DEPARTMENT OF PUBLIC HEALTH AND COMMUNITY MEDICINE
SECTION OF PSYCHIATRY
UNIVERSITY OF VERONA
Ph.D. PROGRAM IN PSYCHOLOGICAL AND PSYCHIATRIC SCIENCES
XXIV CYCLE

COMPARATIVE EFFICACY AND ACCEPTABILITY OF PHARMACOLOGICAL TREATMENTS FOR ACUTE MANIA: A MULTIPLE TREATMENTS META-ANALYSIS

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INDEX

BACKGROUND 2

METHODS 6

Objectives 6

Types of studis 6

Types of participants 6

Outcome measures 7

Search strategy 7

Study selection and data extraction 9

Length of follow-up 9

Quality assessment 10

Comparability of dosages 10

Statistical analysis 11

RESULTS 13

DISCUSSION 23

REFERENCES 27

APPENDIX 1. FULL REVIEW METHODS (AND FULL SEARCH STRATEGY) 42

APPENDIX 2. STUDY PROTOCOL 54

APPENDIX 3. CHARACTERISTICS OF INCLUDED STUDIES 64

APPENDIX 4. RISK OF BIAS 68

APPENDIX 5. NETWORKS FOR ACCEPTABILITY AND EFFICACY AS BINARY OUTCOME 74

APPENDIX 6. VALUES OF I2 AND CORRESPONDING CONFIDENCE INTERVALS 76

APPENDIX 7. MULTIPLE-TREATMENTS META-ANALYSIS 80

APPENDIX 8. STATISTICAL INCONSISTENCY (WITH GRAPHS) 92

APPENDIX 9. SENSITIVITY ANALYSIS 97

APPENDIX 10. SUCRAS AND RANKOGRAMS 116

APPENDIX 11. META-REGRESSION ANALYSIS 134

BACKGROUND

Mania is a condition of excessively raised mood that affects about 1% of the population, usually occurs in association with episodes of depression, and defines the diagnosis of bipolar disorder. Bipolar disorder is a chronic, disabling and heterogeneous condition, and one of the leading causes of worldwide disability and poor quality of life, especially in those aged 15–44 years. A manic episode is defined as a period of seven or more days (or any period if admission to hospital is required) of unusually and continuously effusive and open elated or irritable mood, where the mood is not caused by drugs assumption or a medical illness (e.g., hyperthyroidism), and is causing difficulties at work or in social relationships and activities, or requires admission to hospital to protect the person or others, or the person is suffering psychosis (APA, 2000). To be classed as a manic episode, while the disturbed mood is present at least three (or four if only irritability is present) of the following must have been consistently prominent: grand or extravagant style, or expanded self-esteem; reduced need of sleep (e.g. three hours may be sufficient); talks more often and feels the urge to talk longer; ideas flit through the mind in quick succession, or thoughts race and preoccupy the person; over indulgence in enjoyable behaviors with high risk of a negative outcome (e.g., extravagant shopping, sexual adventures or improbable commercial schemes) (APA, 2000).

The World Health Organization's classification system defines a manic episode as one where mood is higher than the person's situation warrants and may vary from relaxed high spirits to barely controllable exuberance, accompanied by hyperactivity, a compulsion to speak, a reduced sleep requirement, difficulty sustaining attention and, often, increased distractibility (WHO, 1993). Frequently, confidence and self-esteem are excessively enlarged, and grand, extravagant ideas are expressed. Behavior that is out of

character and risky, foolish or inappropriate may result from a loss of normal social restraint. Some people also have physical symptoms, such as sweating, pacing, and weight loss.

The main aim in treating mania, hypomania and mixed episodes is to achieve rapid control of symptoms. This is particularly important as mania can result in disturbed behavior that, when extreme, can be a risk to the safety of the patient and others. Despite the availability of many efficacious pharmacological treatments for mania and hypomania, their management in clinical settings remains a challenge. Mood stabilizers and antipsychotic agents have long been the mainstay of treatment of acute mania, with and without psychotic features (NICE, 2006; Scherk et al., 2007).

Lithium and valproate are held to be effective in acute mania but their onset of action is slower than with antipsychotics. Prior to the introduction of the atypical antipsychotics, the conventional antipsychotics were the frequently used treatment for mania despite a relative lack of randomized controlled trials to support their use. In recent years several atypical antipsychotics agents have been licensed to treat mania (aripiprazole, olanzapine, risperidone and quetiapine). However, there is a debate about the benefits of newer so-called atypical antipsychotic drugs compared with older antipsychotic drugs. A major advantage of the atypical antipsychotics over conventional antipsychotics is the lower risk of extrapyramidal symptoms (EPS) though this differential has largely been demonstrated in trials where the comparator was haloperidol, a high-potency conventional antipsychotic that is associated with a relatively high incidence of EPS.

There is no general consensus about which of these drugs should be used first-line. Guidelines for the treatment of bipolar disorder vary significantly across committees or specialist groups (Fountoulakis et al., 2005). In particular for the treatment of acute mania, some guidelines recommend monotherapy with a mood stabilizer or an

antipsychotic drug as first-line treatment, whereas others recommend a combination of a mood stabilizer and an antipsychotic agent. Adverse effects in short term studies tend to focus on EPS but some atypical antipsychotics, in particular olanzapine and clozapine, are associated with a high risk of significant increase in body weight and this may influence the selection even of short term treatments under some circumstances.

For clinical conditions where many treatment regimens already exist, competing with each other, the real question is how to rank their benefits (and harms) to choose the best option. This has led to the development of meta-analytical techniques that allow the incorporation of evidence from direct and indirect comparisons toward estimating summary treatment effects.

Multiple treatments meta-analysis (MTM) is a statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the treatments have not been directly compared (Salanti et al., 2011, Higgins et al., 1996; Hasselblad et al., 1998; Lumley, 2002) (Figure 1). MTM has already been used successfully in many fields of medicine (Psaty et al., 2003; Elliott et al., 2007; Cipriani et al., 2009). Two fruitful roles for MTM have been identified (Lu and Ades 2004):

(i) to strengthen inferences concerning the relative efficacy of two treatments, by including both direct and indirect comparisons to increase precision and combine both direct and indirect evidence (Salanti et al., 2008);

(ii) to facilitate simultaneous inference regarding all treatments in order for example to select the best treatment.

Considering how important comparative efficacy could be for clinical practice and policy making, it is useful to use all the available evidence to estimate potential differences in efficacy among treatments. MTM rely on a strong assumption that studies of different comparisons are similar in all ways other than the interventions being

compared. The indirect comparisons involved are not randomized comparisons, and may suffer the biases of observational studies, for example due to confounding. In situations when both direct and indirect comparisons are available in a review, any use of multiple-treatments meta-analyses should be to supplement, rather than to replace, the direct comparisons. Expert statistical support, as well as subject expertise, is required for carrying out and interpreting multiple treatments meta-analyses.

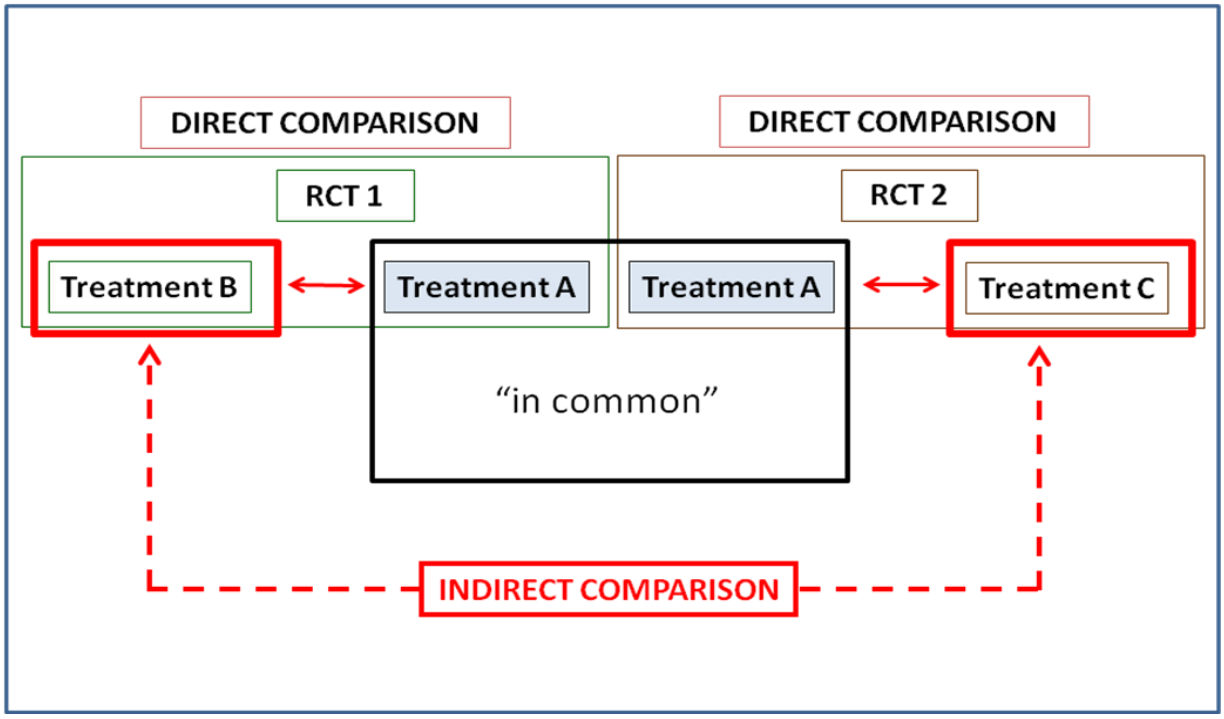

FIGURE 1. Graphic explanation on indirect comparisons to be used in MTM (see text).

The aim of this study was to compare the efficacy and acceptability of pharmacological treatments for acute mania, either against placebo or against one another, in order to inform clinical practice and mental health policies. We carried out a MTM. Reliable information on comparative efficacy is essential for informing clinical practice and policy making and MTM allows us to use all the available evidence to estimate potential differences in efficacy among treatments.

METHODS

OBJECTIVES

To compare individual anti-manic agents in terms of efficacy (both dichotomous and continuous measures) and acceptability (drop-out rate).

TYPES OF STUDIES

Double-blind randomised controlled trials (RCTs) comparing one active drug (antipsychotic, mood stabiliser or benzodiazepine) with another active drug (antipsychotic, mood stabiliser or benzodiazepine) or placebo as oral therapy in the treatment of acute mania were included. All combination studies (when combining drugs of the same class, for instance antipsychotic plus antipsychotic) and augmentation studies (when combining drugs belonging to different classes, for instance antipsychotic plus mood stabiliser) were included as well. We therefore investigated heterogeneity between these different types of studies. Quasi-randomized trials (such as those allocating by using alternate days of the week) were excluded. For trials which have a crossover design, only results from the first randomisation period were considered.

TYPES OF PARTICIPANTS

Patients aged 18 or older of both sexes with a primary diagnosis of acute mania or bipolar disorder (manic or mixed episode) according to the standardised diagnostic criteria used by the study authors. Most recent studies used DSM-IV (APA 1994) or ICD-10 (WHO 1992) criteria. Older studies used ICD-9 (WHO 1978), DSM-III (APA 1980)/DSM-III-R (APA 1987) or other diagnostic systems such as Feighner criteria or Research Diagnostic Criteria. There is no evidence that treatment effects differ depending on the diagnostic criteria used. A concurrent Axis I diagnosis of another

psychiatric disorder was considered as exclusion criteria. A concurrent Axis II diagnosis of psychiatric disorder was not considered as exclusion criteria. Studies with patients with a serious concomitant medical illness as an inclusion criterion were excluded.

OUTCOME MEASURES

(1) ***Overall efficacy of treatment***

1.1 Overall efficacy was primarily measured as the mean change of the total score of the Young Mania Rating Scale (YMRS) from baseline to endpoint. If YMRS results were not available, we used the mean change from baseline to endpoint of other standardised rating scales for acute mania.

1.2 We also estimated efficacy as the proportion of patients who responded to treatment (response was defined as a reduction of at least 50% on the total score between baseline and endpoint on a standardized rating scale for mania possibly YMRS; if not available, other rating scales were used).

(2) ***Acceptability of treatment***

2.1 Treatment discontinuation (acceptability) was defined as the proportion of patients who left the study early for any reason, out of the total number of patients randomly assigned to each treatment arm.

SEARCH STRATEGY

All published and unpublished randomized controlled, double-blind trials that compared oral doses of one of the above mentioned anti-manic drugs with another drug (or placebo) in the treatment of acute mania were identified (full details on the search strategy reported in Appendix 1). We identified relevant trials from systematic searches in the following electronic databases, MEDLINE, EMBASE, CINAHL, PsycINFO, and

the Cochrane Central Register of Controlled Trials. We also consulted trial databases of the following drug-approving agencies - (the Food and Drug Administration in the US, the Medicines and Healthcare products Regulatory Agency in the UK, the European Medicines Agency in the EU, the Pharmaceuticals and Medical Devices Agency in Japan, the Therapeutic Goods Administration in Australia and ongoing trial registers (clinicaltrials.gov in the USA, National Research Register in the UK, Netherlands Trial Register in the Netherlands, EUDRACT in the EU, UMIN-CTR in Japan and the Australian Clinical Trials Registry in Australia) was hand-searched for published, unpublished and ongoing controlled trials. No language restrictions were applied.

Electronic databases were searched using the following strategy: [bipolar disorder or bipolar depression or mania or manic or hypomania or cyclothymic cycle or ultra-rapid cycling or ultradian cycling or RCBD or DMX or mixed depression or mixed bipolar or reactive depression or psychogenic depression or puerperal psychosis or puerperium psychosis or excited psychosis] and combined with a list of antipsychotics, including [(amisulpride or aripiprazole or benperidol or chlorpromazine or chlorprothixene or clozapine or flupentixol or fluspirilene or haloperidol or levomepromazine or olanzapine or paliperidone or pericyazine or perphenazine or pimozide or prochlorperazine or promazine or quetiapine or risperidone or sertindole or sulpiride or trifluoperazine or zotepine) or mood stablisers, including (alprazolam or bromazepam or carbamazepine or chlordiazepoxide or clobazam or clonazepam or clorazepate or delorazepam or diazepam or ethosuximide or flunitrazepam or flurazepam or flutoprazepam or gabapentin or lacosamide or lamotrigine or levetiracetam or lithium or loprazolam or lorazepam or lormetazepam or mexazolam or midazolam or nitrazepam or oxazepam or oxcarbazepine or phenobarbital or phenytoin or prazepam or pregabalin or temazepam or tiagabine or topiramate or

valproic acid or verapamil or vigabatrin or zonisamide)]. All relevant authors and principal manufacturers were contacted to supplement the incomplete report of the original papers. We also checked the websites of these manufacturers for further studies.

STUDY SELECTION AND DATA EXTRACTION

According to study protocol, we used the data that have been extracted for the previous Cochrane reviews carried out by the members of our review team (see Appendix 2). Concerning the update search, three reviewers independently reviewed references and abstracts. If both reviewers agreed that the trial did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles and used the same eligibility criteria to determine which, if any, to exclude at this stage. Any disagreements were solved via discussion with another member of the reviewing team. The same reviewers then independently readed each article, evaluated the completeness of the data abstraction, and confirmed the quality rating. As for previous Cochrane systematic reviews, we designed and used a structured data abstraction form to ensure consistency of appraisal for each study. Information extracted included study characteristics (such as lead author, publication year, journal, study setting, sponsorship), participant characteristics (such as diagnostic criteria, mean baseline score, age), intervention details (such as dose ranges, mean doses of study drugs, concomitant and/or rescue medications) and outcome measures (see above).

LENGTH OF FOLLOW UP

In the present review, acute treatment was defined as a 3-week treatment in all analyses. If 3-week data were not available, we used data ranging between 2 and 6 weeks (we given preference to the time-point given in the original study as the study endpoint).

QUALITY ASSESSMENT

Two independent review authors assessed study quality using the Cochrane risk of bias tool (Higgins et al., 2011). This instrument consists of six items, providing a framework for assessing the whole trial with explicit and transparent judgmental separating the facts from the judgments. Two of the items (adequacy of sequence generation and al location concealment) assess the strength of the randomization process in preventing selection bias in the assignment of participants to interventions; the third item (blinding) assesses the influence of performance bias on the study results and the fourth the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes (this item requires a comparison of published data with trial protocols, when such are available). The final item refers to other sources of bias that are relevant in certain circumstances, such as, for example, sponsorship bias. Where inadequate details of allocation concealment and other characteristics of trials were provided, the trial authors were contacted in order to obtain further information. If the raters disagreed, the final rating was made by consensus with the involvement (if necessary) of another member of the review group.

COMPARABILITY OF DOSAGES

We included only studies randomizing patients to drugs within the therapeutic dose (both fixed-dose and flexible-dose designs were allowed). There was the possibility that some trials compared one agent at the upper limit of its therapeutic range with another agent at the lower limit of its therapeutic range within the same study. We looked at heterogeneity and then added a variable (yes/no) that reported if dosages were comparable and use this information for analysis.

STATISTICAL ANALYSIS

The efficacy outcome of this review was the change of the total score of the YMRS. Dichotomous outcomes were analysed on an intention-to-treat (ITT) basis: drop-outs were always included in this analysis. When data on drop-outs were carried forward and included in the evaluation (Last Observation Carried Forward, LOCF), they were analysed according to the primary studies.

SYNTHESIS OF RESULTS

We generated descriptive statistics for trial and study population characteristics across all eligible trials, describing the types of comparisons and some important variables, either clinical or methodological (such as year of publication, age, severity of illness, sponsorship). For each pair-wise comparison between anti-manic drugs, the standardized mean difference (SMD) was calculated as the effect size for continuous outcomes and the odds ratio was calculated for dichotomous outcomes, both with a 95% CI. We first performed pair-wise meta-analyses by synthesizing studies that compare the same interventions using a random effects model (DerSimonian & Laird, 1986) to incorporate the assumption that the different studies were estimating different, yet related, treatment effects (Higgins & Green, 2006). Visual inspection of the forest plots was used to investigate the possibility of statistical heterogeneity. This was supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error (Higgins et al., 2003). 95% confidence intervals was calculated for I-squared, and a P value from a standard test for heterogeneity was used to assess evidence of its presence.

We conducted a MTM which is a method of synthesizing information from a network of trials addressing the same question but involving different interventions. For a given

comparison, say A versus B, direct evidence is provided by studies that compare these two treatments directly. However, indirect evidence is provided when studies that compare A versus C and B versus C are analyzed jointly. The combination of the direct and indirect into a single effect size can increase precision while randomization is respected. The combination of direct and indirect evidence for any given treatment comparison can be extended when ranking more than three types of treatments according to their effectiveness: every study contributes evidence about a subset of these treatments.

We performed MTM within a Bayesian framework (Ades et al., 2006). This enabled us to estimate the probability for each intervention to be the best for each positive outcome, given the results of the MTM.

The analysis was performed using WinBUGS (MRC Biostatistics Unit, Cambridge, U.K., http://www.mrcbsu.cam.ac.uk/bugs/winbugs/contents.shtml).

MTM should be used carefullly, and the underlying assumptions of the analysis should be investigated carefully. Key among these is that the network is coherent, meaning that direct and indirect evidence on the same comparisons agree. Joint analysis of treatments can be misleading if the network is substantially incoherent, i.e., if there is disagreement between indirect and direct estimates. So, as a first step, we calculated the difference between indirect and direct estimates in each closed loop formed by the network of trials as a measure of incoherence and we subsequently examined whether there are any material discrepancies. In case of significant incoherence we investigated possible sources of it. Incoherence may result as an uneven distribution of effect modifiers across groups of trials that compare different treatments. Therefore, we investigated the distribution of clinical and methodological variables that we suspected may be potential

sources of either heterogeneity or incoherence in each comparison-specific group of trials.

SUBGROUP AND META-REGRESSION ANALYSES

We carried out a subgroup analysis based on the type of study treatment (combination/augmentation treatments vs monotherapy) and a meta-regression analysis for sponsorship (Salanti et al., 2009).

RESULTS

The electronic searches yielded 582 potentially relevant studies. Of all these items, 188 potentially eligible articles were analysed. We excluded 125 reports that did not meet eligibility criteria. A further 9 unpublished trials eligible for the MTM were identified from searching websites of pharmaceutical industries. Overall, 68 trials from 1980 to 2010 were available and were used for the MTM (Figure 2). For references to included studies see the reference list at the end of the document.

In total, 14 treatments were analysed: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, paliperidone, quetiapine, risperidone, topiramate, ziprasidone, and placebo. Most trials (54 of 68, 79%) were two-grouped studies and the rest were three-grouped studies in which one active comparator was usually haloperidol. 17 trials had a combination design, in which the anti-manic drugs of interest were added to lithium or valproate. Of these trials, only one was a three-grouped study and the remaining 16 were two-grouped (see Appendix 3).

