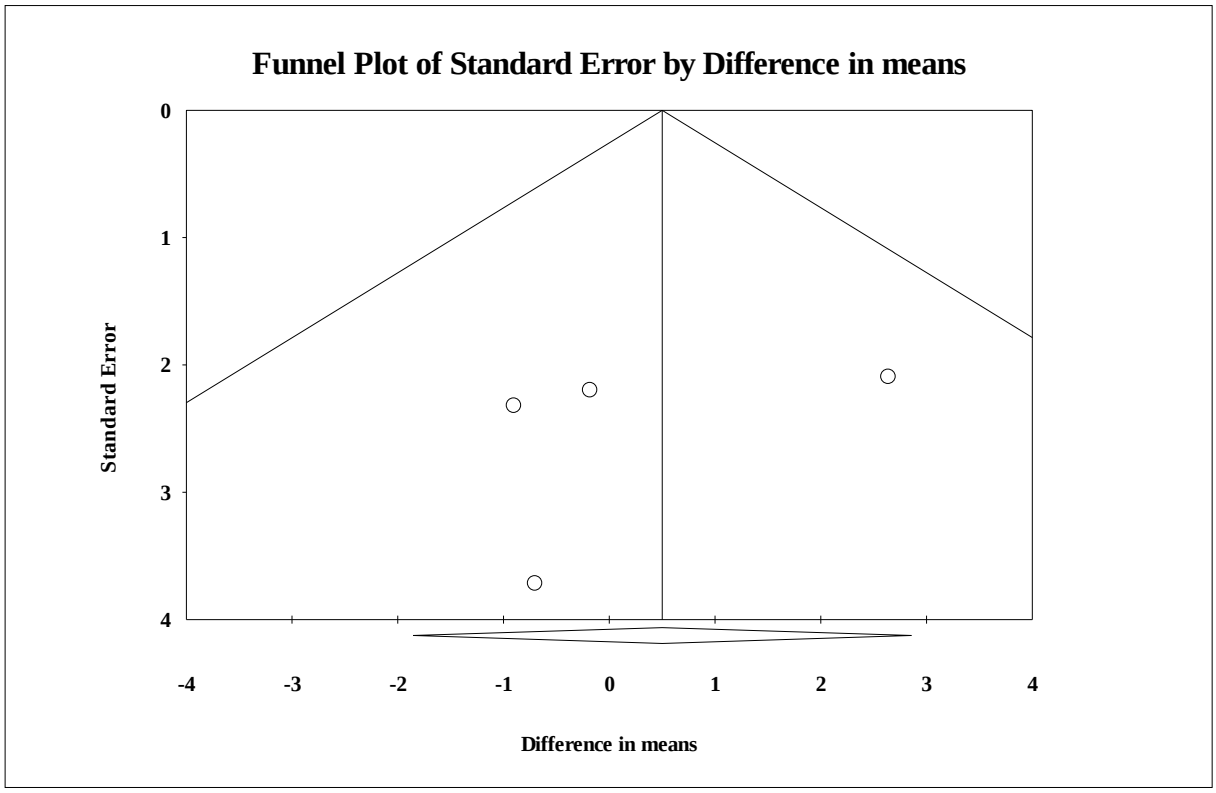


Fail-safe calculation: does not apply, because the difference was not statistically significant.

Egger's regression intercept

Intercept	-1,312
Standard error	0,661
95% lower limit (2-tailed)	-3,012
95% upper limit (2-tailed)	0,387
t-value	1,985
df	5,000
P-value (1-tailed)	0,052
P-value (2-tailed)	0,104