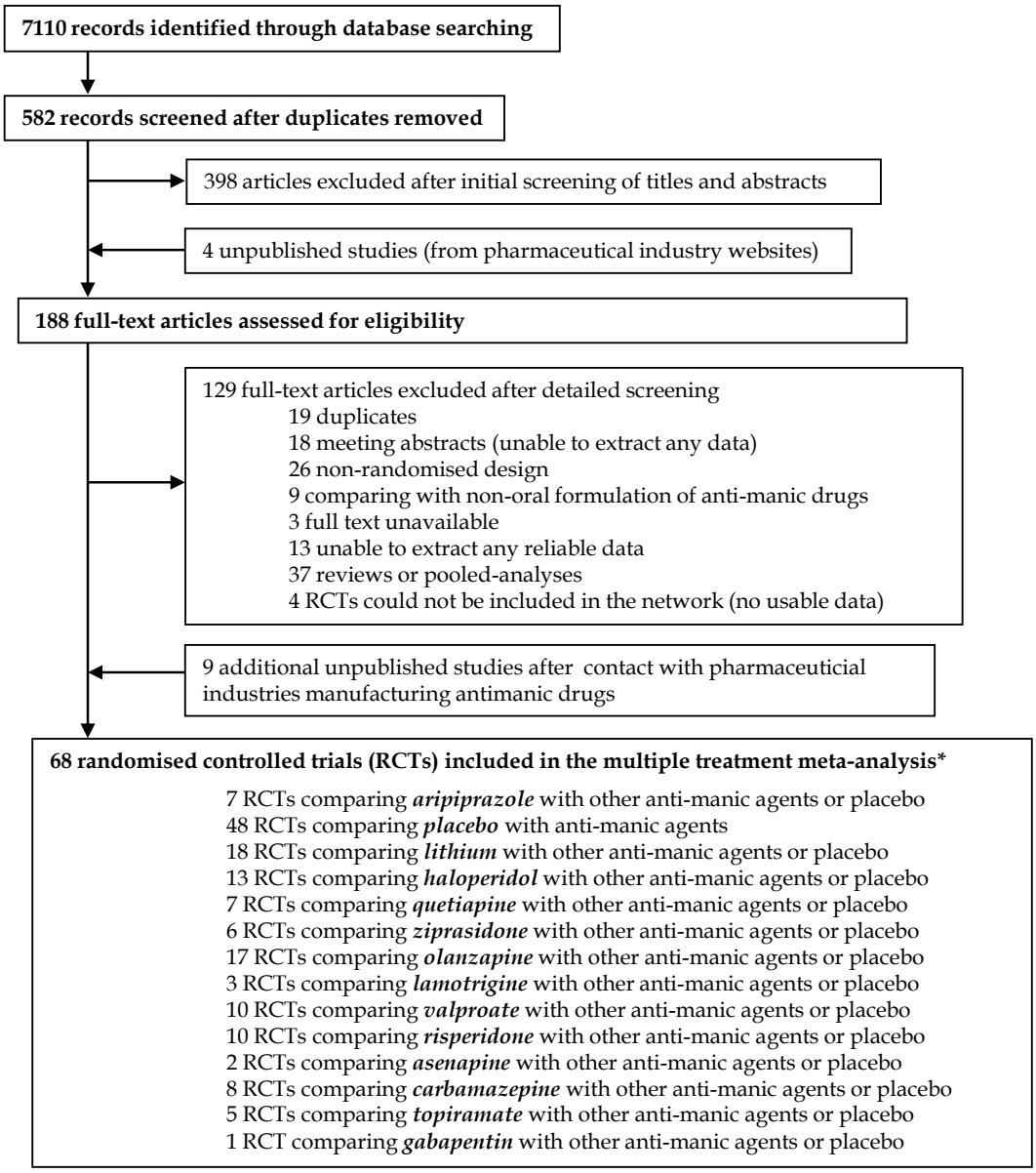

FIGURE 2. Included and excluded studies (PRISMA flow-diagram, www.prisma-statement.org).

Overall, 16 073 patients were randomized to one of the 14 anti-manic treatments or to placebo and were included in the multiple-treatments meta-analysis. 15 673 patients contributed to the efficacy analysis as continuous outcome (63 studies) and 15 626 to the acceptability analysis (65 studies). 47 studies provided data for dichotomous efficacy secondary outcome (12 649 participants). The mean duration of studies was 3.4 weeks (SD 1.1; one study lasted 2 weeks, 49 lasted 3 weeks, and 17 ranged between 4 and 6 weeks), and the mean sample size was 105.7 patients per group (minimum–maximum 7–

458). Supplementary unpublished information was obtained from trial investigators for 26 of the 68 included studies (38%).

Most of included studies recruited patients rated as having moderate to severe manic symptoms, and 52 trials (76%, 13 436 participants) were done in inpatient clinics (only two in outpatient clinics and in the remaining studies the setting was unclear). The overall quality of studies assessed with the Cochrane Collaboration bias tool was rated as good, even though some studies did not record details about randomization process and allocation concealment and there were only few randomized trials at low risk of bias in every question-based entry (Figure 3 and Appendix 4).

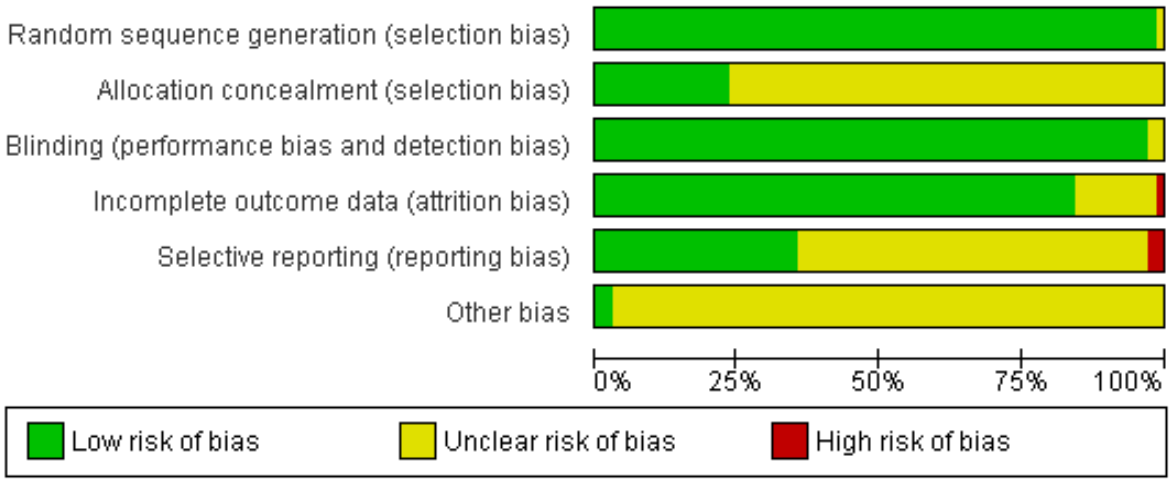

FIGURE 3. Study quality evaluation using the Cochrane Collaboration risk of bias tool (Higgins et al., 2011).

Figure 4 shows the network of eligible comparisons for primary efficacy outcome of the multiple-treatments meta-analysis: this pattern of comparisons is called geometry of the treatment network. This network's geometry reflects the wide clinical context of the multiple competing treatments for acute mania. In this network many treatments are compared with others or with placebo. The thickness of the lines is proportional to the number of trials addressing each specific comparison (co-occurrence), each node

corresponds to a different drug under investigation (diversity) and the size of every node is proportional to the number of randomized participants (sample size).

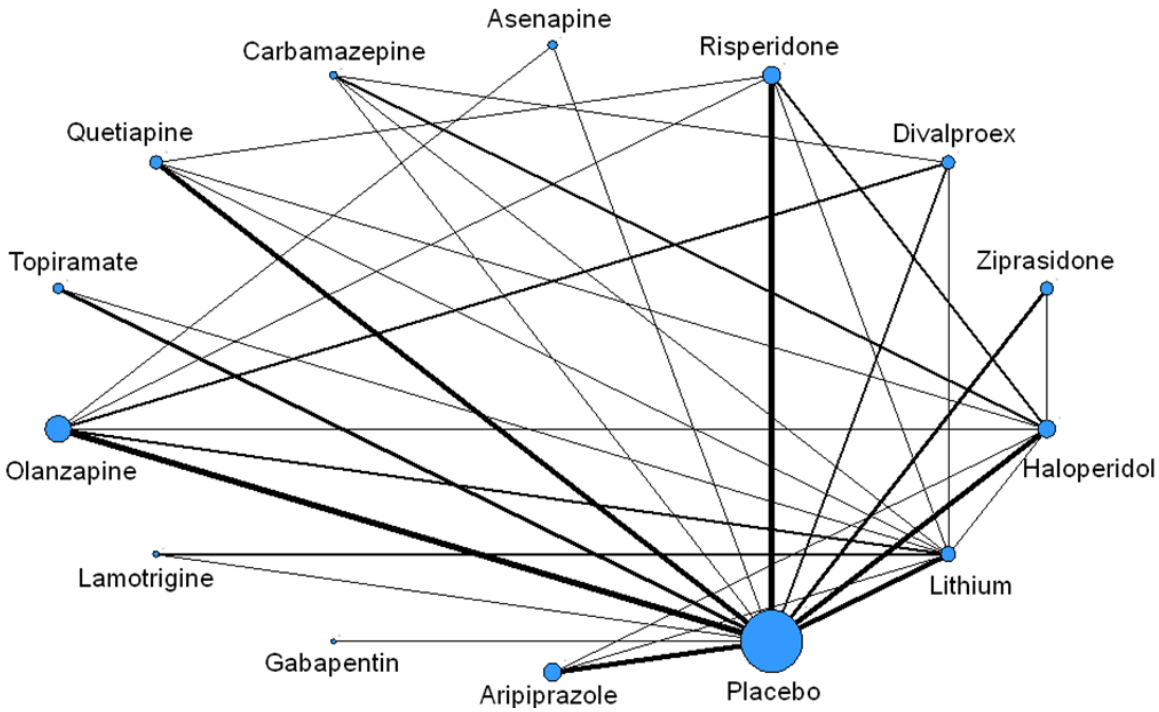

FIGURE 4. Network of eligible comparisons for the multiple-treatments meta-analysis for efficacy. The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomized participants (sample size). The networks of eligible comparisons for acceptability analysis dropout rate) and for efficacy as binary outcome are similar (see Appendix 5).

Of the 91 possible pair-wise comparisons between the 14 treatments, 33 have been studied directly in one or more trials for efficacy as continuous outcome, 27 for efficacy as binary outcome, and 34 for acceptability. All anti-manic drugs had at least one placebo-controlled randomized trial. Most of them were directly compared with at least three other drugs. For primary outcomes, meta-analysis of the direct comparisons showed significant efficacy for all anti-manic treatments compared with placebo, with the exception of topiramate and gabapentin. In the comparisons between active drugs, olanzapine, lithium, and carbamazepine were more than valproate; haloperidol more than lithium, quetiapine, and ziprasidone; olanzapine more than asenapine; and lithium

more than topiramate. These results arise from 33 independent analyses without adjustment for multiple testing (so roughly two CIs would be expected to exclude 0 by chance alone). Risperidone, olanzapine, and quetiapine had fewer dropouts than did placebo, and placebo fewer than did topiramate. Haloperidol had fewer discontinuations than did quetiapine; quetiapine than lithium; and olanzapine than risperidone and asenapine.

Overall, statistical heterogeneity was moderate, although for most comparisons 95% CIs were wide and included values indicating very high or no heterogeneity, which portrayed the small number of studies available for every pair-wise comparison (see Appendix 6). In the meta-analyses of direct comparisons for efficacy, I^2 values higher than 75% were recorded for the comparisons ziprasidone versus placebo (I^2=76.6%) and olanzapine versus lithium (I^2=89.2%), with five and three studies, respectively. For acceptability, I^2 values higher than 75% were recorded for the comparisons aripiprazole versus haloperidol (I^2=84.1%) and lithium versus lamotrigine (I^2=82.0%), with two and three studies in the meta-analysis, respectively.

Haloperidol, risperidone, olanzapine, lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate, and ziprasidone were significantly more effective than placebo, while gabapentin, lamotrigine, and topiramate were not. For drop-outs, olanzapine, risperidone, and quetiapine were significantly better than placebo (Figure 5 and Appendix 7).

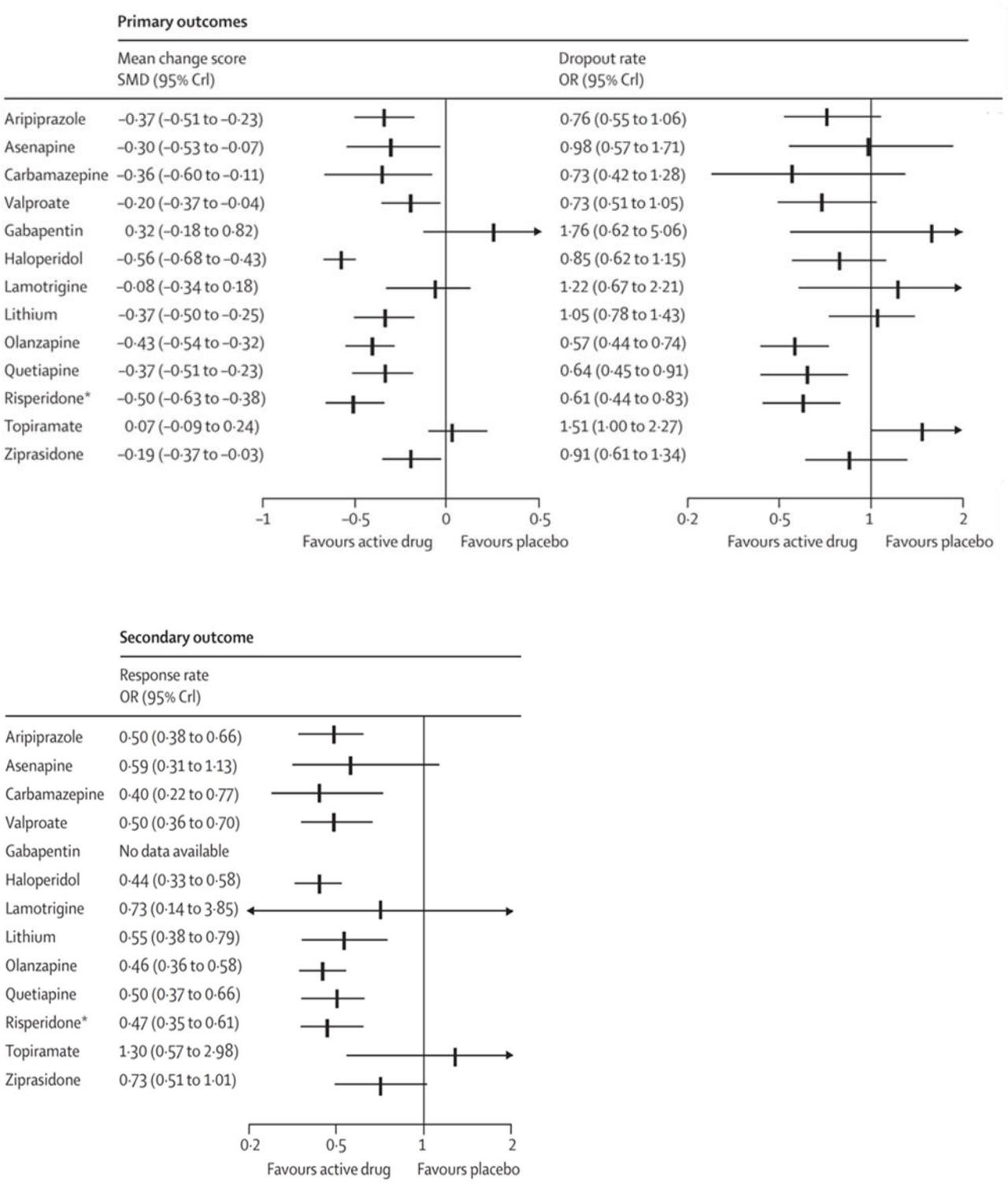

FIGURE 5. Forest plots of MTM results for efficacy outcomes and dropout rate with placebo as reference compound. Standardised mean differences lower than 0 and ORs lower than 1 favour active compound. *As stated in the protocol, data from risperidone and paliperidone were merged. MTM= multiple-treatments meta-analysis. OR=odds ratio. CrI=credibilty interval.

On the secondary dichotomous outcome for efficacy, the results were consistent with continuous outcome, but less clear cut and with wider CIs. Asenapine, ziprasidone, lamotrigine, and topiramate were not significantly more effective than placebo and no binary efficacy data were available for gabapentin (Figure 5). The few data made it difficult to draw clear conclusions for this outcome. In head-to-head comparisons, haloperidol had the highest number of significant differences compared with other anti-manic drugs, partly because it was often used as an active comparator (Figure 6).

Haloperidol was significantly more effective than lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Risperidone and olanzapine had a very similar profile of comparative efficacy, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Topiramate and gabapentin were significantly less effective than all the other anti-manic drugs. In terms of dropout rate, haloperidol was significantly inferior to olanzapine; lithium inferior to olanzapine, risperidone, and quetiapine; lamotrigine inferior to olanzapine and risperidone; gabapentin inferior to olanzapine; topiramate inferior to many other anti-manic treatments, such as haloperidol, olanzapine, risperidone, quetiapine, aripiprazole, carbamazepine, and valproate (Figure 6).

Most loops (networks of three comparisons that arise when collating studies involving different selections of competing treatments) were consistent, since their 95% CIs included 0 (ie, the direct estimate of the summary effect does not differentiate from the indirect estimate) according to the forest plots. Analysis of inconsistency indicated that there was inconsistency in three of the total 33 loops for efficacy measured as a continuous outcome (aripiprazole-placebo-haloperidol; olanzapine-placebo-risperidone; quetiapine-placebo-haloperidol), but none for acceptability (34 loops) or binary efficacy (18 loops) (for full details see Appendix 8).

FIGURE 6. Efficacy and acceptability of all anti-manic drugs according to multiple-treatments meta-analysis (primary outcomes). Comparisons between treatments should be read from left to right and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For efficacy, SMD below 0 favour the column-defining treatment · For acceptability, ORs higher than 1 favour the column-defining treatment

HAL	1·40 (0·93 to 2·11)	**1·49 (1·03 to 2·15)**	0·81 (0·53 to 1·22)	1·32 (0·85 to 2·06)	1·11 (0·75 to 1·66)	1·16 (0·63 to 2·14)	0·86 (0·46 to 1·60)	1·16 (0·73 to 1·86)	0·93 (0·59 to 1·49)	0·69 (0·36 to 1·36)	0·85 (0·62 to 1·15)	**0·56 (0·34 to 0·93)**	0·48 (0·16 to 1·44)
−0·06 (−0·22 to 0·11)	RIS	1·06 (0·72 to 1·56)	**0·58 (0·37 to 0·88)**	0·94 (0·60 to 1·47)	0·80 (0·51 to 1·25)	0·83 (0·44 to 1·57)	0·62 (0·33 to 1·16)	0·83 (0·51 to 1·34)	0·67 (0·41 to 1·10)	**0·50 (0·25 to 0·98)**	**0·61 (0·44 to 0·83)**	**0·40 (0·24 to 0·68)**	0·34 (0·11 to 1·03)
−0·12 (−0·28 to 0·02)	−0·07 (−0·22 to 0·08)	OLZ	**0·54 (0·37 to 0·79)**	0·88 (0·58 to 1·36)	0·75 (0·49 to 1·13)	0·78 (0·43 to 1·44)	0·58 (0·33 to 1·00)	0·78 (0·52 to 1·17)	0·63 (0·40 to 1·00)	**0·47 (0·24 to 0·89)**	**0·57 (0·44 to 0·74)**	**0·38 (0·23 to 0·61)**	**0·32 (0·11 to 0·95)**
−0·19 (−0·36 to −0·01)	−0·13 (−0·30 to 0·04)	−0·06 (−0·22 to 0·10)	LIT	**1·63 (1·06 to 2·54)**	1·38 (0·91 to 2·12)	1·44 (0·81 to 2·60)	1·07 (0·57 to 2·00)	1·44 (0·92 to 2·28)	1·15 (0·71 to 1·91)	0·86 (0·47 to 1·59)	1·05 (0·78 to 1·43)	0·70 (0·44 to 1·11)	0·60 (0·20 to 1·77)
−0·19 (−0·37 to −0·01)	−0·13 (−0·31 to 0·04)	−0·07 (−0·24 to 0·11)	−0·01 (−0·18 to 0·17)	QTP	0·85 (0·52 to 1·35)	0·88 (0·46 to 1·70)	0·66 (0·34 to 1·25)	0·88 (0·53 to 1·46)	0·71 (0·42 to 1·20)	0·53 (0·27 to 1·05)	**0·64 (0·45 to 0·91)**	**0·43 (0·25 to 0·73)**	0·36 (0·12 to 1·10)
−0·19 (−0·36 to −0·02)	−0·13 (−0·31 to 0·05)	−0·06 (−0·23 to 0·11)	−0·01 (−0·18 to 0·17)	0·00 (−0·19 to 0·20)	ARI	1·04 (0·55 to 1·98)	0·77 (0·41 to 1·47)	1·05 (0·64 to 1·70)	0·84 (0·51 to 1·39	0·62 (0·32 to 1·24)	0·76 (0·55 to 1·06)	**0·50 (0·30 to 0·85)**	0·43 (0·14 to 1·29)
−0·20 (−0·36 to −0·01)	−0·14 (−0·42 to 0·12)	−0·08 (−0·34 to 0·18)	−0·02 (−0·28 to 0·24)	−0·01 (−0·30 to 0·26)	−0·01 (−0·29 to 0·26)	CBZ	0·74 (0·34 to 1·62)	1·00 (0·52 to 1·91)	0·80 (0·41 to 1·59)	0·60 (0·27 to 1·33)	0·73 (0·42 to 1·28)	**0·48 (0·25 to 0·96)**	0·41 (0·13 to 1·37)
−0·26 (−0·52 to −0·01)	−0·20 (−0·46 to 0·05)	−0·14 (−0·36 to 0·10)	−0·08 (−0·41 to 0·27)	−0·07 (−0·34 to 0·20)	−0·07 (−0·34 to 0·20)	−0·06 (−0·39 to 0·28)	ASE	1·35 (0·71 to 2·58)	1·08 (0·56 to 2·14)	0·81 (0·36 to 1·83)	0·98 (0·57 to 1·72)	0·65 (0·33 to 1·30)	0·56 (0·17 to 1·82)
−0·36 (−0·56 to −0·15)	**−0·30 (−0·50 to −0·10)**	**−0·23 (−0·40 to −0·06)**	−0·10 (−0·41 to 0·23)	−0·17 (−0·38 to 0·05)	−0·17 (−0·38 to 0·05)	−0·15 (−0·44 to 0·13)	−0·10 (−0·37 to 0·18)	VAL	0·80 (0·47 to 1·37)	0·60 (0·30 to 1·20)	0·73 (0·51 to 1·05)	**0·48 (0·28 to 0·83)**	0·41 (0·13 to 1·25)
−0·36 (−0·56 to −0·15)	**−0·31 (−0·51 to −0·10)**	**−0·24 (−0·43 to −0·03)**	−0·15 (−0·44 to 0·16)	−0·17 (−0·39 to 0·05)	−0·18 (−0·39 to 0·04)	−0·16 (−0·45 to 0·14)	−0·10 (−0·39 to 0·18)	−0·01 (−0·24 to 0·23)	ZIP	0·75 (0·37 to 1·51)	0·91 (0·61 to 1·34)	0·61 (0 34 to 1 06)	0·52 (0 17 to 1 58)
−0·48 (−0·77 to −0·19)	**−0·43 (−0·71 to −0·14)**	**−0·36 (−0·64 to −0·08)**	−0·32 (−0·67 to 0·06)	−0·29 (−0·58 to 0·00)	−0·29 (−0·58 to 0·00)	−0·28 (−0·63 to 0·08)	−0·22 (−0·57 to 0·12)	−0·13 (−0·43 to 0·18)	−0·12 (−0·43 to 0·19)	LAM	1·22 (0·67 to 2·21)	0·81 (0·40 to 1·65)	0·69 (0·21 to 2·30)
−0·56 (−0·69 to −0·43)	**−0·50 (−0·63 to −0·38)**	**−0·43 (−0·54 to −0·32)**	**−0·37 (−0·63 to −0·11)**	**−0·37 (−0·51 to −0·23)**	**−0·37 (−0·51 to −0·23)**	**−0·36 (−0·60 to −0·11)**	**−0·30 (−0·53 to −0·07)**	**−0·20 (−0·37 to −0·04)**	**−0·20 (−0·37 to −0·03)**	−0·08 (−0·34 to 0·18)	PBO	0·66 (0·44 to 1·00)	0·57 (0·20 to 1·62)
−0·63 (−0·84 to −0·43)	**−0·58 (−0·78 to −0·37)**	**−0·51 (−0·70 to −0·31)**	**−0·45 (−0·75 to −0·14)**	**−0·44 (−0·66 to −0·23)**	**−0·45 (−0·66 to −0·23)**	**−0·43 (−0·72 to −0·14)**	**−0·38 (−0·66 to −0·09)**	**−0·28 (−0·52 to −0·04)**	**−0·27 (−0·51 to −0·04)**	−0·15 (−0·46 to 0·15)	−0·07 (−0·24 to 0·09)	TOP	0·85 (0·28 to 2·63)
−0·88 (−1·40 to −0·36)	**−0·83 (−1·34 to −0·31)**	**−0·76 (−1·27 to −0·24)**	**−0·70 (−1·21 to −0·18)**	**−0·69 (−1·21 to −0·17)**	**−0·69 (−1·21 to −0·17)**	**−0·68 (−1·23 to −0·12)**	**−0·62 (−1·17 to −0·07)**	−0·53 (−1·05 to 0·01)	−0·52 (−1·05 to 0·01)	−0·40 (−0·96 to 0·16)	−0·32 (−0·82 to 0·18)	−0·25 (−0·77 to 0·28)	GBT

Treatment Efficacy (SMD with 95% CrI) Dropout rate (OR with 95% CrI)

refitted accordingly and no material change in either the groups of estimated SMDs or ORs was recorded. The secondary analysis including risperidone and paliperidone as separate drugs did not produce materially different results. In this secondary analysis, some modest differences might be expected to arise by chance alone, but we noted that the joint effect of risperidone and paliperidone was mainly due to the effectiveness of risperidone rather than paliperidone. Figure 7 presents all anti-manic drugs ordered by their overall probability to be the best treatment in terms of both efficacy and acceptability, showing the separate contributions to the overall scores of efficacy and acceptability.

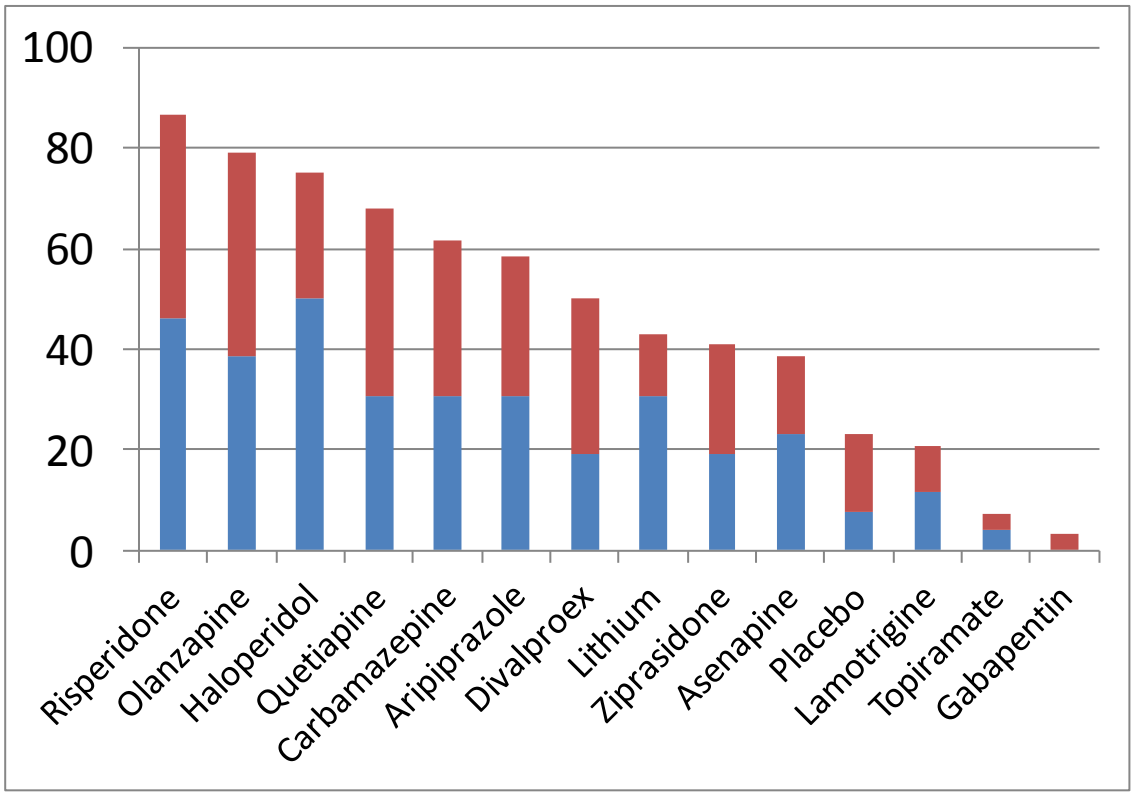

FIGURE 7. Drugs ordered by overall probability to be the best treatment in terms of both efficacy (blue) and acceptability (red), showing the separate contributions to the overall scores of efficacy and acceptability.

Haloperidol, risperidone, and olanzapine were among the most effective treatments, and olanzapine, risperidone, and quetiapine were better than the other drugs in terms of acceptability. We ranked anti-manic drugs according to these two dimensions (Figure 8).

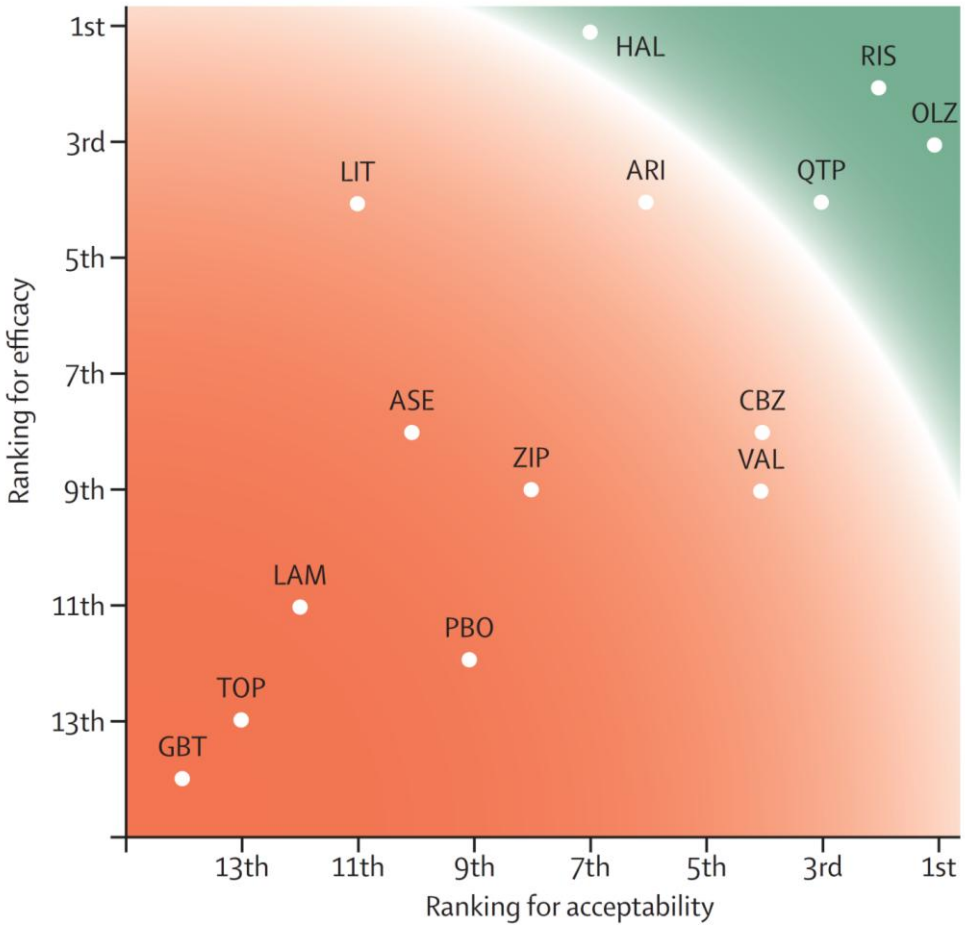

FIGURE 8. Ranking of anti-manic agents according to primary outcomes.

The common heterogeneity SD was 0.14 (95% CrI 0.09–0.21) for the efficacy SMD and 0.37 (95% CrI 0.26–0.50) for the OR for dropout. After the meta-regression analysis, the SMDs, Ors and the final rankings did not change appreciably. For full details on analyses, see Appendices 9 and 10. For efficacy we showed that overall sponsorship slightly favoured investigational drugs over placebo although only asenapine lost evidence of significant superiority to placebo after adjustment (see Appendix 11).

The three best treatments in terms of acceptability (risperidone, olanzapine, and quetiapine) and valproate scored better after adjustment for sponsorship.

DISCUSSION

This MTM is the first analysis that incorporates direct and indirect comparisons between pharmacological treatments for acute mania. Study results show both statistically and clinically significant differences between drugs for the treatment of acute mania.

Haloperidol, risperidone, and olanzapine were better than other drugs for efficacy profile. In terms of tolerability, olanzapine, risperidone, and quetiapine were better than haloperidol. Antipsychotic drugs were, overall, significantly more effective than mood stabilisers. Of the antipsychotic drugs, the two treatments likely to be ranked as superior for efficacy and acceptability were risperidone and olanzapine.

Other antipsychotics (asenapine and ziprasidone), valproate, and lithium showed generally inferior efficacy and acceptability profiles, making them less obvious initial choices for prescription of pharmacological treatment of acute mania. Lamotrigine, topiramate, and gabapentin were not significantly better than placebo in terms of efficacy, so there seems to be no reason to use them in the treatment of mania. With the large number of treatment options, meta-analyses of direct comparisons are inevitably limited by the relatively small number of studies that assessed a particular pair of treatments. Multiple-treatments meta-analysis reduces this issue by creating indirect comparisons and allowing data synthesis that can help identify the most effective treatment. Nonetheless, we found no usable data for chlorpromazine, a first-generation antipsychotic drug that is still frequently used in clinical practice. Less recent studies did not provide outcome data, so new studies are needed to assess the efficacy and acceptability of such an important compound.

Our study has several strengths. The review methods were systematic and comprehensive, retrieving a significant amount of unpublished evidence. We applied a

mixed model, which is thought to be the most appropriate method for multiple-treatments meta-analysis. Although our pooled estimates were with a particular degree of heterogeneity, the random effect approach took into account variations at the study level. Our results show that some medicines are beneficial for acute mania, although effect sizes for most treatments versus placebo were modest. We also assessed the role of sponsorship in influencing trials results. We found that the efficacy estimates for most drugs were slightly higher in trials done by the drug manufacturer, although the results of this sensitivity analysis are inconsistent, suggesting that manufacturers' trials could even underestimate acceptability. Extrapolation of data from mania trials to ordinary practice should be done with caution. The trials were invariably short term, most as short as 3 weeks. Furthermore, because only patients who were less severely affected could provide informed consent, those with more severe disease were excluded. Discontinuation of drug treatment also provides a crude composite measure of acceptability. We did not directly investigate specific side-effects, toxic effects, personal or social functioning, or quality of life, which limits the confidence with which we can say that risperidone and olanzapine have the most favourable balance between benefits and acceptability. We based this statement on rates of dropout rather than direct measures of patient's experience.

The best treatment in terms of efficacy alone was haloperidol, although it was of low acceptability. Moreover, despite the increasing number of randomized trials assessing drugs for mania in recent years, the total number of studies and patients randomly assigned is still low compared with disorders such as schizophrenia or depressive disorder. This low number might indicate specific difficulties associated with doing randomized trials in acute mania, which may go beyond the difficulties generally inherent in psychopharmacological drug trials because of the excited mental state of

participants. All statements comparing the merits of one medicine with another must be tempered by the potential biases and uncertainties that result from choice of dose and choice of patients.

The selected dose is an important tolerability issue for haloperidol because, in the past, high doses of haloperidol (up to 30 mg daily) were routinely used for manic patients: the incidence of extra-pyramidal side-effects was common and generally accepted as a cost of treatment. In the included trials, doses were generally lower than the high doses used in the past so our findings broadly apply to doses of haloperidol of about 10 mg per day. However, the lowest dose that is effective for haloperidol has not been reliably established. The use of doses of haloperidol of around 10 mg might still favour comparators, because extra-pyramidal side-effects are seen early in treatment even at this dose. Moreover, other adverse effects associated with newer antipsychotic drugs, such as weight gain and metabolic effects, will probably not contribute to early discontinuations to the same extent as the extra-pyramidal side-effects. Haloperidol is one of the oldest available anti-manic drugs and is still frequently used worldwide as standard treatment for mania, notwithstanding the known risk of inducing extra-pyramidal symptoms and, possibly, depression. The choice of patients for trials will have been influenced by eligibility related to previous exposure to or intolerance of trial treatment options. This fact will obviously have some effect on trials comparing an old drug such as haloperidol with a new option. More generally, to enter manic patients into randomized trials is difficult, so those who are entered might not be fully representative of those who cannot be.

Our results apply only to the acute manic phase of bipolar disorder (3-week treatment) and do not inform the clinically important issue of which pharmacological treatments best prevent relapse and stabilize mood in the medium and long term. Drugs that are

most effective in the acute phase might not be the best choice for long term treatment. An analysis done with the methods of mixed treatment comparison showed stronger evidence for lithium as first-line maintenance treatment of bipolar disorder and possibly also for lamotrigine and valproate. This conclusion must be made cautiously, however, since few maintenance studies for bipolar disorder have been done so far.

Nonetheless, our findings suggest the use of antipsychotics to treat the acute manic phase and mood stabilizers, possibly in combination and particularly with lithium, for long-term treatment. Results from this study emphasize the need for new treatment to show either greater efficacy or acceptability than the existing best standard treatments and serve as a disincentive to the development of drugs that offer little to patients other than increased costs.

Application of our results should take into account any limitations of the analysis and the specific clinical situation. We have to consider that the geometry of a network is only a snapshot of the status quo at the time when meta-analysis is conducted. A network may evolve over time as more trials involving more or different treatments are conducted. In all cases, it is important to study the evolving geometry of the network. This would help determine whether the evolution of the research agenda is justified scientifically or is driven by selective preferences based on nonscientific reasons.

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A multicenter, randomized, double-blind, parallel group study, comparing thee and tolerability of ziprasidone (zeldox, geodon) vs olanzapine (zyprexa) in the treatment and maintenance of response in patients with acute mania. F:\MTM acute mania\Ziprasidone\Unpublished_ziprasidone vs olanzapine\Ziprasidone versus olanzapine for MANIA_NCT00329108_with results.htm (accessed Nov 26, 20111).

A multicenter, double-blind, randomized, parallel-group, placebo controlled, phase III study of the efficacy and safety of quetiapine fumarate (SEROQUEL®) sustained-release as monotherapy in adult patients with acute bipolar mania.

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A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of flexibly-dosed extended-release paliperidone as adjunctive therapy to mood stabilizers in the treatment of acute manic and mixed episodes associated with bipolar I disorder. http://download.veritasmedicine.com/PDF/CR010855_CSR.pdf (accessed Nov 26, 2011).

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A three-week, double-blind, multicenter, placebo-controlled study evaluating the efficacy and safety of add-on oral ziprasidone in subjects with acute mania treated with lithium or divalproex. F:\MTM acute mania\Ziprasidone\Unpublished_Ziprasidone With Either Lithium or Divalproex versus placebo\Ziprasidone versus palcebo for MANIA_NCT00312494.htm (accessed Nov 26, 2011).

A Phase III, Randomized, Placebo-Controlled, Double-Blind Trial Evaluating the Safety and Efficacy of Sublingual Asenapine vs. Olanzapine and Placebo in In-Patients With an Acute Manic Episode. http://clinicaltrials.gov/show/NCT00159744 (accessed Nov 26, 2011).

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Appendix 1

Full review methods (and full search strategy)

METHODS

Study selection, patients' characteristics and data collection

We identified all randomized, double-blind trials comparing one active anti-manic drug at a therapeutic dose (first or second generation antipsychotics and the so-called mood stabilizers) with another active anti-manic drug or with placebo as oral therapy in the treatment of adults with acute mania. Combination studies (when combining drugs of the same class, for instance antipsychotic plus antipsychotic) and augmentation studies (when combining drugs belonging to different classes, for instance antipsychotic plus mood stabilizer) were also included. The participants were both males and females or, aged 18 years or older and with a primary diagnosis of bipolar I disorder (manic or mixed episode) according to standardized diagnostic criteria. Both fixed-dose and flexible-dose designs were allowed. Only studies recruiting participants with a serious concomitant medical illness as an inclusion criterion were excluded.

We searched EMBASE (1980 to 2010 Week 44), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1950 to Present), PsycINFO (1806 to November Week 3 2010), CINAHL (up to November 25th 2010), and the Cochrane Central Register of Controlled Trials (CENTRAL) (up to November 25th 2010). [1]

We also searched the trial databases of the US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency, the European Medicines Agency, the Australian Therapeutic Goods Administration. Trial registers

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[1] The Cochrane Central Register of Controlled Trials (CENTRAL) serves as the most comprehensive source of reports of controlled trials. CENTRAL is published as part of *The Cochrane Library* and is updated quarterly. As of January 2008 (Issue 1, 2008), CENTRAL contains nearly 530,000 citations to reports of trials and other studies potentially eligible for inclusion in Cochrane reviews, of which 310,000 trial reports are from MEDLINE, 50,000 additional trial reports are from EMBASE and the remaining 170,000 are from other sources such as other databases and hand-searching.

Many of the records in CENTRAL have been identified through systematic searches of MEDLINE and EMBASE. CENTRAL, however, includes citations to reports of controlled trials that are not indexed in MEDLINE, EMBASE or other bibliographic databases; citations published in many languages; and citations that are available only in conference proceedings or other sources that are difficult to access. It also includes records from trials registers and trials results registers (full details available at http://www.cochrane-handbook.org/).

CENTRAL is available free of charge to all CRGs through access to *The Cochrane Library*. The web address for *The Cochrane Library* is: http://www.thecochranelibrary.com.