Figure V.c: Clozapine versus quetiapine

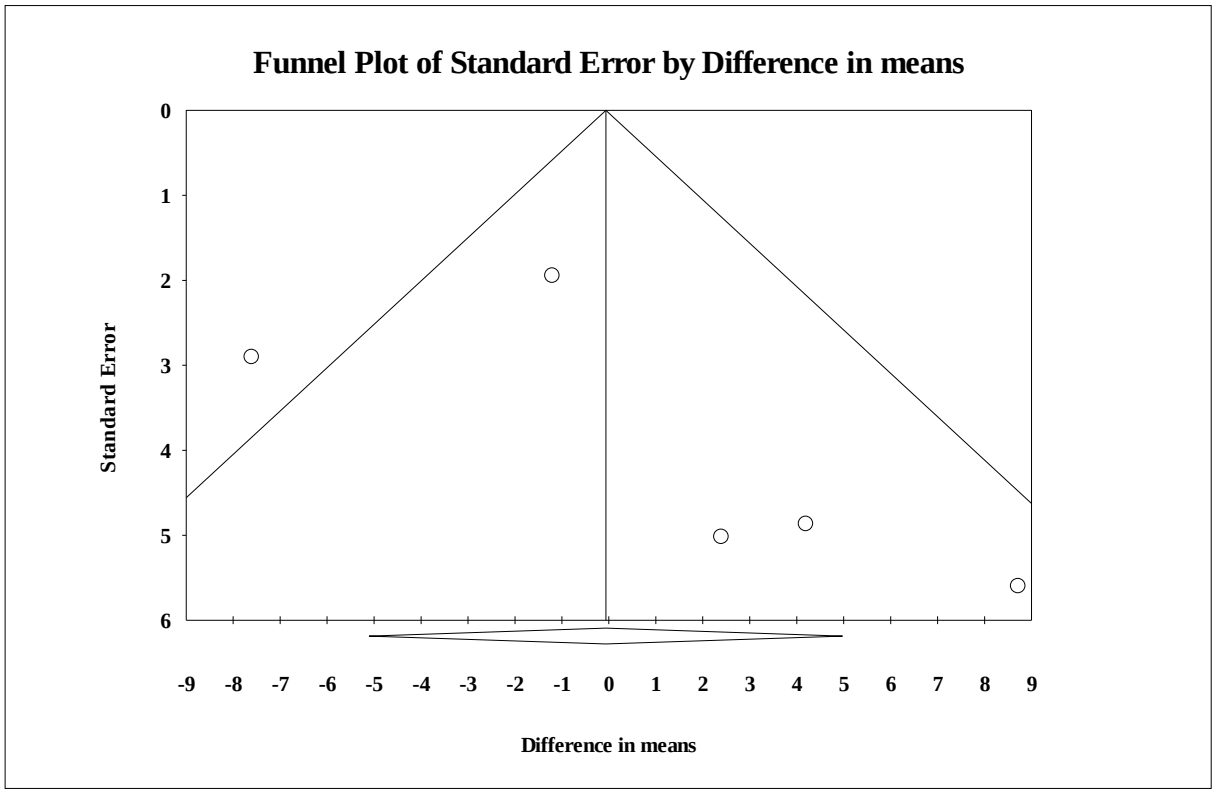


Fail-safe calculation: does not apply, because the difference was not statistically significant.

Egger's regression intercept

Intercept	-1,385
Standard error	2,056
95% lower limit (2-tailed)	-10,232
95% upper limit (2-tailed)	7,462
t-value	0,674
df	2,000
P-value (1-tailed)	0,285
P-value (2-tailed)	0,570

Figure V.d: Clozapine versus risperidone

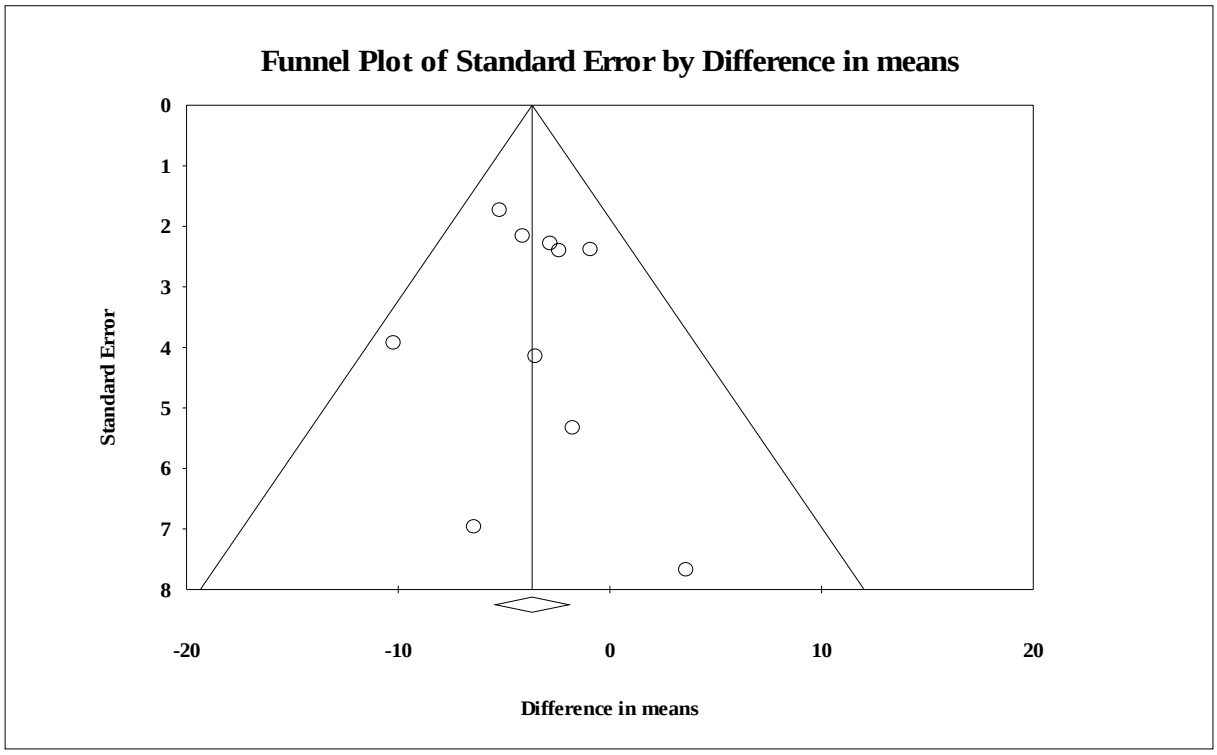


Fail-safe calculation: does not apply, because the difference was not statistically significant.

Egger's regression intercept

Intercept	1,968
Standard error	1,641
95% lower limit (2-tailed)	-3,253
95% upper limit (2-tailed)	7,189
t-value	1,200
df	3,000
P-value (1-tailed)	0,158
P-value (2-tailed)	0,316