(ClinicalTrials.gov in the USA, ISRCTN and National Research Register in the UK, Netherlands Trial Register in the Netherlands, EUDRACT in the EU and the Australian Clinical Trials Registry in Australia) and websites of pharmacological industries were hand-searched for published, unpublished and ongoing RCTs.

No language restrictions were applied.

Electronic databases were searched using the following strategy: *[bipolar disorder or bipolar depression or mania or manic or hypomania or cyclothymic cycle or ultra-rapid cycling or ultradian cycling or RCBD or DMX or mixed depression or mixed bipolar or reactive depression or psychogenic depression or puerperal psychosis or puerperium psychosis or excited psychosis] and combined with a list of antipsychotics, including [(amisulpride or aripiprazole or benperidol or chlorpromazine or chlorprothixene or clozapine or flupentixol or fluspirilene or haloperidol or levomepromazine or olanzapine or paliperidone or pericyazine or perphenazine or pimozide or prochlorperazine or promazine or quetiapine or risperidone or sertindole or sulpiride or trifluoperazine or zotepine) or mood stablisers, including (alprazolam or bromazepam or carbamazepine or chlordiazepoxide or clobazam or clonazepam or clorazepate or delorazepam or diazepam or ethosuximide or flunitrazepam or flurazepam or flutoprazepam or gabapentin or lacosamide or lamotrigine or levetiracetam or lithium or loprazolam or lorazepam or lormetazepam or mexazolam or midazolam or nitrazepam or oxazepam or oxcarbazepine or phenobarbital or phenytoin or prazepam or pregabalin or temazepam or tiagabine or topiramate or valproic acid or verapamil or vigabatrin or zonisamide)]*.

MEDLINE – OVID SP interface

- **Population group**

exp affective disorders, psychotic/
((bipolar or bi?polar or bi polar) adj5 (disorder$ or depress$)).tw.
(mania$ or manic$ or hypomania$).tw.
(((cyclothymi$ or rapid or ultradian) adj5 cycl$) or RCBD).tw.
(dmx$1 or (mixed adj3 (depress$ or bipolar or bi polar))).tw.
((reactive or psychogenic) and depress$).mp.
exp psychotic disorders/ and exp puerperal disorders/
((puerperal or post partum or postpartum or puerperium) adj3 psychos$).tw.
(excit$ and (psychos$ or psychotic$)).tw.

- **Interventions**

Antipsychotics

exp antipsychotic agents/
(antipsychotic$ or anti psychotic$ or (major adj2 (butyrophenon$ or phenothiazin$ or tranquil$)) or neuroleptic$).tw.
(amisulprid$ or aminosultoprid$ or amisulpirid$ or dan 2163 or dan2163 or sertol$ or socian or solian).tw.
(aripiprazol$ or abilify or abilitat).tw.
benperidol/ or (benperidol$ or anquil or benperidon$ or benzoperidol$ or benzperidol$ or frenactil$ or frenactyl or glianimon$ or phenactil$).tw.
chlorpromazine/ or (chlorpromazin$ or aminazin$ or chlorazin$ or chlordelazin$ or contomin$ or fenactil$ or largactil$ or propaphenin$ or thorazin$).tw.
chlorprothixene/ or (chlorprothixen$ or aminasin$ or aminasin$ or aminazin$ or aminazin$ or ampliactil$ or amplictil$ or ancholactil$ or chlopromazin$ or chlor pz or chlorbromasin$ or chlordelazin$ or chlorderazin$ or chloropromazin$ or chlorpromanyl or chlorpromazin$ or chlorprotixen$ or clordelazin$ or clorpromazin$ or contomin$ or elmarin$ or fenactil$ or hibanil$ or hibernal$ or hiberno$l or klorpromex or largactil$ or largactyl or megaphen$ or neurazin$ or novomazin$ or phenathyl or plegomazin$ or plegomazin$ or proma or promacid$ or promactil$ or promapar or promazil$ or propaphen$ or propaphenin$ or prozil or psychozin$ or sanopron$ or solidon$ or sonazin$ or taractan$ or taroctil$ or thor prom or thorazen$ or thorazin$ or torazin$ or vegetamin a or vegetamin b or wintamin$ or wintermin$ or zuledin$).tw.
clozapine/ or (clozapin$ or alemoxan$ or azaleptin$ or clozari$1 or dorval or dozapin$ or fazaclo or lapenax or leponex or wander compound).tw.
flupenthixol/ or (flupentixol$ or flupenthixol$ or depixol$ or emergil$ or fluanxol$ or flupentixol$ or emergil$ or fluanxol$ or piperazineethanol$ or viscoleo).tw.
fluspirilene/ or (fluspirilen$ or fluspi or imap or kivat or redeptin$ or spirodiflamin$).tw.
haloperidol/ or (haloperidol$ or aloperidin$ or celenase or cerenace or fortunan$ or haldol or halidol or haloneural$ or haloperitol$ or halosten or keselan or linton or serenace or serenase or siegoperidol$ or sigaperidol$).tw.
methotrimeprazine/ or (levomepromazin$ or 2 methoxytrimeprazin$ or hirnamin$ or

levo promazin$ or levomeprazin$ or levopromazin$ or levoprom$ or mepromazin$ or methotrimeprazin$ or methotrimperazin$ or milezin$ or minozinan$ or neozin$ or neuractil$ or neurocil$ or nirvan or nozinan$ or sinogan or tisercin$ or tizercin$ or tizertsin$ or veractil$).tw.
(olanzapin$ or lanzac or midax or olansek or zydis or zyprex$).tw.
(paliperidon$ or 9 hydroxyrisperidon$ or invega).tw.
(pericyazin$ or aolept or neulactil$ or neuleptil$ or periciazin$ or properciazin$ or propericiazin$).tw.
perphenazine/ or (perphenazin$ or chlorperphenazin$ or chlorpiprazin$ or chlorpiprozin$ or decentan$ or etaperazin$ or ethaperazin$ or fentazin$ or perfenazin$ or perfenazin$ or perferazin$ or perphenan$ or perphenezin$ or thilatazin$ or tranquisan$ or trifalon$ or trilafan$ or trilafon$ or trilifan$ or triliphan$).tw.
pimozide/ or (pimozid$ or antalon$ or opiran$ or orap or pimocid$ or pimorid$ or pinozid$).tw.
prochlorperazine/ or (prochlorperazin$ or capazin$ or chlormeprazin$ or chlorpeazin$ or chlorperazin$ or compazin$ or dicopal$ or emelent or kronocin$ or meterazin$ or metherazin$ or nipodal$ or prochlor perazin$ or prochlorpemazin$ or prochlorperacin$ or prochlorperzin$ or prochlorpromazin$ or proclorperazin$ or tementil$ or temetil$).tw.
promazine/ or (promazin$ or alofen$ or alophen$ or ampazin$ or amprazim$ or centractyl or delazin$ or esparin$ or lete or liranol$ or neo hibernex or neuroplegil$ or piarin$ or prazin$ or pro tan or promantin$ or promanyl$ or promilen$ or promwill or protactil$ or protactyl$ or romthiazin$ or romtiazin$ or sediston$ or sinophenin$ or sparin$ or tomil or varophen$ or verophen$).tw.
(quetiapin$ or seroquel or tienapin$).tw.
risperidone/ or (risperidon$ or belivon$ or risolept or risperdal$).tw.
(sertindol$ or indole or serdolect or serlect).tw.
sulpiride/ or (sulpirid$ or abilit or aiglonyl$ or arminol$ or deponerton$ or desisulpid$ or digton or dobren or dogmatil$ or dogmatyl or dolmatil$ or eglonyl or ekilid or equilid or guastil$ or isnamid$ or leboprid$ or levopraid or levosulpirid$ or meresa or mirado$l or neogama or pontirid$ or psicocen$ or sulfirid$ or sulp$1 or sulperid$ or sulpitil$ or sulpivert or sulpor or sulpyride or synedil$ or tepavil$ or vertigo meresa or vertigo neogama or vipral).tw.
trifluoperazine/ or (trifluoperazin$ or apotrifluoperazine$ or calmazin$ or

dihydrochlorid$ or eskazin$ or eskazin$ or eskazinyl or fluoperazin$ or flupazin$ or jatroneural$ or modalina or stelazin$ or terfluzin$ or terfluzin$ or trifluoperazid$ or trifluoperazin$ or trifluoperzin$ or trifluoroperazin$ or trifluorperacin$ or trifluperazin$ or triflurin$ or triftazin$ or triftazinum or triphtazin$ or triphthasin$ or triphthazin$).tw.
(zotepin$ or lodopin$ or nipolept).tw.
clopenthixol/ or (zuclopenthixol$ or acuphase or clopenthixol$ or clopixol or cisordinol$ or sedanxol$).tw.

Benzodiazepines

exp benzodiazepines/
(benzo$1 or benzodiazepin$).tw.
alprazolam/ or (alprazolam or alprox or apo alpraz or apoalpraz or aprazolam$ or cassadan$ or constan$2 or esparon$ or helex or kalma or novo alprazol$ or novoalprazol$ or nu alpraz or nualpraz or ralozam or solanax or tafil$1 or trankimazin$ or valeans or xanax or xanor).tw.
bromazepam/ or (bromazepam or anxyrex or bartul or bromalich or bromazanil$ or bromazep von ct or durazanil$ or lectopam$ or lexamil$ or lexatin$ or lexaurin$ or lexilium or lexomil$ or lexotan$ or lexotanil$ or lexotanil$ or normoc or sintrogel$).tw.
chlordiazepoxide/ or (chlordiazepoxid$ or methaminodiazepoxid$ or elenium$ or librium$ or chlozepid$ or ansiacal$ or a poxide or benzodiapin$ or cebrum$1 or chlordiazepoxyd$ or chlorodiazepoxid$ or clopoxid$ or contol$ or decacil$ or defobin$ or disarim$ or dizepin$ or dopoxid$ or droxol$ or eden psich or elenium$ or elenum$ or equibral$ or kalmocaps or labican$ or librelease or libritabs or librium or lipoxide or mesural$ or metaminodiazepoxid$ or methaminodiazepoxid$ or mildmen$ or mitran$ or multum$ or murcil$ or napoton$ or napoton$ or novosed$ or psichial$ or psicosan$ or psicoterin$ or radepur or reliberan$ or reposans 10 or risolid or seren vita or servium or silibrin$ or sk lygen or sonimen$ or timosin$ or viansin$ or viopsicol$).tw.
(clobazam or chlorepin$ or clobazepam or clorepin$ or frisium or noiafren$ or urbadan$ or urbanil$ or urbanyl).tw.
clonazepam/ or (clonazepam or antelepsin$ or clonopin$ or iktorivil$ or klonazepam or klonopin$ or landsen$ or rivotril$).tw.
clorazepate dipotassium/ or (clorazepat$ or carboxylic acid or chlorazepat$ or chloroazepat$ or clorazepic acid or tranxen$ or tranxilium).tw.

(delorazepam or briantum$ or chlordemethyldiazepam or chlordesmethyldiazepam or chloro n demethyldiazepam or chlorodemethyldiazepam or chlorodesmethyldiazepam or
chloronordiazepam or (diazepam adj2 chloro$)).tw.
diazepam/ or (diazepam or alupram or ansiolin$ or antenex or apaurin$ or apaurin$ or apozepam or assiva$l or audium$ or bialzepam or bialzepan$ or calmpos$ or cercin$ or cercin$ or cersin$ or chlordiazepam or diastat or diazelium or diazemuls or diazidem or ducen$ or duxen$ or eridan or eurosan$ or evacalm$ or fanstan$ or faustan$ or faustan$ or gewacalm$ or lamra or lembrol$ or lipodiazepam or lorinon$ or methyldiazepinon$ or methyldiazepinon$ or morosan$ or neocalm$ or neurolytril$ or noan or novazam or paceum or plidan or psychopax or relanium or sedapam or seduxen$ or serendin$ or setonil$ or sibazon$ or sonacon$ or stesolid$ or stesolin$ or tanquo tablinen$ or tranimul$ or tranquo puren or umbrium$ or valaxon$ or valiquid$ or valium or valpam or valreleas$ or vatran$ or vival$ or vivol4 or zetran$).tw.
flunitrazepam/ or (flunitrazepam or flurazepam or fluridrazepam or darkene or flunibeta or flunimerck or fluninoc or flunipam or flunita or flunitrax or flunizep von ct or hypnodorm$ or hypnosedon$ or inervon$ or narcozep or parnox or rohipnol$ or rohypnol$ or roipnol$ or silece or valsera).tw.
flurazepam/ or (flurazepam or benozil$ or dalmadorm$ or dalman$ or dalmate or dormodor$ or lunipax or staurodorm$ or dalman$ or dormodor$ or dalmadorm$).tw.
(flutoprazepam or restas).tw.
loprazolam.tw.
lorazepam/ or (lorazepam or almazin$ or alzapam or apolorazepam or ativan or bonatranquan$ or donix or duralozam or durazolam or idalprem or kendol$ or laubeel or lorabenz or loranas$ or loranaz$ or lorans or lorax or lorazep von ct or loridem$ or lorivan$ or mesmerin$ or novo lorazem$ or novolorazem$ or novo lorazem$ or nu loraz or nuloraz or orfidal or orifadal$ or pro dorm or quait or securit or sedicepan$ or sinestron$ or somagerol$ or tavor or temesta or tolid wypax).tw.
(lormetazepam or loramet or (lorazepam adj2 methyl) or methyllorazepam or minians or minias or noctamid$ or pronoctan$).tw.
(mexazolam or melex or sedoxil$).tw.
midazolam/ or (midazolam or dormicum or dormonid$ or hypnova$l or hypnovel$ or hypnoyvel$ or versed).tw.
nitrazepam/ or (nitrazepam or alodorm or atempol$ or benzalin$ or dormalon$ or

dormo puren or dumolid or eatan or eunoctin$ or hypnotex or imadorm or imeson$ or insomin$ or mogadan$ or mogadon$ or nelbon$ or nirven$ or nitra zepam or nitrados or nitravet or nitrazadon$ or nitrazep or nitrodiazepam or novanox or pacisyn or radedorm$ or remnos or restorem$ or sedamon$ or serenade or somnased$ or somnibel$ or somnit$).tw.
oxazepam/ or (oxazepam or abboxapam or adumbran$ or alopam or anxiolit$ or azutranquil$ or durazepam or expidet$ or hilong or isodin$ or linbial$ or noctazepam or oxapuren$ or oxepam or praxiten$ or serax or serenid$ or serepax or seresta or serpax or sigacalm$ or sobril$ or tazepam$ or uskan).tw.
prazepam/ or (prazepam or centrax or demetrin$ or lysanxia or mono demetrin$ or monodemetrin$ or reapam or sedapran$ or verstran).tw.
temazepam/ or (temazepam or apo-temazepam or dasuen or euhypnos or hydroxydiazepam or levanxol$ or methyloxazepam or nocturne$ or norkotral tema or normison$ or normitab or nortem or oxydiazepam or planum or pronervon t or remestan$ or restoril$ or signopam or temaz$1 or temazep von ct or temazepax or temtabs or tenox or texapam).tw.

Anticonvulsants

exp anticonvulsants/ or antimanic agents/ or tranquilizing agents/
((mood adj2 stabili$) or ((antimanic or anti manic) adj2 (agent$ or drug$ or stabil$)) or anticonvuls$ or anti convuls$ or tranquil?li?er$ or tranquil?i?ing).tw.
carbamazepine/ or (carbamazepin$ or amizepin$ or amizepin$ or amizepin$ or atretol or biston or calepsin$ or carbategral$ or carbatrol$ or carbazepin$ or convulin$ or epimax or epitol or equetro or finlepsin$ or finlepsin$ or lexin or mazepin$ or neurotol or neurotop or servimazepin$ or sirtal or tegral or tegretal or tegretol or tegrital or telesmin or teril or timonil).tw.
ethosuximide/ or (ethosuximid$ or asamid$ or emesid$ or ethosuccimid$ or ethosuccinimid$ or ethylmethylsuccimid$ or ethylsuximid$ or ethymal$ or etosuximid$ or mesentol$ or pemal or petinimid$ or petnidan$ or petnidan$ or pyknolepsin$ or ronton$ or simatin$ or succinutin$ or sucsilep or suxilep or suxinutin$ or zarontin$ or zarontin$).tw.
(gabapentin$ or neurontin$ or neurotonin$).tw.
(lacosamid$ or erlosamid$ or harkoserid$ or n acetyl o methyl dextro serine

benzylamid$).tw.
(lamotrigin$ or labileno or lamictal).tw.
(levetiracetam or etirazetam or etiracetam or keppra).tw.
lithium$.sh. or (lithium$ or camcolit or candamid$ or carbolith or carbolitium or cibalith s or contemnol$ or dilithium or eskalith or hypnorex or li salt or limas or linthane or liskonium or liskonum or litarex or lithane or lithiofor or lithionit or lithiophor or lithobid or lithocarb or lithonate or lithotabs or maniprex or mesin or micalith or neurolepsin or neurolithium or plenur or priadel or quilinormretard or quilonorm or quilonum or teralithe or theralite or theralithe lp).tw.
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(tiagabin$ or gabitril$ or tiabex).tw.
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aminobutyric acid or sabril or sabrilex).tw.
(zonisamid$ or excegran or excemid or zonegran).tw.

- **RCT filter -** this is an adaptation of a filter designed by the Health Information Research Unit of the McMaster University, Ontario.

exp clinical trial/ or cross over studies/ or double blind method/ or random allocation/ or randomized controlled trials as topic/ or single blind method/
(clinical adj2 trial$).tw.
(crossover or cross over).tw.
(((single$ or doubl$ or trebl$ or tripl$) adj5 blind$) or mask$ or dummy or singleblind$ or doubleblind$ or trebleblind$ or tripleblind$).tw.
(placebo$ or random$).tw.
(clinical trial$ or controlled clinical trial$ or random$).pt.

- **Websites of pharmaceutical companies** (last accessed on Nov 30th 2010)
  Eli Lilly: www.lilly.com
  Lundbeck: www.lundbeck.com
  Organon: www.organon.com
  Solvay: www.solvay.com
  Pfizer: www.pfizer.com
  GlaxoSmithKline: www.gsk.com
  Bristol Myers Squibb: www.mbs.com
  Wyeth: www.wyeth.com

- **Medical Control Agencies** (last accessed on November 30th 2010)
  Food and Drug Administration (USA): www.fda.gov
  European Medicines Agency (EU): www.emea.europa.eu
  Therapeutic Goods Administration (Australia): www.tga.gov.au

All relevant authors and principal manufacturers were contacted to supplement the incomplete report of the original papers or to provide new data for unpublished studies. We also checked the websites of these manufacturers for further studies.

The Cochrane risk of bias tool was used to assess study quality.[11] This instrument consists of six items, providing a framework for assessing the whole trial with explicit and transparent criteria separating facts from judgments. Two of the items (adequacy of sequence generation and allocation concealment) assess the strength of the randomization process in preventing selection bias in the assignment of participants to interventions; the third item (blinding) assesses the influence of performance bias on the study results and the fourth the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes (this item requires a comparison of published data with trial protocols, when such are available). The final item refers to other sources of bias that are relevant in certain circumstances, such as, for example, sponsorship bias.

Outcome measures

Acute treatment was defined as a 3-week treatment in both the efficacy and acceptability analyses. If 3-week data were not available, data ranging between 2 to 6 weeks were used (the time point given in the original study as the study endpoint was given preference). Mean change scores on the Young Mania Rating Scale (YMRS) and dropout rates (treatment discontinuation) were chosen as primary outcomes to represent respectively the most sensible and sensitive estimate of acute treatment efficacy and acceptability. If YMRS results were not available, we used the mean changes of other standardized rating scales for acute mania. Treatment discontinuation (acceptability) was defined as the number of patients who left the study early for any reason during the first 3 weeks of treatment, out of the total number of patients randomly assigned to each treatment arm. As a secondary analysis we also estimated the proportion of patients who responded to treatment. Response was defined as a reduction of at least 50% on the total score between baseline and endpoint on a standardized rating scale for mania (possibly YMRS; if not available, other rating scales were used).

Appendix 2

Study protocol

BACKGROUND

The main aim in treating mania, hypomania and mixed episodes is to achieve rapid control of symptoms. This is particularly important as mania can result in disturbed behavior that, when extreme, can be a risk to the safety of the patient and others. Mood stabilizers and antipsychotic agents have long been the mainstay of treatment of acute mania (with and without psychotic features) (NICE, 2006; Scherk et al., 2007).

Lithium and valproate are held to be effective in acute mania but their onset of action is slower than with antipsychotics. Prior to the introduction of the atypical antipsychotics, the conventional antipsychotics were the frequently used treatment for mania despite a relative lack of randomised controlled trials to support their use. In recent years several atypical antipsychotics agents have been licensed to treat mania (aripiprazole, olanzapine, risperidone and quetiapine). However, there is a debate about the benefits of newer so-called atypical antipsychotic drugs compared with older antipsychotic drugs. A major advantage of the atypical antipsychotics over conventional antipsychotics is the lower risk of extrapyramidal symptoms (EPSs) though this differential has largely been demonstrated in trials where the comparator was haloperidol, a high-potency conventional antipsychotic that is associated with a relatively high incidence of EPS. There is no general consensus about which of these drugs should be used first-line. Guidelines for the treatment of bipolar disorder vary significantly across committees or specialist groups (Fountoulakis et al., 2005). In particular for the treatment of acute mania, some guidelines recommend monotherapy with a mood stabilizer or an antipsychotic drug as first-line treatment, whereas others recommend a combination of a mood stabilizer and an antipsychotic agent.