Figure V.e: Olanzapine versus quetiapine



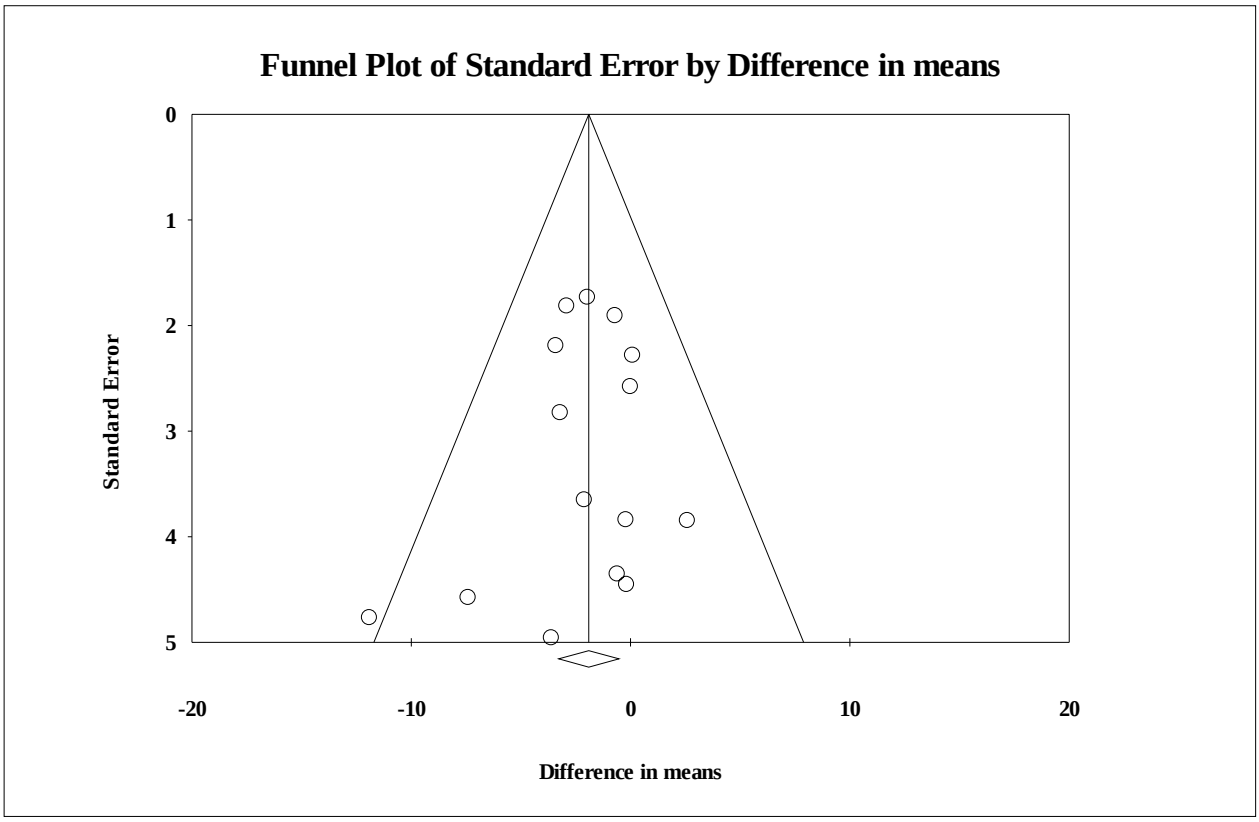
Classic fail-safe N

Z-value for observed studies	-3,694
P-value for observed studies	0,000
Alpha	0,050
Tails	2,000
Z for alpha	1,960
Number of observed studies	10,000
Number of missing studies that would bring p-value to > alpha	26,000

Egger's regression intercept

Intercept	0,178
Standard error	0,698
95% lower limit (2-tailed)	-1,431
95% upper limit (2-tailed)	1,787
t-value	0,255
df	8,000
P-value (1-tailed)	0,402
P-value (2-tailed)	0,805

Figure V.f: Olanzapine versus risperidone



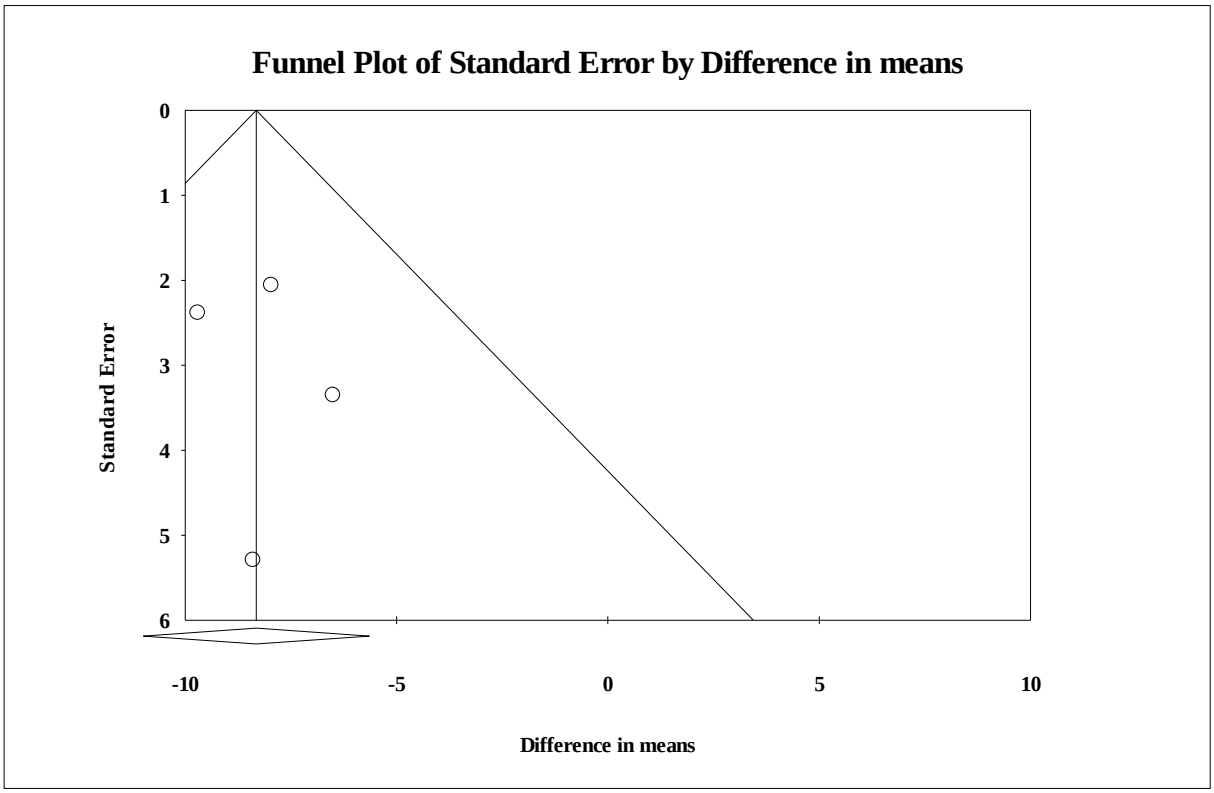
Classic fail-safe N

Z-value for observed studies	-2,763
P-value for observed studies	0,006
Alpha	0,050
Tails	2,000
Z for alpha	1,960
Number of observed studies	15,000
Number of missing studies that would bring p-value to > alpha	15,000

Egger's regression intercept

Intercept	-0,459
Standard error	0,643
95% lower limit (2-tailed)	-1,850
95% upper limit (2-tailed)	0,931
t-value	0,714
df	13,000
P-value (1-tailed)	0,244
P-value (2-tailed)	0,488

Figure V.g: Olanzapine versus ziprasidone



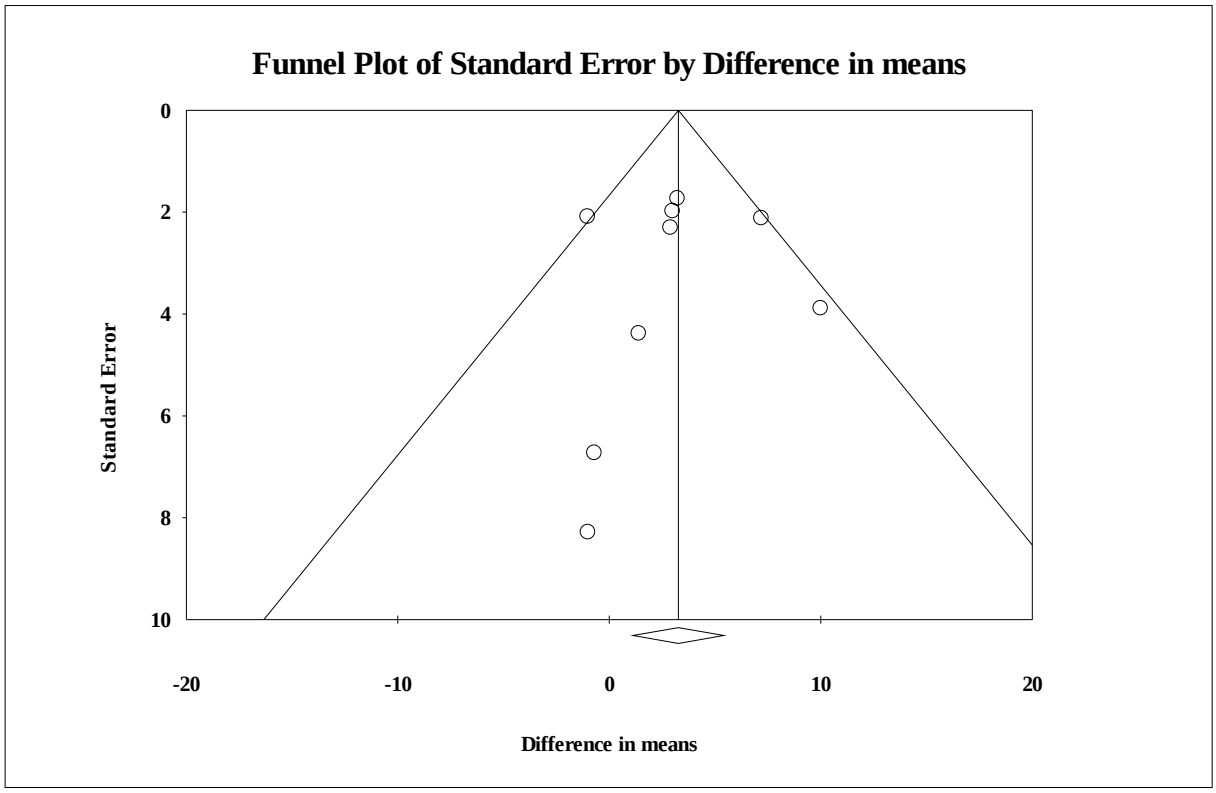
Classic fail-safe N

Z-value for observed studies	-5,733
P-value for observed studies	0,000
Alpha	0,050
Tails	2,000
Z for alpha	1,960
Number of observed studies	4,000
Number of missing studies that would bring p-value to > alpha	31,000

Egger's regression intercept

Intercept	0,313
Standard error	0,897
95% lower limit (2-tailed)	-3,547
95% upper limit (2-tailed)	4,173
t-value	0,349
df	2,000
P-value (1-tailed)	0,380
P-value (2-tailed)	0,760