Adverse effects in short term studies tend to focus on EPS but some atypical antipsychotics, in particular olanzapine and clozapine, are associated with a high risk of significant increase in body weight and this may influence the selection even of short term treatments under some circumstances.

The aim of this study is to compare the efficacy and acceptability of pharmacological treatments for acute mania, in order to inform clinical practice and mental health policies. We will carry out a multiple-treatments meta-analysis (MTM). MTM is a

statistical technique that allows both direct and indirect comparisons to be undertaken, even when two of the treatments have not been directly compared (Higgins et al., 1996; Hasselblad et al., 1998; Lumley, 2002). Reliable information on comparative efficacy is essential for informing clinical practice and policymaking and MTM allows us to use all the available evidence to estimate potential differences in efficacy among treatments.

OBJECTIVES

To compare individual anti-manic agents in terms of:

(1) Efficacy (as continuous outcome), measured by the total score of the Young Mania Rating Scale (YMRS - Young et al., 1978) or another standardised rating scale, if fYMRS was not used.

(2) Efficacy (as dichotomous outcome), measured by the total number of patients who had a reduction of at least 50% on the total score between baseline and endpoint on a standardized rating scale for mania (YMRS or another standardised rating scale, if YMRS was not used).

(3) Acceptability of treatment, defined as the proportion of patients who left the study early by any cause.

METHODS

Criteria for considering studies for this review

Types of studies

Double-blind RCTs comparing one active drug (antipsychotic, mood stabiliser or benzodiazepine) with another active drug (antipsychotic, mood stabiliser or benzodiazepine) or placebo as oral therapy in the treatment of acute mania will be included. All combination studies (when combining drugs of the same class, for instance antipsychotic plus antipsychotic) and augmentation studies (when combining drugs belonging to different classes, for instance antipsychotic plus mood stabiliser) will be included as well. We therefore will investigate heterogeneity between these different types of studies. Quasi-randomized trials (such as those allocating by using alternate

days of the week) will be excluded. For trials which have a crossover design only results from the first randomisation period will be considered.

Types of participants

Patients aged 18 or older of both sexes with a primary diagnosis of acute mania or bipolar disorder (manic or mixed episode) according to the standardised diagnostic criteria used by the study authors. Most recent studies are likely to have used DSM-IV (APA 1994) or ICD-10 (WHO 1992) criteria. Older studies may have used ICD-9 (WHO 1978), DSM-III (APA 1980)/DSM-III-R (APA 1987) or other diagnostic systems such as Feighner criteria or Research Diagnostic Criteria. There is no evidence that treatment effects differ depending on the diagnostic criteria used. A concurrent Axis I diagnosis of another psychiatric disorder will be considered as exclusion criteria. A concurrent Axis II diagnosis of psychiatric disorder will not be considered as exclusion criteria. Studies with patients with a serious concomitant medical illness as an inclusion criterion will be excluded.

Outcome measures

(1) Overall efficacy of antipsychotic treatment

1.1 Overall efficacy will be primarily measured as the mean change of the total score of the YMRS from baseline to endpoint. If YMRS results are not available, we will use the mean change from baseline to endpoint of other standardised rating scales for acute mania.

1.2 We will also estimate efficacy as the proportion of patients who responded to treatment (response is defined as a reduction of at least 50% on the total score between baseline and endpoint on a standardized rating scale for mania (possibly YMRS; if not available, other rating scales will be used).

(2) Acceptability of treatment

Treatment discontinuation (acceptability) is defined as the proportion of patients who left the study early for any reason, out of the total number of patients randomly assigned to each treatment arm.

Search strategy

All published and unpublished randomized controlled, double-blind trials that compared oral doses of one of the above mentioned anti-manic drugs with another drug (or placebo) in the treatment of acute mania will be identified.

We will identify relevant trials from systematic searches in the following electronic databases, MEDLINE, EMBASE, CINAHL, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL). We will also consult trial databases of the following drug-approving agencies - (the Food and Drug Administration (FDA) in the USA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, the European Medicines Agency (EMEA) in the EU, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the Therapeutic Goods Administration (TGA) in Australia) and ongoing trial registers (clinicaltrials.gov in the USA, ISRCTN and National Research Register in the UK, Netherlands Trial Register in the Netherlands, EUDRACT in the EU, UMIN-CTR in Japan and the Australian Clinical Trials Registry in Australia) will be hand-searched for published, unpublished and ongoing controlled trials. No language restrictions will be applied. Electronic databases will be searched using the following strategy: [bipolar disorder or bipolar depression or mania or manic or hypomania or cyclothymic cycle or ultra-rapid cycling or ultradian cycling or RCBD or DMX or mixed depression or mixed bipolar or reactive depression or psychogenic depression or puerperal psychosis or puerperium psychosis or excited psychosis] and combined with a list of antipsychotics, including [(amisulpride or aripiprazole or benperidol or chlorpromazine or chlorprothixene or clozapine or flupentixol or fluspirilene or haloperidol or levomepromazine or olanzapine or paliperidone or pericyazine or perphenazine or pimozide or prochlorperazine or promazine or quetiapine or risperidone or sertindole or sulpiride or trifluoperazine or zotepine) or mood stablisers, including (alprazolam or bromazepam or carbamazepine or chlordiazepoxide or clobazam or clonazepam or clorazepate or delorazepam or diazepam or ethosuximide or flunitrazepam or flurazepam or flutoprazepam or gabapentin or lacosamide or lamotrigine or levetiracetam or lithium or loprazolam or lorazepam or lormetazepam or mexazolam or midazolam or nitrazepam or oxazepam or oxcarbazepine or phenobarbital or phenytoin or prazepam or pregabalin or temazepam or tiagabine or topiramate or valproic acid or verapamil or vigabatrin or zonisamide)].

All relevant authors and principal manufacturers will be contacted to supplement the incomplete report of the original papers. We will also check the websites of these manufacturers for further studies.

Study selection and data extraction

We will use the data that have been extracted for the previous Cochrane reviews carried out by the members of our review team (JG, JR, AC, GG). Concerning the update search, three reviewers (AC, JR and CB) will independently review references and abstracts. If both reviewers agree that the trial doesn't meet eligibility criteria, we will exclude it. We will obtain the full text of all remaining articles and use the same eligibility criteria to determine which, if any, to exclude at this stage. Any disagreements will be solved via discussion with another member of the reviewing team (JG or GG). The same reviewers (AC, JR and CB) will then independently read each article, evaluate the completeness of the data abstraction, and confirm the quality rating. As for previous Cochrane systematic reviews, we will design and use a structured data abstraction form to ensure consistency of appraisal for each study. Information extracted will include study characteristics (such as lead author, publication year, journal, study setting, sponsorship), participant characteristics (such as diagnostic criteria, mean baseline score, age), intervention details (such as dose ranges, mean doses of study drugs, concomitant and/or rescue medications) and outcome measures (see above).

Length of follow up

In the present review, acute treatment will be defined as a 3-week treatment in all analyses. If 3-week data are not available, we will use data ranging between 2 and 6 weeks (we will give preference to the time-point given in the original study as the study endpoint).

Quality Assessment

To assess the quality (internal validity) of trials, we will use predefined criteria based on those developed by the Cochrane Collaboration. Inadequate concealment undermines the principle of randomization, because participants may then be allocated to a treatment according to prognostic variables rather than by pure chance. Therefore, two independent review authors (AC, JR or CB) will independently assess trial quality in accordance with the Cochrane Handbook (Higgins & Green, 2005). This pays particular attention to the adequacy of the random allocation concealment and double blinding. Studies will be given a quality rating of A (adequate), B (unclear), and C (inadequate) according to these two items. Studies which will score A or B on these criteria constitute the final list of included studies. Where inadequate details of allocation concealment and other characteristics of trials are provided, the trial authors will be contacted in order to obtain further information. If the raters disagree, the final rating will be made by consensus with the involvement (if necessary) of another member of the review group.

Comparability of dosages

We will include only studies randomizing patients to drugs within the therapeutic dose (both fixed-dose and flexible-dose designs will be allowed). There is the possibility that some trials compare one agent at the upper limit of its therapeutic range with another agent at the lower limit of its therapeutic range within the same study. We may look at heterogeneity and then add a variable (yes/no) that report if dosages are comparable and use this information for analysis.

STATISTICAL ANALYSIS

The efficacy outcome of this review will be the change of the total score of the YMRS. Dichotomous outcomes will be analysed on an intention-to-treat (ITT) basis: drop-outs will always be included in this analysis. When data on drop-outs are carried forward and included in the evaluation (Last Observation Carried Forward, LOCF), they will be analysed according to the primary studies.

Synthesis of results

We will generate descriptive statistics for trial and study population characteristics across all eligible trials, describing the types of comparisons and some important variables, either clinical or methodological (such as year of publication, age, severity of illness, sponsorship).

For each pair-wise comparison between anti-manic drugs, the standardized mean difference Hedges's adjusted g (SMD) will be calculated as the effect size for continuous outcomes and the odds ratio will be calculated for dichotomous outcomes, both with a 95% CI. We will first perform pair-wise meta-analyses by synthesizing studies that compare the same interventions using a random effects model (DerSimonian & Laird, 1986) to incorporate the assumption that the different studies are estimating different, yet related, treatment effects (Higgins & Green, 2006). Visual inspection of the forest plots will be used to investigate the possibility of statistical heterogeneity. This will be supplemented using, primarily, the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error (Higgins et al., 2003). 95% confidence intervals will be calculated for I-squared, and a P value from a standard test for heterogeneity will be used to assess evidence of its presence.

We will conduct a MTM which is a method of synthesizing information from a network of trials addressing the same question but involving different interventions. For a given comparison, say A versus B, direct evidence is provided by studies that compare these two treatments directly. However, indirect evidence is provided when studies that compare A versus C and B versus C are analyzed jointly. The combination of the direct and indirect into a single effect size can increase precision while randomization is respected. The combination of direct and indirect evidence for any given treatment comparison can be extended when ranking more than three types of treatments according to their effectiveness: every study contributes evidence about a subset of these treatments. We will perform MTM within a Bayesian framework (Ades et al., 2006). This enables us to estimate the probability for each intervention to be the best for each positive outcome, given the results of the MTM. The analysis will be performed using WinBUGS (MRC Biostatistics Unit, Cambridge, U.K., http://www.mrcbsu cam.ac.uk/bugs/winbugs/contents.shtml).

MTM should be used carefullly, and the underlying assumptions of the analysis should be investigated carefully. Key among these is that the network is coherent, meaning that

direct and indirect evidence on the same comparisons agree. Joint analysis of treatments can be misleading if the network is substantially incoherent, i.e., if there is disagreement between indirect and direct estimates. So, as a first step, we will calculate the difference between indirect and direct estimates in each closed loop formed by the network of trials as a measure of incoherence and we will subsequently examine whether there are any material discrepancies. In case of significant incoherence we will investigate possible sources of it. Incoherence may result as an uneven distribution of effect modifiers across groups of trials that compare different treatments. Therefore, we will investigate the distribution of clinical and methodological variables that we suspect may be potential sources of either heterogeneity or incoherence in each comparison-specific group of trials.

Subgroup analysis

We will carry out a subgroup analysis based on study treatment (combination/augmentation treatments vs monotherapy).

Meta-regression analysis

We will carry out a meta-regression analysis for sponsorship (Salanti et al., 2009).

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Appendix 3

Characteristics of included studies

Study	Drug A	Drug B	Drug C *	Add-on	F-up (wks)	Setting	Rating scale	Diagnosis	Sample			Dose (mg)			Sponsor
									A	B	C	A	B	C	
Berk 1999	LIT	OLZ	-	n	4	in	MAS	DSM-IV	15	15	-	800 mg	10 mg	-	unclear
Berwaerts 2010	PAL#	-	PBO	n	3	in & out	YMRS	DSM-IV	347		122	3-12 mg	-	Placebo	Johnson & Johnson
Bowden 1994	DVX	LIT	PBO	n	3	in	MRS	RDC	69	36	74	max: 150 µg/mL	max: 1.5 mEq/L	Placebo	Abbott
Bowden 2005	QTP	LIT	PBO	n	3	in	YMRS	DSM-IV	107	98	97	400-800 mg	0.6-1.4 mEq/L	Placebo	AstraZeneca
Bowden 2006	DVX#	-	PBO	n	3	in	MRS	DSM-IV	192	-	185	2961 mg (m)	-	Placebo	Abbott
Brown 1989	CBZ	HAL	-	n	2	n/s	YMRS	DSM-III	8	9	-	200-1600 mg	10-80 mg	-	unclear
Chengappa 2006	TOP	-	PBO	y	3	out	YMRS	DSM-IV	143	-	144	50-400 mg	-	Placebo	Otho-McNeil
El Mallakh 2010	ARI	-	PBO	n	3	in	YMRS	DSM-IV	267	-	134	15-30 mg	-	Placebo	BMS
Freeman 1992	LIT	DVX	-	n	3	n/s	BPRS	DSM-III-R	13	14	-	0.8-1.4 mEq/L	98 µg/mL (m)	-	unclear
Garfinkel 1980	HAL	LIT	-	n	3	n/s	BPRS	Feighner	7	7	-	1.2 mEq/L (m)	28 mg (m)	-	unclear
Hirschfeld 2004	RIS	-	PBO	n	3	in	YMRS	DSM-IV	134	-	125	4.1 mg (m)	-	Placebo	Johnson & Johnson
Hirschfeld 2010	DVX#	-	PBO	n	3	in	MRS	DSM-IV	147	-	78	77.9 µg/mL (m)	-	Placebo	Abbott
Houston 2009	OLZ	-	PBO	y	6	in & out	YMRS	DSM-IV	101	-	101	5-20 mg	-	Placebo	Eli Lilly
Ichim 2000	LAM	LIT	-	n	4	in	MRS	DSM-IV	15	15	-	100 mg	800 mg	-	unclear
Keck 2003a	ZIP	-	PBO	n	3	in	MRS	DSM-IV	140	-	70	80-160 mg	-	Placebo	Pfizer
Keck 2003b	ARI	-	PBO	n	3	in	YMRS	DSM-IV	130	-	132	15-30 mg	-	Placebo	BMS
Keck 2009	ARI	LIT	PBO	n	3	in	YMRS	DSM-IV	155	160	165	15-30 mg	900-1500 mg	Placebo	BMS
Khanna 2005	RIS	-	PBO	n	3	in	YMRS	DSM-IV	146	-	145	1-6 mg	-	Placebo	Johnson & Johnson
Kushner 2006a	TOP	LIT	PBO	n	3	in	YMRS	DSM-IV	220	113	111	200-400 mg	1500 mg	Placebo	Otho-McNeil
Kushner 2006b	TOP	-	PBO	n	3	in	YMRS	DSM-IV	214	-	100	400-600 mg	-	Placebo	Otho-McNeil
Kushner 2006c	TOP	-	PBO	n	3	in	YMRS	DSM-IV	109	-	106	400 mg	-	Placebo	Otho-McNeil
Kushner 2006d	TOP	LIT	PBO	n	3	in	YMRS	DSM-IV	116	114	112	400 mg	1500 mg	Placebo	Otho-McNeil
Lerer 1987	CBZ	LIT	-	n	4	n/s	BPRS	DSM-III	15	19	-	1400 mg (m)	0.87 mmol/l (m)	-	unclear
Li 2008	QTP	LIT	-	n	4	in	YMRS	CCMD-3	78	77	-	200-800 mg	0.6-1.2 mmol/l	-	AstraZeneca
McIntyre 2005	QTP	HAL	PBO	n	3	in	YMRS	DSM-IV	102	99	101	400-800 mg	2-8 mg	Placebo	AstraZeneca
McIntyre 2009	ASE	OLZ	PBO	n	3	in	YMRS	DSM-IV	194	190	105	10-20 mg	5-20 mg	Placebo	Schering-Plough
Müller-O. 2000	DVX	-	PBO	y	3	in	YMRS	ICD-10	69	-	67	20 mg/kg	-	Placebo	GmbH
Niufan 2008	OLZ	LIT	-	n	4	in & out	YMRS	DSM-IV	69	71	-	5-20 mg	600-1800 mg	-	Eli Lilly

Ortega-Soto 1993	CBZ	HAL	-	n	5	n/s	MAS	DSM-III-R	10	10	-	600-1600 mg	15-40 mg	-	unclear
Pande 2000	GBT	-	PBO	y	3	out	YMRS	DSM-IV	59	-	59	600-3600 mg	-	Placebo	Warner-Lambert
Perlis 2006	OLZ	RIS	-	n	3	in	YMRS	DSM-IV	165	164	-	15-20 mg	3-6 mg	-	Eli Lilly
Pope 1991	DVX	-	PBO	n	3	n/s	YMRS	DSM-III-R	20	-	22	50-100 mg/L	-	Placebo	unclear
Potkin 2005	ZIP	-	PBO	n	3	in	MRS	DSM-IV	140	-	66	80-160 mg	-	Placebo	Pfizer
Sachs 2002	RIS	HAL	PBO	y	3	in	YMRS	DSM-IV	52	53	51	2-6 mg	4-12 mg	-	Janssen
Sachs 2004	QTP	-	PBO	y	3	in	YMRS	DSM-IV	91	-	100	200-800 mg	-	Placebo	AstraZeneca
Sachs 2006	ARI	-	PBO	n	3	in	YMRS	DSM-IV	137	-	135	15-30 mg	-	Placebo	BMS
Segal 1998	RIS	LIT	HAL	n	4	in	MRS	DSM-IV	15	15	15	6 mg	800-1200 mg	10 mg	Janssen
Shafti 2010	OLZ	LIT	-	n	3	in	MSRS	DSM-IV-TR	20	20	-	20.52 mg (m)	0.78 mmol/l (m)	-	Independent
Small 1991	CBZ	LIT	-	n	6	in	MRS	DSM-III-R	27	25	-	1052 mg (m)	0.66 mmol/l (m)	-	NIMH
Small 1995	CBZ	HAL	-	y	3	in	YMRS	DSM-III-R	17	16		900-1200 mg	11-13.5 mg	-	unclear
Smulevich 2005	RIS	HAL	PBO	n	3	n/s	YMRS	DSM-IV	154	144	140	1-6 mg	2-12 mg	Placebo	Johnson & Johnson
Tohen 1999	OLZ	-	PBO	n	3	in	YMRS	DSM-IV	70		69	5-20 mg	-	Placebo	Eli Lilly
Tohen 2000	OLZ	-	PBO	n	4	in & out	YMRS	DSM-IV	55	-	60	5-20 mg	-	Placebo	Eli Lilly
Tohen 2002a	OLZ	DVX	-	n	3	in	YMRS	DSM-IV	125	126	-	5-20 mg	500-2500 mg	-	Eli Lilly
Tohen 2002b	OLZ	-	PBO	y	6	in & out	YMRS	DSM-IV	229	-	115	5-20 mg	-	Placebo	Eli Lilly
Tohen 2003	OLZ	HAL	-	n	6	in & out	YMRS	DSM-IV	234	219	-	5-20 mg	3-15 mg	-	Eli Lilly
Tohen 2008b	OLZ	-	PBO	y	6	in	YMRS	DSM-IV	58	-	60	10-30 mg	-	Placebo	Eli Lilly
Tohen 2008a	OLZ	DVX	PBO	n	3	in & out	YMRS	DSM-IV	215	201	105	5-20 mg	500-2500 mg	Placebo	Eli Lilly
Vasudev 2000	CBZ	DVX	-	n	4	in	YMRS	DSM-III-R	15	15	-	800-1200 mg	800-1400 mg	-	unclear
Vieta 2005	ARI	HAL	-	n	3	in & out	YMRS	DSM-IV	175	172	-	15-30 mg	10-15 mg	-	BMS
Vieta 2008	ARI	-	PBO	y	6	n/s	YMRS	DSM-IV	253	-	131	15-30 mg	-	Placebo	BMS
Vieta 2010a	PAL#	QTP	PBO	n	3	n/s	YMRS	DSM-IV	195	193	105	3-12 mg	400-800 mg	Placebo	Johnson & Johnson
Vieta 2010b	ZIP	HAL	PBO	n	3	in	MRS	DSM-IV	178	172	88	80-160 mg	8-30 mg	Placebo	Pfizer
Weisler 2004	CBZ#	-	PBO	n	3	in	YMRS	DSM-IV	101	-	103	200-1600 mg	-	Placebo	Shire
Weisler 2005	CBZ#	-	PBO	n	3	in	YMRS	DSM-IV	122	-	117	200-1600 mg	-	Placebo	Shire
Yatham 2003	RIS	-	PBO	y	3	in & out	YMRS	DSM-IV	75	-	76	4 mg (m)	-	Placebo	Janssen
Yatham 2007	QTP	-	PBO	y	3	in	YMRS	DSM-IV	106	-	105	400-800 mg	-	Placebo	AstraZeneca
Young 2009	ARI	HAL	PBO	n	3	in	YMRS	DSM-IV	167	165	153	15-30 mg	5-15 mg	Placebo	BMS
Zajecka 2002	DVX	OLZ	-	n	3	in	MRS	DSM-IV	63	57	-	20 mg/kg +/- 1000 mg	10-20 mg	-	Abbott

D144CC00004	QTP#	-	PBO	n	3	in & out	YMRS	DSM-IV-TR	155	-	161	400-800 mg	-	Placebo	AstraZeneca
SCAA2009	LAM	LIT	PBO	n	6	n/s	MRS	DSM-IV	74	78	77	100 mg	0.7-1.3 mEq/L	Placebo	GSK
SCAA2008	LAM	LIT	PBO	n	3	in	MRS	DSM-IV	85	36	95	50 mg	0.8-1.3 mEq/L	Placebo	GSK
NCT00129220	OLZ	HAL	PBO	n	3	in & out	YMRS	DSM-IV	105	20	99	5-20 mg	2.5-10 mg	Placebo	Eli Lilly
A 1281143	ZIP	-	PBO	y	3	in	YMRS	DSM-IV	458	-	222	40-160 mg	-	Placebo	Pfizer
A 7501004	ASE	OLZ	PBO	n	3	in	YMRS	DSM-IV	185	205	98	10-20 mg	5-20 mg	Placebo	Schering-Plough
A 1280620	ZIP	-	PBO	y	3	n/s	MRS	DSM-IV	102	-	103	80-160 mg	-	Placebo	Pfizer
A 1281147	ZIP	OLZ	-	n	3	n/s	YMRS	DSM-IV	15	14	-	120-160 mg	15-20 mg	-	Pfizer
CR010855	PAL#	-	PBO	y	6	n/s	YMRS	DSM-IV	150	-	150	3-12 mg	-	Placebo	Johnson & Johnson

Legend:

n/s: not stated; in: inpatients; out: outpatients; in & out: both inpatients and outpatients; * : or placebo; #: extended-release formulation; YMRS: Young Mania Rating Scale; MRS: Mania Rating Scale; MSRS: Manic State Rating Scale; BPRS: Brief Psychiatric Rating Scale; DSM III-R: Diagnostic Statistic Manual (Third Edition – Revised); DSM IV: Diagnostic Statistic Manual (Fourth Edition); DSM IV-TR: Diagnostic Statistic Manual (Fourth Edition – Text Revision); RDC: Research Diagnostic Criteria ; CCDM-3: Chinese Classification and Diagnosis Criteria of Mental Disorder, 3rd version; Feighner: Feighner criteria for mania (Feighner et al., 1972); F-up (wks): week of follow-up with outcome data available for analysis; (m): mean dose; Add-on: combination/augmentation strategy.

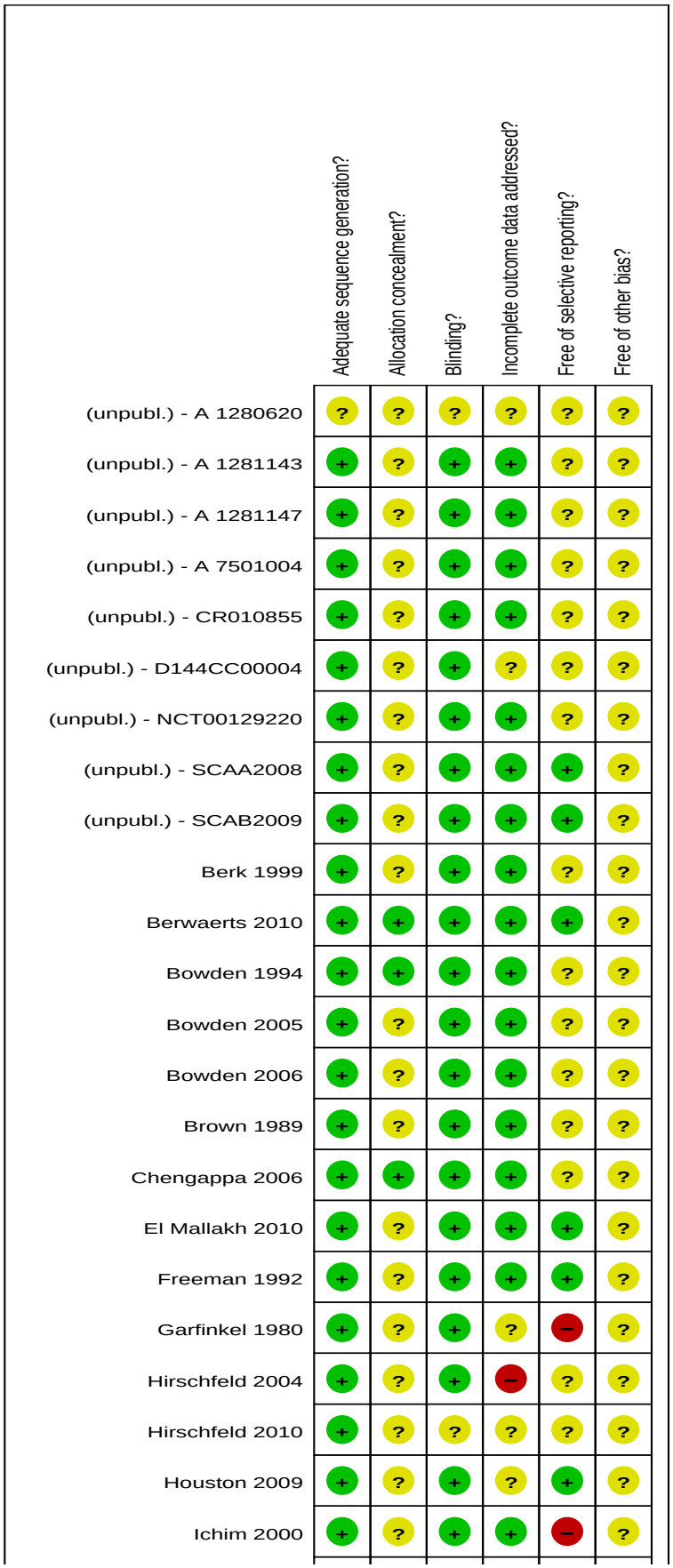
Appendix 4

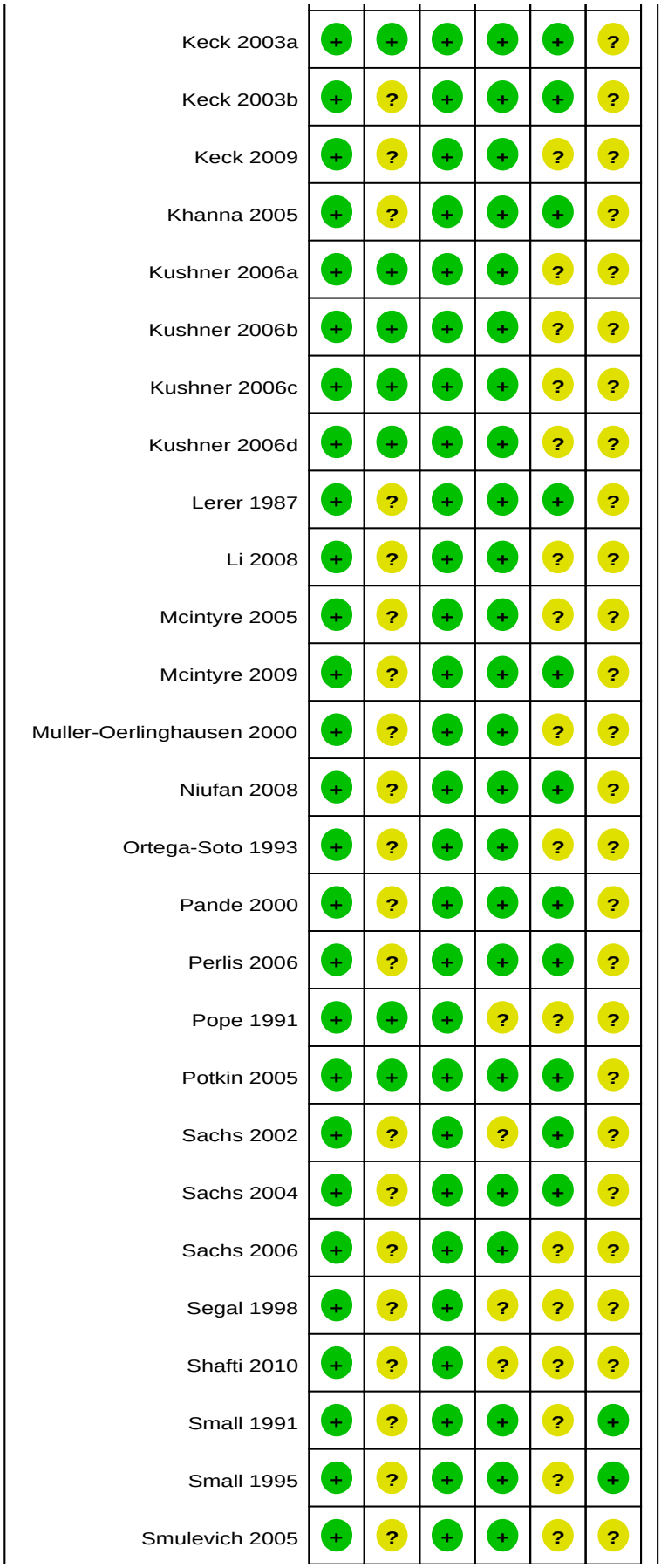
Risk of bias

We followed the recommended approach for assessing risk of bias in studies included in Cochrane reviews. It is a two-part tool, addressing the six specific domains (namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'). Two of the items (adequacy of sequence generation and allocation concealment) assess the strength of the randomization process in preventing selection bias in the assignment of participants to interventions; the third item (blinding) assesses the influence of performance bias on the study results and the fourth the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes (this item requires a comparison of published data with trial protocols, when such are available). The final item refers to other sources of bias that are relevant in certain circumstances, such as, for example, sponsorship bias. Each domain includes one or more specific entries in a 'Risk of bias' table. Within each entry, the first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. This is achieved by answering a pre-specified question about the adequacy of the study in relation to the entry, such that a judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias, and 'Unclear' indicates unclear or unknown risk of bias.

Domain	Description	Review authors' judgement
Sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	*Was the allocation sequence adequately generated?*
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	*Was allocation adequately concealed?*
Blinding of participants, personnel and outcome assessors	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	*Was knowledge of the allocated intervention adequately prevented during the study?*
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	*Were incomplete outcome data adequately addressed?*
Selective outcome reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	*Are reports of the study free of suggestion of selective outcome reporting?*
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool.	*Was the study apparently free of other problems that could put it at a high risk of bias?*

- Risk of bias graph: it is a plot of the distribution of judgments (Yes, Unclear and No) across studies for each risk of bias item.


Adequate sequence generation?
Allocation concealment?
Blinding?
Incomplete outcome data addressed?
Free of selective reporting?
Free of other bias?
(unpubl.) - A 1280620
(unpubl.) - A 1281143
(unpubl.) - A 1281147
(unpubl.) - A 7501004
(unpubl.) - CR010855
(unpubl.) - D144CC00004
(unpubl.) - NCT00129220
(unpubl.) - SCAA2008
(unpubl.) - SCAB2009
Berk 1999
Berwaerts 2010
Bowden 1994
Bowden 2005
Bowden 2006
Brown 1989
Chengappa 2006
El Mallakh 2010
Freeman 1992
Garfinkel 1980
Hirschfeld 2004
Hirschfeld 2010
Houston 2009
Ichim 2000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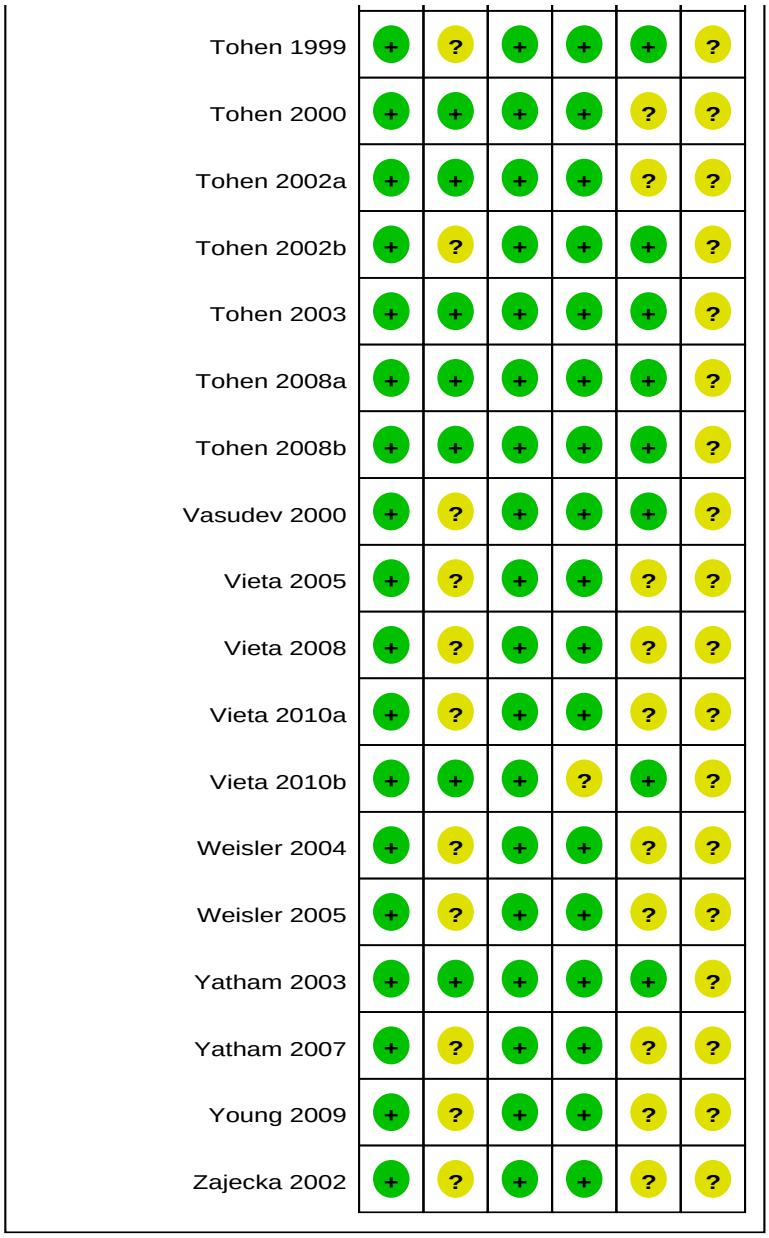
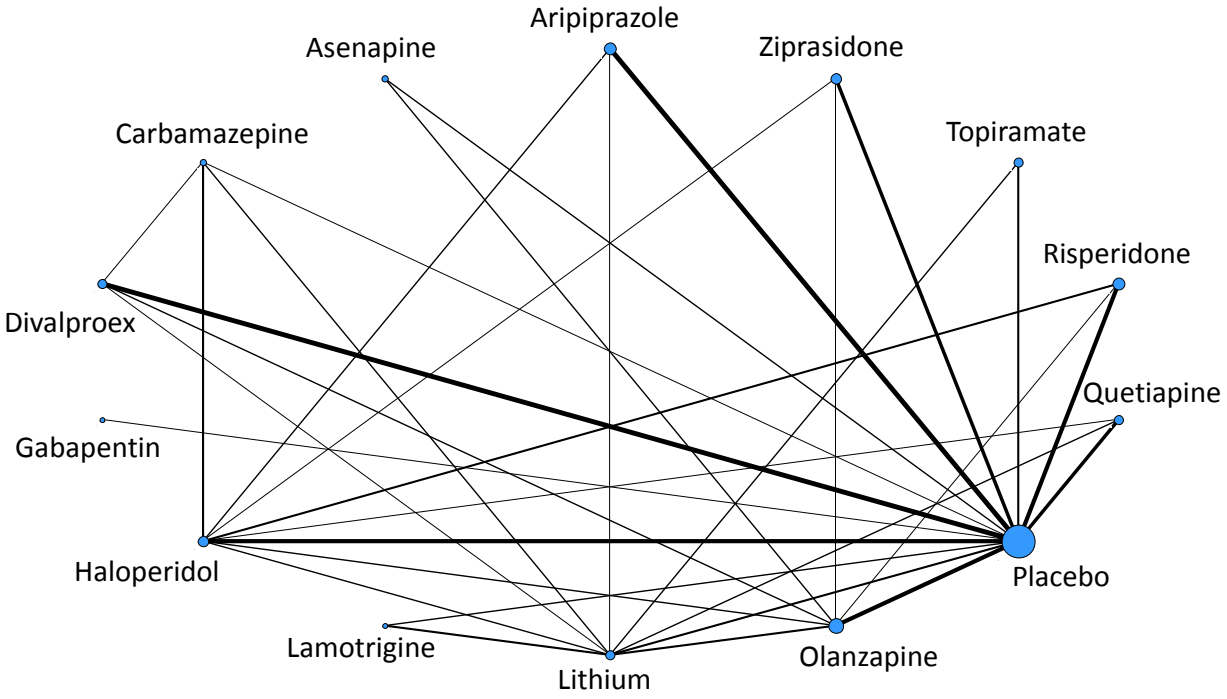
Keck 2009
Khanna 2005
Kushner 2006a
Kushner 2006b
Kushner 2006c
Kushner 2006d
Lerer 1987
Li 2008
Mcintyre 2005
Mcintyre 2009
Muller-Oerlinghausen 2000
Niufan 2008
Ortega-Soto 1993
Pande 2000
Perlis 2006
Pope 1991
Potkin 2005
Sachs 2002
Sachs 2004
Sachs 2006
Segal 1998
Shafti 2010
Small 1991
Small 1995
Smulevich 2005


Tohen 1999
Tohen 2000
Tohen 2002a
Tohen 2002b
Tohen 2003
Tohen 2008a
Tohen 2008b
Vasudev 2000
Vieta 2005
Vieta 2008
Vieta 2010a
Vieta 2010b
Weisler 2004
Weisler 2005
Yatham 2003
Yatham 2007
Young 2009
Zajecka 2002

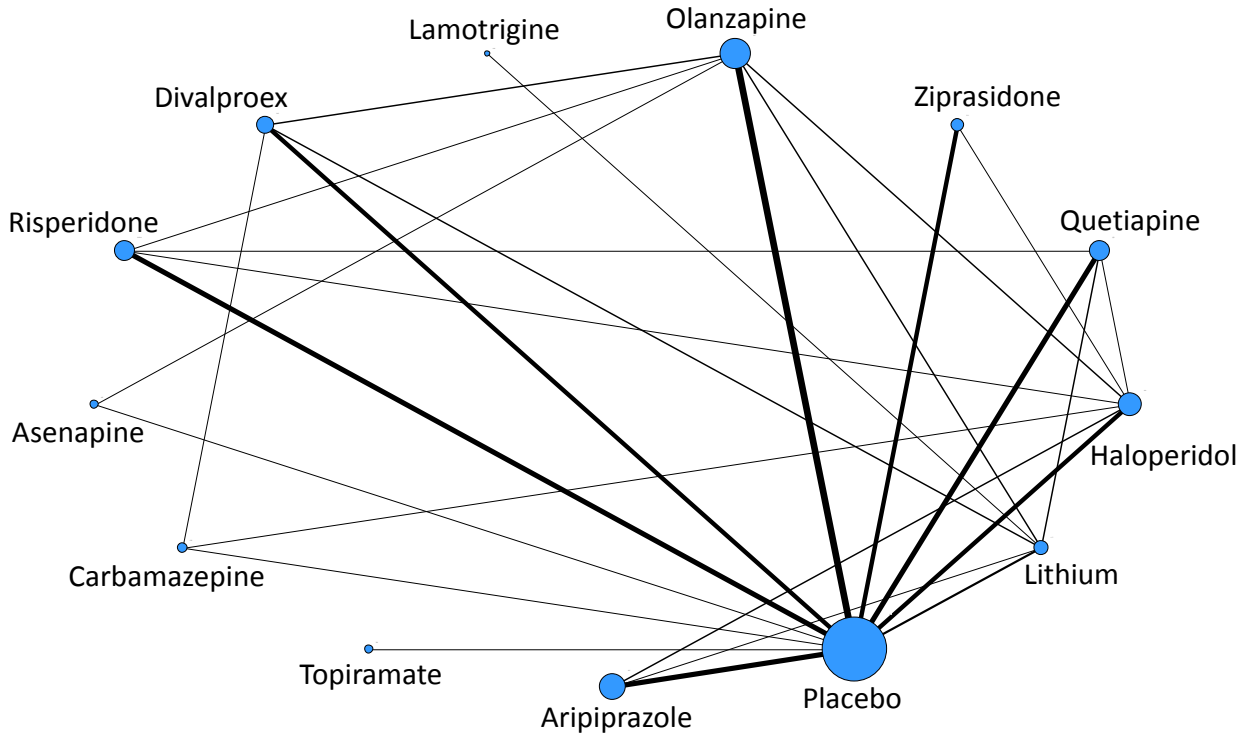
Appendix 5

Networks for acceptability and

efficacy as binary outcome (response rate)



Network of eligible comparisons in the multiple-treatments meta-analysis for acceptability (65 studies)



Network of eligible comparisons in the multiple-treatments meta-analysis for responders (42 studies)