Figure V.h: Quetiapine versus risperidone



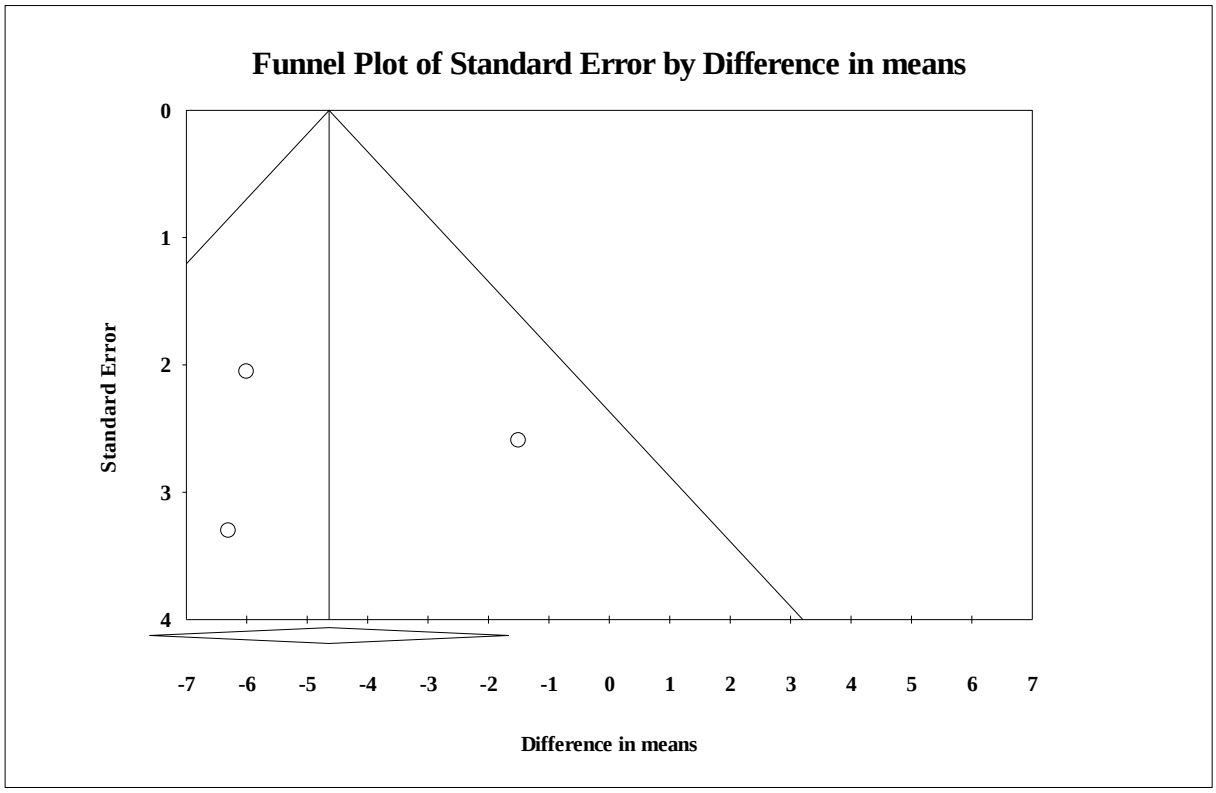
Classic fail-safe N

Z-value for observed studies	3,403
P-value for observed studies	0,001
Alpha	0,050
Tails	2,000
Z for alpha	1,960
Number of observed studies	9,000
Number of missing studies that would bring p-value to > alpha	19,000

Egger's regression intercept

Intercept	-0,118
Standard error	1,046
95% lower limit (2-tailed)	-2,591
95% upper limit (2-tailed)	2,356
t-value	0,113
df	7,000
P-value (1-tailed)	0,457
P-value (2-tailed)	0,913

Figure V.i: Risperidone versus ziprasidone



Classic fail-safe N

Z-value for observed studies	-3,123
P-value for observed studies	0,002
Alpha	0,050
Tails	2,000
Z for alpha	1,960
Number of observed studies	3,000
Number of missing studies that would bring p-value to > alpha	5,000

Egger's regression intercept

Intercept	0,613
Standard error	4,449
95% lower limit (2-tailed)	-55,918
95% upper limit (2-tailed)	57,143
t-value	0,138
df	1,000
P-value (1-tailed)	0,456
P-value (2-tailed)	0,913

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