Appendix 6

Values of I^2 and corresponding confidence intervals

EFFICACY - Continuous response		
Comparison	**I^{2} ****	**95% CI**
Aripiprazole vs Placebo	27.77%	0.00 – 70.18%
Aripiprazole vs Haloperidol	0.00%	NA
Placebo vs Quetiapine	35.98%	0.00 – 74.43%
Lithium vs Quetiapine	56.19%	NA
Placebo vs Ziprasidone	76.56%	42.93 – 90.37%
Lithium vs Olanzapine	89.23%	70.70 – 96.04%
Placebo vs Olanzapine	39.74%	0.00 – 72.26%
Olanzapine vs Divalproex	0.00%	0.00 – 81.58%
Haloperidol vs Olanzapine	0.00%	NA
Placebo vs Risperidone	68.95%	35.11 – 85.15%
Placebo vs Divalproex	0.00%	0.00 – 71.93%
Haloperidol vs Carbamazepine	0.00%	0.00 – 0.00%
Lithium vs Lamotrigine	0.00%	0.00 – 59.95%
Placebo vs Topiramate	0.00%	0.00 – 31.94%
Lithium vs Carbamazepine	0.00%	NA
Placebo vs Lithium	29.46%	0.00 – 71.15%
Placebo vs Haloperidol	58.58%	0.00 – 83.21%
Haloperidol vs Risperidone	0.00%	0.00 – 87.97%
Placebo vs Asenapine	0.00%	NA
Olanzapine vs Asenapine	0.00%	NA
Placebo vs Lamotrigine	0.00%	NA
Lithium vs Topiramate	0.00%	NA

ACCEPTABILITY - Binary droupout		
Comparison	**I^{2} ****	**95% CI**
Aripiprazole vs Placebo	62.60%	9.11 – 84.61%
Aripiprazole vs Haloperidol	84.07%	NA
Placebo vs Quetiapine	63.07%	10.43 – 84.77%
Lithium vs Quetiapine	19.97%	NA
Placebo vs Ziprasidone	67.63%	16.25 – 87.49%
Lithium vs Olanzapine	1.03%	0.00 – 89.71%
Placebo vs Olanzapine	60.54%	18.06 – 80.99%
Olanzapine vs Divalproex	0.00%	NA
Haloperidol vs Olanzapine	62.59%	NA
Placebo vs Risperidone	43.76%	0.00 – 76.34%
Placebo vs Divalproex	0.00%	0.00 – 59.12%
Haloperidol vs Carbamazepine	67.47%	0.00 – 90.59%
Lithium vs Lamotrigine	81.99%	44.42 – 94.17%
Placebo vs Topiramate	5.15%	0.00 – 80.27%
Lithium vs Haloperidol	54.22%	NA
Lithium vs Carbamazepine	71.24%	NA
Placebo vs Lithium	60.46%	9.36 – 82.75%
Placebo vs Haloperidol	49.54%	0.00 – 79.96%
Haloperidol vs Risperidone	24.07%	0.00- 92.10%
Placebo vs Asenapine	0.00%	NA
Olanzapine vs Asenapine	0.00%	NA
Placebo vs Lamotrigine	0.00%	NA
Lithium vs Topiramate	38.08%	NA

EFFICACY - Binary response		
Comparison	**I^{2} ****	**95% CI**
Aripiprazole vs Placebo	39.02%	0.00 – 75.79%
Aripiprazole vs Haloperidol	49.55%	NA
Placebo vs Quetiapine	11.45%	0.00 – 77.53%
Lithium vs Quetiapine	68.08%	NA
Placebo vs Ziprasidone	50.08%	0.00 – 81.69%
Placebo vs Olanzapine	43.62%	0.00 – 75.05%
Olanzapine vs Divalproex	56.59%	NA
Haloperidol vs Olanzapine	4.41%	NA
Placebo vs Risperidone	74.05%	40.82 – 88.62%
Lithium vs Divalproex	58.28%	NA
Placebo vs Divalproex	42.13%	0.00 – 78.70%
Lithium vs Olanzapine	63.16%	NA

Legend. We have excluded subgroups of head-to-head comparisons with undefined I^2, that is $I^2 = NA$. ** The variation in OR attributable to heterogeneity; CI Confidence Interval.
Note: between group heterogeneity not calculated; only valid with inverse variance method

Appendix 7

Multiple-treatments meta-analysis
(combination of direct and indirect comparisons)

Code names for NODES

1 Aripiprazole
2 Placebo
3 Lithium
4 Haloperidol
5 Quetiapine
6 Ziprasidone
7 Olanzapine
8 Lamotrigine
9 Divalproex
10 Risperidone+Paliperidone
11 Asenapine
12 Carbamazepine
13 Topiramate
14 Gabapentin

ANALYSIS of EFFICACY as CONTINUOUS OUTCOME (Standardized Mean Difference – SMD)

NODE	2.5%	MEDIAN	97.5%
SMD[1,2]	-0.5082	-0.3711	-0.2329
SMD[1,3]	-0.1724	0.003057	0.1824
SMD[1,4]	0.0235	0.1876	0.356
SMD[1,5]	-0.1959	-0.002	0.1915
SMD[1,6]	-0.3875	-0.1755	0.04159
SMD[1,7]	-0.1102	0.06387	0.2348
SMD[1,8]	-0.5841	-0.2934	-0.001902
SMD[1,9]	-0.3823	-0.1673	0.04741
SMD[1,10]	-0.04877	0.1324	0.3142
SMD[1,11]	-0.3377	-0.07191	0.1959
SMD[1,12]	-0.2942	-0.01183	0.2577
SMD[1,13]	-0.6601	-0.4467	-0.2322
SMD[1,14]	-1.212	-0.6922	-0.1748
SMD[2,3]	0.247	0.3738	0.503
SMD[2,4]	0.4319	0.5591	0.6862
SMD[2,5]	0.2281	0.3688	0.5133
SMD[2,6]	0.03014	0.1954	0.3664
SMD[2,7]	0.3235	0.4349	0.5433
SMD[2,8]	-0.1824	0.0774	0.3381
SMD[2,9]	0.03554	0.204	0.3698
SMD[2,10]	0.3807	0.5033	0.6272
SMD[2,11]	0.06895	0.3	0.5315
SMD[2,12]	0.1083	0.3593	0.599

NODE	LOW	MEDIAN	HIGH
SMD[2,13]	-0.2418	-0.0754	0.09268
SMD[2,14]	-0.823	-0.3229	0.1788
SMD[3,4]	0.01392	0.1854	0.3554
SMD[3,5]	-0.1788	-0.004925	0.169
SMD[3,6]	-0.386	-0.178	0.03253
SMD[3,7]	-0.09744	0.06094	0.2153
SMD[3,8]	-0.5558	-0.2968	-0.03764
SMD[3,9]	-0.3732	-0.1701	0.02979
SMD[3,10]	-0.04201	0.1291	0.3
SMD[3,11]	-0.3359	-0.07399	0.1856
SMD[3,12]	-0.2847	-0.01471	0.2434
SMD[3,13]	-0.6425	-0.4491	-0.2577
SMD[3,14]	-1.213	-0.696	-0.1824
SMD[4,5]	-0.3701	-0.1904	-0.009481
SMD[4,6]	-0.5598	-0.3636	-0.1624
SMD[4,7]	-0.278	-0.1241	0.02695
SMD[4,8]	-0.7672	-0.4822	-0.1948
SMD[4,9]	-0.5586	-0.3555	-0.1521
SMD[4,10]	-0.217	-0.05596	0.106
SMD[4,11]	-0.518	-0.2596	-3.552E-4
SMD[4,12]	-0.4648	-0.2003	0.05377
SMD[4,13]	-0.8431	-0.6342	-0.4262
SMD[4,14]	-1.396	-0.8819	-0.3646
SMD[5,6]	-0.3918	-0.1732	0.04701
SMD[5,7]	-0.113	0.06636	0.2392
SMD[5,8]	-0.5802	-0.2915	-9.06E-4
SMD[5,9]	-0.3846	-0.1651	0.05077
SMD[5,10]	-0.04295	0.1342	0.3105
SMD[5,11]	-0.3406	-0.06855	0.1991
SMD[5,12]	-0.2964	-0.009827	0.2647
SMD[5,13]	-0.6616	-0.4442	-0.2294
SMD[5,14]	-1.212	-0.6909	-0.17
SMD[6,7]	0.03479	0.2394	0.4346
SMD[6,8]	-0.4275	-0.1181	0.1885
SMD[6,9]	-0.2315	0.008507	0.2402
SMD[6,10]	0.09958	0.3081	0.5118
SMD[6,11]	-0.1817	0.1049	0.3878
SMD[6,12]	-0.139	0.1636	0.4493
SMD[6,13]	-0.5105	-0.2709	-0.03524
SMD[6,14]	-1.048	-0.5181	0.008375
SMD[7,8]	-0.6362	-0.3574	-0.07597
SMD[7,9]	-0.4016	-0.2315	-0.05893
SMD[7,10]	-0.08404	0.06852	0.2228
SMD[7,11]	-0.3604	-0.1353	0.09616

NODE	LOW	MEDIAN	HIGH
SMD[7,12]	-0.3429	-0.0762	0.1831
SMD[7,13]	-0.7048	-0.5106	-0.31
SMD[7,14]	-1.269	-0.7573	-0.2418
SMD[8,9]	-0.1803	0.127	0.4285
SMD[8,10]	0.1425	0.4257	0.7091
SMD[8,11]	-0.1244	0.2223	0.5675
SMD[8,12]	-0.07889	0.2817	0.6282
SMD[8,13]	-0.4573	-0.1523	0.1483
SMD[8,14]	-0.963	-0.4005	0.1572
SMD[9,10]	0.09626	0.2997	0.5049
SMD[9,11]	-0.1779	0.09596	0.3718
SMD[9,12]	-0.132	0.1551	0.4357
SMD[9,13]	-0.5153	-0.2791	-0.0425
SMD[9,14]	-1.05	-0.526	0.005634
SMD[10,11]	-0.4614	-0.2028	0.05409
SMD[10,12]	-0.4204	-0.1446	0.1214
SMD[10,13]	-0.7844	-0.5789	-0.3721
SMD[10,14]	-1.338	-0.8264	-0.3079
SMD[11,12]	-0.283	0.05971	0.3869
SMD[11,13]	-0.6598	-0.3753	-0.09134
SMD[11,14]	-1.172	-0.622	-0.06794
SMD[12,13]	-0.7235	-0.4343	-0.1356
SMD[12,14]	-1.235	-0.6804	-0.1195
SMD[13,14]	-0.775	-0.2469	0.2778

ANALYSIS of ACCEPTABILITY AS BINARY OUTCOME (Odds Ratio – OR)

NODE	2.5%	MEDIAN	97.5%
OR[1,2]	0.5464	0.7583	1.055
OR[1,3]	0.4885	0.7531	1.158
OR[1,4]	0.5963	0.8899	1.33
OR[1,5]	0.7393	1.184	1.907
OR[1,6]	0.5074	0.8331	1.387
OR[1,7]	0.8607	1.304	1.977
OR[1,8]	0.3208	0.6355	1.255
OR[1,9]	0.638	1.037	1.687
OR[1,10]	0.7994	1.251	1.969
OR[1,11]	0.4034	0.7669	1.46
OR[1,12]	0.5003	0.9653	1.858
OR[1,13]	0.3027	0.508	0.858
OR[1,14]	0.1412	0.429	1.293
OR[2,1]	0.9481	1.319	1.83

NODE	LOW	MEDIAN	HIGH
OR[2,3]	0.7248	0.9928	1.355
OR[2,4]	0.8607	1.174	1.596
OR[2,5]	1.105	1.562	2.219
OR[2,6]	0.7484	1.098	1.629
OR[2,7]	1.316	1.72	2.251
OR[2,8]	0.4585	0.8367	1.537
OR[2,9]	0.9481	1.368	1.968
OR[2,10]	1.202	1.65	2.271
OR[2,11]	0.5818	1.01	1.767
OR[2,12]	0.7118	1.273	2.271
OR[2,13]	0.4448	0.6703	1.01
OR[2,14]	0.1957	0.5661	1.628
OR[3,1]	0.8632	1.328	2.047
OR[3,2]	0.738	1.007	1.38
OR[3,4]	0.7765	1.183	1.801
OR[3,5]	1.021	1.573	2.449
OR[3,6]	0.679	1.106	1.835
OR[3,7]	1.167	1.733	2.588
OR[3,8]	0.461	0.8435	1.552
OR[3,9]	0.8668	1.379	2.183
OR[3,10]	1.075	1.661	2.59
OR[3,11]	0.5422	1.017	1.923
OR[3,12]	0.6939	1.281	2.379
OR[3,13]	0.4235	0.6745	1.078
OR[3,14]	0.1893	0.569	1.721
OR[4,1]	0.752	1.124	1.677
OR[4,2]	0.6267	0.852	1.162
OR[4,3]	0.5552	0.8454	1.288
OR[4,5]	0.8573	1.332	2.074
OR[4,6]	0.5921	0.9354	1.497
OR[4,7]	1.01	1.467	2.129
OR[4,8]	0.3634	0.7128	1.398
OR[4,9]	0.7289	1.166	1.864
OR[4,10]	0.9361	1.406	2.121
OR[4,11]	0.4626	0.8602	1.612
OR[4,12]	0.5786	1.085	2.027
OR[4,13]	0.3429	0.5712	0.9482
OR[4,14]	0.1602	0.4829	1.449
OR[5,1]	0.5244	0.8443	1.353
OR[5,2]	0.4506	0.6401	0.9053
OR[5,3]	0.4084	0.6356	0.9792
OR[5,4]	0.4822	0.7506	1.167
OR[5,6]	0.4212	0.7032	1.184
OR[5,7]	0.7107	1.101	1.699

NODE	LOW	MEDIAN	HIGH
OR[5,8]	0.2689	0.5352	1.066
OR[5,9]	0.5274	0.8757	1.441
OR[5,10]	0.6729	1.057	1.65
OR[5,11]	0.3363	0.6468	1.243
OR[5,12]	0.4174	0.8139	1.579
OR[5,13]	0.2507	0.429	0.7259
OR[5,14]	0.1187	0.3621	1.097
OR[6,1]	0.7212	1.2	1.971
OR[6,2]	0.614	0.9107	1.336
OR[6,3]	0.545	0.9038	1.473
OR[6,4]	0.6681	1.069	1.689
OR[6,5]	0.8445	1.422	2.374
OR[6,7]	0.9857	1.566	2.459
OR[6,8]	0.3695	0.7621	1.561
OR[6,9]	0.7277	1.245	2.098
OR[6,10]	0.9118	1.501	2.463
OR[6,11]	0.4663	0.9202	1.792
OR[6,12]	0.5761	1.157	2.293
OR[6,13]	0.345	0.6103	1.063
OR[6,14]	0.1661	0.515	1.571
OR[7,1]	0.5058	0.767	1.162
OR[7,2]	0.4443	0.5815	0.7602
OR[7,3]	0.3864	0.5769	0.8567
OR[7,4]	0.4697	0.6819	0.9904
OR[7,5]	0.5886	0.9083	1.407
OR[7,6]	0.4067	0.6387	1.015
OR[7,8]	0.2525	0.4861	0.9449
OR[7,9]	0.5291	0.7946	1.196
OR[7,10]	0.6508	0.9591	1.421
OR[7,11]	0.3384	0.5869	1.022
OR[7,12]	0.3942	0.7393	1.384
OR[7,13]	0.2401	0.3898	0.6342
OR[7,14]	0.1106	0.3293	0.9788
OR[8,1]	0.797	1.574	3.117
OR[8,2]	0.6506	1.195	2.181
OR[8,3]	0.6442	1.186	2.169
OR[8,4]	0.7155	1.403	2.752
OR[8,5]	0.9385	1.869	3.719
OR[8,6]	0.6408	1.312	2.706
OR[8,7]	1.059	2.057	3.96
OR[8,9]	0.809	1.633	3.267
OR[8,10]	0.9985	1.971	3.898
OR[8,11]	0.5292	1.207	2.731
OR[8,12]	0.6621	1.521	3.447

NODE	LOW	MEDIAN	HIGH
OR[8,13]	0.3921	0.8	1.634
OR[8,14]	0.1992	0.6739	2.279
OR[9,1]	0.5929	0.9643	1.567
OR[9,2]	0.5082	0.7312	1.055
OR[9,3]	0.4581	0.7253	1.154
OR[9,4]	0.5365	0.8578	1.372
OR[9,5]	0.6941	1.142	1.896
OR[9,6]	0.4765	0.803	1.374
OR[9,7]	0.8363	1.258	1.89
OR[9,8]	0.3061	0.6124	1.236
OR[9,10]	0.7523	1.207	1.96
OR[9,11]	0.3865	0.7384	1.42
OR[9,12]	0.4791	0.9308	1.814
OR[9,13]	0.2843	0.49	0.8465
OR[9,14]	0.1347	0.4139	1.27
OR[10,1]	0.5079	0.7993	1.251
OR[10,2]	0.4403	0.6061	0.8317
OR[10,3]	0.3861	0.6019	0.93
OR[10,4]	0.4716	0.7114	1.068
OR[10,5]	0.6059	0.9458	1.486
OR[10,6]	0.4061	0.6664	1.097
OR[10,7]	0.704	1.043	1.537
OR[10,8]	0.2565	0.5074	1.002
OR[10,9]	0.5102	0.8286	1.329
OR[10,11]	0.3257	0.612	1.152
OR[10,12]	0.3979	0.7718	1.486
OR[10,13]	0.2416	0.4062	0.678
OR[10,14]	0.1135	0.3435	1.024
OR[11,1]	0.6849	1.304	2.479
OR[11,2]	0.5659	0.9897	1.719
OR[11,3]	0.5201	0.9837	1.844
OR[11,4]	0.6204	1.163	2.162
OR[11,5]	0.8046	1.546	2.974
OR[11,6]	0.5581	1.087	2.144
OR[11,7]	0.9789	1.704	2.955
OR[11,8]	0.3661	0.8283	1.89
OR[11,9]	0.7044	1.354	2.588
OR[11,10]	0.868	1.634	3.07
OR[11,12]	0.5655	1.262	2.806
OR[11,13]	0.3338	0.663	1.322
OR[11,14]	0.1697	0.5596	1.853
OR[12,1]	0.5381	1.036	1.999
OR[12,2]	0.4403	0.7858	1.405
OR[12,3]	0.4203	0.7809	1.441

NODE	LOW	MEDIAN	HIGH
OR[12,4]	0.4933	0.9219	1.728
OR[12,5]	0.6332	1.229	2.396
OR[12,6]	0.4362	0.8641	1.736
OR[12,7]	0.7226	1.353	2.537
OR[12,8]	0.2902	0.6575	1.51
OR[12,9]	0.5514	1.074	2.088
OR[12,10]	0.6734	1.296	2.513
OR[12,11]	0.3564	0.7926	1.768
OR[12,13]	0.2617	0.5267	1.063
OR[12,14]	0.1328	0.445	1.486
OR[13,1]	1.165	1.969	3.304
OR[13,2]	0.9899	1.492	2.248
OR[13,3]	0.9277	1.483	2.361
OR[13,4]	1.055	1.751	2.916
OR[13,5]	1.378	2.331	3.989
OR[13,6]	0.941	1.639	2.898
OR[13,7]	1.577	2.565	4.164
OR[13,8]	0.612	1.25	2.551
OR[13,9]	1.181	2.041	3.517
OR[13,10]	1.475	2.462	4.14
OR[13,11]	0.7563	1.508	2.996
OR[13,12]	0.9409	1.899	3.821
OR[13,14]	0.2716	0.8443	2.613
OR[14,1]	0.7734	2.331	7.081
OR[14,2]	0.6144	1.766	5.109
OR[14,3]	0.581	1.758	5.284
OR[14,4]	0.69	2.071	6.242
OR[14,5]	0.9121	2.762	8.424
OR[14,6]	0.6365	1.942	6.022
OR[14,7]	1.022	3.037	9.043
OR[14,8]	0.4387	1.484	5.02
OR[14,9]	0.7872	2.416	7.423
OR[14,10]	0.9762	2.911	8.811
OR[14,11]	0.5396	1.787	5.891
OR[14,12]	0.6731	2.247	7.529
OR[14,13]	0.3827	1.184	3.682

ANALYSIS of EFFICACY AS BINARY OUTCOME (Odds Ratio – OR)

NODE	LOW	MEDIAN	HIGH
OR[1,2]	1.518	2.004	2.66
OR[1,3]	0.7177	1.103	1.686

NODE	LOW	MEDIAN	HIGH
OR[1,4]	0.6276	0.8893	1.252
OR[1,5]	0.6729	0.9974	1.476
OR[1,6]	0.9401	1.455	2.238
OR[1,7]	0.6447	0.9217	1.322
OR[1,8]	0.2767	1.457	7.826
OR[1,9]	0.6553	1.009	1.543
OR[1,10]	0.6348	0.935	1.38
OR[1,11]	0.583	1.182	2.393
OR[1,12]	0.4175	0.8094	1.65
OR[1,13]	1.092	2.601	6.245
OR[2,1]	0.376	0.499	0.6589
OR[2,3]	0.3817	0.55	0.7868
OR[2,4]	0.3324	0.4437	0.5859
OR[2,5]	0.3701	0.4975	0.6655
OR[2,6]	0.5143	0.7261	1.012
OR[2,7]	0.3619	0.4596	0.5846
OR[2,8]	0.1392	0.7275	3.852
OR[2,9]	0.3588	0.5037	0.6973
OR[2,10]	0.3527	0.467	0.6158
OR[2,11]	0.3065	0.5891	1.13
OR[2,12]	0.2201	0.4049	0.7731
OR[2,13]	0.5669	1.297	2.98
OR[3,1]	0.593	0.9066	1.393
OR[3,2]	1.271	1.818	2.62
OR[3,4]	0.5217	0.8056	1.252
OR[3,5]	0.6038	0.9042	1.362
OR[3,6]	0.8068	1.319	2.152
OR[3,7]	0.5609	0.8354	1.254
OR[3,8]	0.2655	1.322	6.715
OR[3,9]	0.5802	0.9151	1.441
OR[3,10]	0.5447	0.848	1.33
OR[3,11]	0.5143	1.071	2.236
OR[3,12]	0.3646	0.737	1.553
OR[3,13]	0.9637	2.357	5.831
OR[4,1]	0.7989	1.124	1.593
OR[4,2]	1.707	2.254	3.008
OR[4,3]	0.7989	1.241	1.917
OR[4,5]	0.7664	1.121	1.651
OR[4,6]	1.083	1.636	2.461
OR[4,7]	0.7438	1.037	1.459
OR[4,8]	0.3099	1.64	8.837
OR[4,9]	0.7431	1.135	1.727
OR[4,10]	0.7298	1.053	1.523
OR[4,11]	0.6585	1.328	2.682

NODE	LOW	MEDIAN	HIGH
OR[4,12]	0.4732	0.9123	1.848
OR[4,13]	1.23	2.926	7.082
OR[5,1]	0.6777	1.003	1.486
OR[5,2]	1.503	2.01	2.702
OR[5,3]	0.7343	1.106	1.656
OR[5,4]	0.6057	0.8918	1.305
OR[5,6]	0.9321	1.46	2.268
OR[5,7]	0.6434	0.9231	1.336
OR[5,8]	0.2796	1.463	7.861
OR[5,9]	0.654	1.012	1.556
OR[5,10]	0.6447	0.9378	1.368
OR[5,11]	0.5834	1.185	2.415
OR[5,12]	0.4144	0.8144	1.665
OR[5,13]	1.087	2.608	6.299
OR[6,1]	0.4468	0.6874	1.064
OR[6,2]	0.9882	1.377	1.944
OR[6,3]	0.4646	0.7583	1.24
OR[6,4]	0.4063	0.6112	0.9238
OR[6,5]	0.4409	0.6849	1.073
OR[6,7]	0.4232	0.6333	0.9622
OR[6,8]	0.1873	1	5.413
OR[6,9]	0.4332	0.6938	1.11
OR[6,10]	0.4184	0.6425	0.9985
OR[6,11]	0.391	0.8109	1.694
OR[6,12]	0.2797	0.558	1.167
OR[6,13]	0.7349	1.79	4.417
OR[7,1]	0.7564	1.085	1.551
OR[7,2]	1.711	2.176	2.763
OR[7,3]	0.7974	1.197	1.783
OR[7,4]	0.6853	0.9645	1.345
OR[7,5]	0.7485	1.083	1.554
OR[7,6]	1.039	1.579	2.363
OR[7,8]	0.3012	1.584	8.432
OR[7,9]	0.7603	1.095	1.559
OR[7,10]	0.7203	1.014	1.425
OR[7,11]	0.6704	1.282	2.432
OR[7,12]	0.4585	0.8816	1.756
OR[7,13]	1.197	2.818	6.693
OR[8,1]	0.1278	0.6865	3.614
OR[8,2]	0.2596	1.375	7.184
OR[8,3]	0.149	0.7562	3.767
OR[8,4]	0.1132	0.6099	3.227
OR[8,5]	0.1272	0.6833	3.577
OR[8,6]	0.1848	0.9997	5.339

NODE	LOW	MEDIAN	HIGH
OR[8,7]	0.1186	0.6314	3.32
OR[8,9]	0.1285	0.6901	3.675
OR[8,10]	0.1188	0.641	3.413
OR[8,11]	0.1382	0.8095	4.751
OR[8,12]	0.09614	0.558	3.241
OR[8,13]	0.2778	1.776	11.13
OR[9,1]	0.6481	0.991	1.526
OR[9,2]	1.434	1.985	2.787
OR[9,3]	0.6938	1.093	1.724
OR[9,4]	0.5789	0.8812	1.346
OR[9,5]	0.6428	0.988	1.529
OR[9,6]	0.9006	1.441	2.308
OR[9,7]	0.6416	0.9135	1.315
OR[9,8]	0.2722	1.449	7.782
OR[9,10]	0.6103	0.9275	1.424
OR[9,11]	0.572	1.172	2.41
OR[9,12]	0.4121	0.8053	1.634
OR[9,13]	1.068	2.578	6.312
OR[10,1]	0.7246	1.07	1.575
OR[10,2]	1.624	2.141	2.835
OR[10,3]	0.7519	1.179	1.836
OR[10,4]	0.6564	0.9501	1.37
OR[10,5]	0.7309	1.066	1.551
OR[10,6]	1.002	1.556	2.39
OR[10,7]	0.7015	0.9858	1.388
OR[10,8]	0.2932	1.56	8.416
OR[10,9]	0.7025	1.078	1.639
OR[10,11]	0.6264	1.264	2.544
OR[10,12]	0.4448	0.8683	1.755
OR[10,13]	1.159	2.784	6.69
OR[11,1]	0.4179	0.8462	1.715
OR[11,2]	0.8849	1.697	3.263
OR[11,3]	0.4472	0.934	1.945
OR[11,4]	0.3729	0.7532	1.519
OR[11,5]	0.4141	0.8436	1.714
OR[11,6]	0.5902	1.233	2.558
OR[11,7]	0.4113	0.7803	1.492
OR[11,8]	0.2105	1.235	7.236
OR[11,9]	0.4149	0.853	1.748
OR[11,10]	0.3932	0.791	1.596
OR[11,12]	0.2856	0.6877	1.738
OR[11,13]	0.7734	2.201	6.36
OR[12,1]	0.6061	1.235	2.396
OR[12,2]	1.294	2.47	4.544

NODE	LOW	MEDIAN	HIGH
OR[12,3]	0.644	1.357	2.743
OR[12,4]	0.5411	1.096	2.113
OR[12,5]	0.6006	1.228	2.414
OR[12,6]	0.8567	1.792	3.575
OR[12,7]	0.5697	1.134	2.181
OR[12,8]	0.3085	1.792	10.4
OR[12,9]	0.6119	1.242	2.427
OR[12,10]	0.57	1.152	2.248
OR[12,11]	0.5753	1.454	3.501
OR[12,13]	1.117	3.198	8.896
OR[13,1]	0.1601	0.3845	0.9155
OR[13,2]	0.3356	0.7712	1.764
OR[13,3]	0.1715	0.4242	1.038
OR[13,4]	0.1412	0.3418	0.8131
OR[13,5]	0.1588	0.3834	0.9196
OR[13,6]	0.2264	0.5585	1.361
OR[13,7]	0.1494	0.3549	0.8356
OR[13,8]	0.08992	0.5631	3.6
OR[13,9]	0.1584	0.388	0.9365
OR[13,10]	0.1495	0.3592	0.8631
OR[13,11]	0.1573	0.4543	1.293
OR[13,12]	0.1124	0.3127	0.8956

Appendix 8

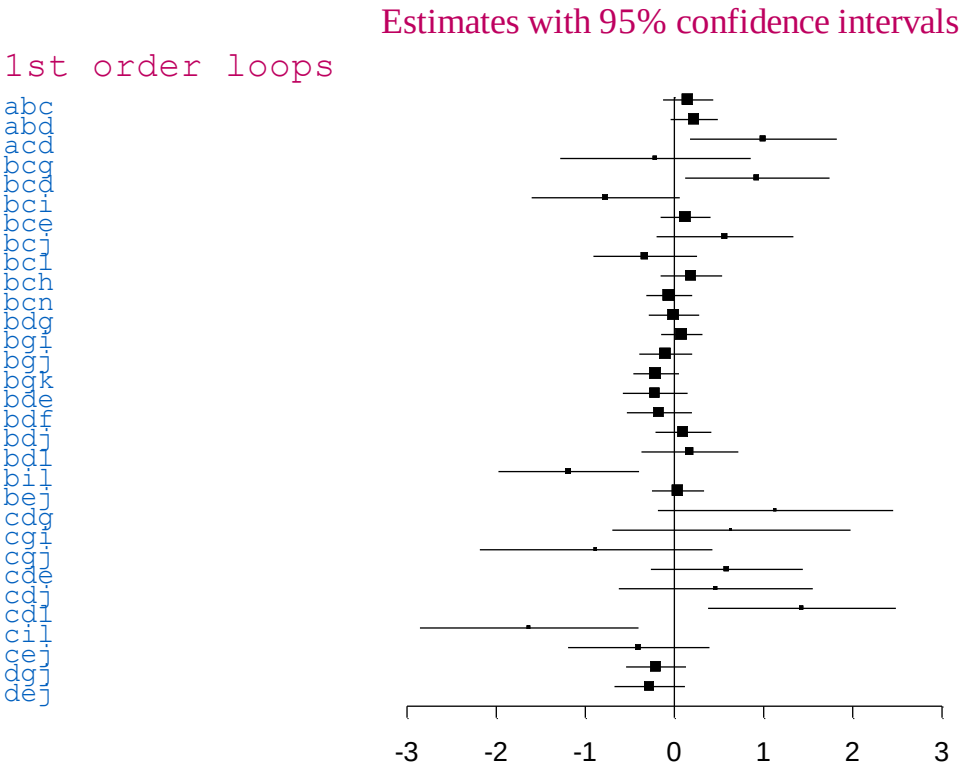
Statistical inconsistency (with graphs)

The great majority of loops was consistent, since their 95% CIs seem to include 0 (that is the direct estimate of the summary effect does not differentiate from the indirect estimate) according to the forest plots. Analysis of inconsistency indicated that there was inconsistency in five out of a total of 31 loops for efficacy measured as a continuous outcome (aripiprazole–lithium–haloperidol; placebo–lithium–haloperidol; lithium–divalproex–carbamazepine; lithium–haloperidol–carbamazepine; placebo–divalproex–carbamazepine), in three out of 33 loops for acceptability (aripiprazole-placebo-haloperidol; olanzapine-placebo-risperidone; quetiapine-placebo-haloperidol), but none for binary efficacy (18 loops). Data extraction and data entry were found to be correct. We could not identify any important variables that differed across comparisons in those loops, but the number of included studies was very small in the inconsistent loops. We also fit the model for the continuous efficacy data assuming no consistency. The models (with and without consistency) were very similar in terms of balance between model fit and complexity fit (Deviance Information Criteria 265.1 and 264.1 respectively). Some different parameterizations of the three arm trials did not considerably changed the similarity of the two models.

Code	Name
a	Aripiprazole
b	Placebo
c	Lithium
d	Haloperidol
e	Quetiapine
f	Ziprasidone
g	Olanzapine
h	Lamotrigine
i	Divalproex
j	Risperidone (and Paliperidone)
k	Asenapine
l	Carbamazepine
m	Topiramate
n	Gabapentin

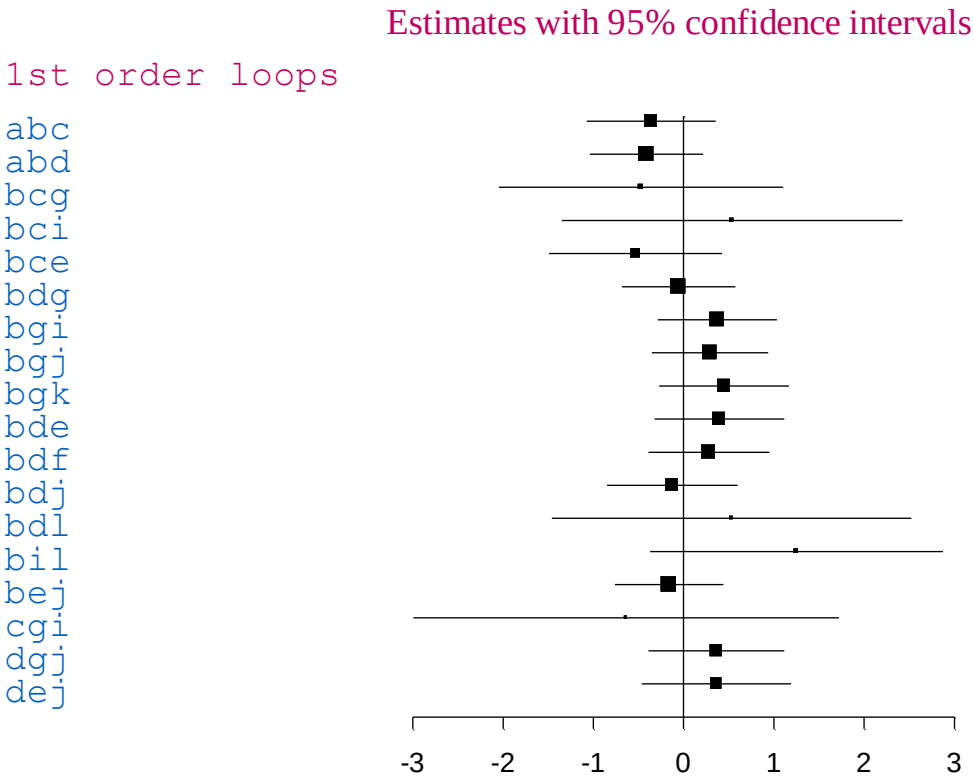
Continuous efficacy data

Evaluation of coherence within first order closed loops

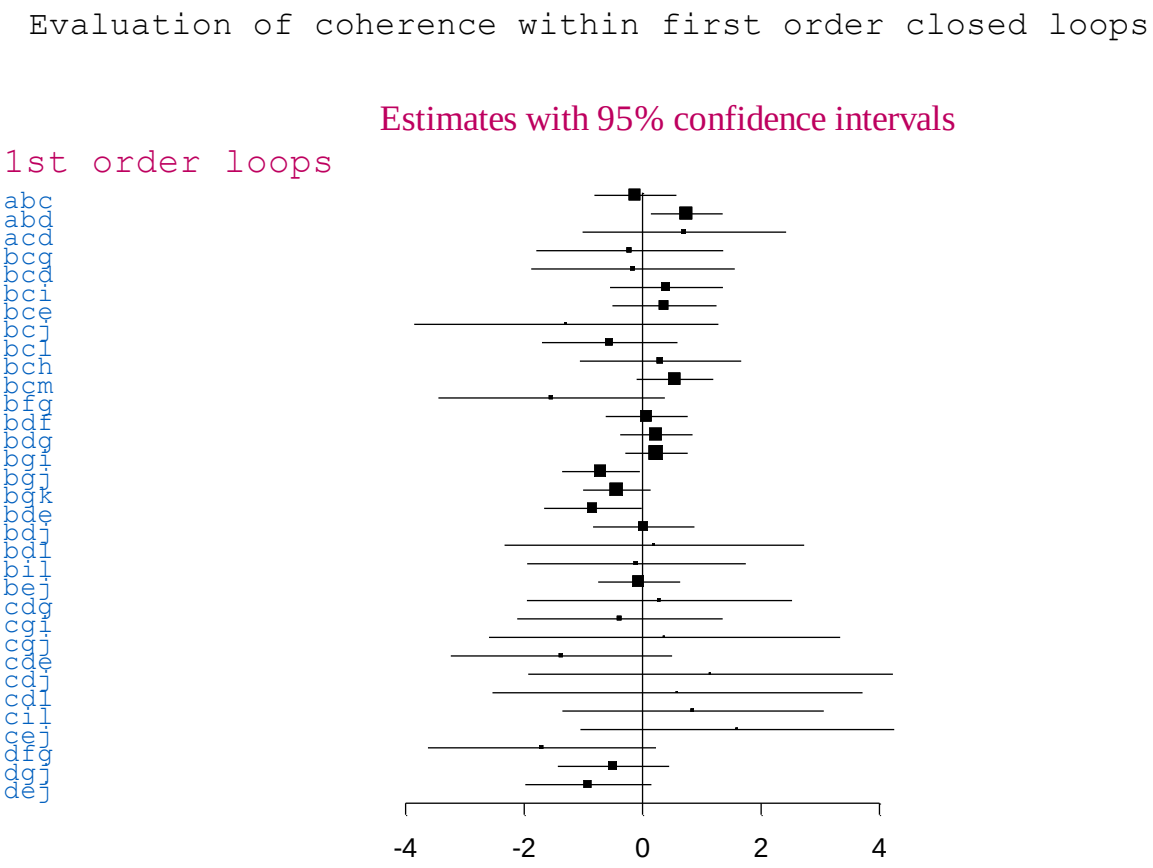


Binary efficacy data (response rate)

Evaluation of coherence within first order closed loops



Binary acceptability data (dropout rate)



Appendix 9

Sensitivity analysis
Combination/augmentation treatment strategies

Meta-analysis of Continuous Response Outcome Excluding Studies with Combination Strategy

Code	Name	Code	Name
1	Aripiprazole	8	Lamotrigine
2	Placebo	9	Divalproex
3	Lithium	10	Risperidone
4	Haloperidol	11	Asenapine
5	Quetiapine	12	Carbamazepine
6	Ziprasidone	14	Topiramate
7	Olanzapine	16	Paliperidone

Study	SMD	[95% Conf.	Interval]	% Weight
1vs2				
2	-0.501	-0.744	-0.258	1.38
4	-0.340	-0.592	-0.088	1.37
5	-0.063	-0.306	0.181	1.38
54	-0.360	-0.582	-0.138	1.41
55	-0.248	-0.469	-0.027	1.41
Sub-total				
D+L pooled SMD	-0.302	-0.440	-0.164	6.94
1vs4				
3	-0.005	-0.219	0.209	1.42
55	0.109	-0.108	0.326	1.41
Sub-total				
D+L pooled SMD	0.051	-0.101	0.204	2.83
3vs5				
8	0.283	-0.034	0.601	1.28
56	-0.040	-0.314	0.234	1.34
Sub-total				
D+L pooled SMD	0.111	-0.205	0.427	2.62
2vs5				
9	0.379	0.153	0.604	1.40
56	0.672	0.388	0.956	1.32
57	0.251	-0.027	0.529	1.33
70	0.438	0.196	0.679	1.38
Sub-total				
D+L pooled SMD	0.429	0.272	0.587	5.44
2vs6				
10	0.375	0.077	0.673	1.31
11	0.502	0.203	0.802	1.30
58	0.401	0.143	0.660	1.36
Sub-total				
D+L pooled SMD	0.423	0.260	0.587	3.97
3vs7				
15	0.310	-0.467	1.086	0.68
41	0.393	0.058	0.728	1.25
48	-1.271	-1.956	-0.585	0.77
Sub-total				
D+L pooled SMD	-0.173	-1.206	0.861	2.71

```
2vs7
16                   |    0.425     0.085     0.765          1.25
17                   |    0.524     0.143     0.904          1.19
59                   |    0.239    -0.002     0.481          1.38
63                   |    0.663     0.416     0.909          1.38
64                   |    0.628     0.378     0.877          1.37
71                   |    0.478     0.197     0.758          1.33
 Sub-total           |
  D+L pooled SMD     |    0.493     0.354     0.633          7.89
--------------------+-------------------------------------------------
     7vs9
18                   |   -0.307    -0.557    -0.057          1.37
21                   |   -0.142    -0.508     0.225          1.21
59                   |   -0.141    -0.341     0.058          1.43
 Sub-total           |
  D+L pooled SMD     |   -0.196    -0.339    -0.052          4.01
--------------------+-------------------------------------------------
     4vs7
20                   |   -0.146    -0.332     0.040          1.45
71                   |   -0.165    -0.644     0.314          1.04
 Sub-total           |
  D+L pooled SMD     |   -0.149    -0.322     0.025          2.49
--------------------+-------------------------------------------------
     2vs10
23                   |    0.846     0.604     1.088          1.38
25                   |    0.609     0.353     0.865          1.36
62                   |    0.487     0.254     0.721          1.39
 Sub-total           |
  D+L pooled SMD     |    0.646     0.436     0.857          4.14
--------------------+-------------------------------------------------
     7vs10
26                   |   -0.039    -0.255     0.177          1.41
 Sub-total           |
  D+L pooled SMD     |   -0.039    -0.255     0.177          1.41
--------------------+-------------------------------------------------
     3vs9
27                   |   -1.008    -1.817    -0.199          0.65
 Sub-total           |
  D+L pooled SMD     |   -1.008    -1.817    -0.199          0.65
--------------------+-------------------------------------------------
     2vs9
28                   |    0.229     0.023     0.435          1.42
49                   |    0.128    -0.148     0.404          1.34
59                   |    0.096    -0.148     0.340          1.38
 Sub-total           |
  D+L pooled SMD     |    0.162     0.026     0.299          4.14
--------------------+-------------------------------------------------
     9vs12
30                   |   -0.851    -1.603    -0.099          0.70
 Sub-total           |
  D+L pooled SMD     |   -0.851    -1.603    -0.099          0.70
--------------------+-------------------------------------------------
     2vs12
33                   |    0.497     0.304     0.690          1.44
 Sub-total           |
  D+L pooled SMD     |    0.497     0.304     0.690          1.44
--------------------+-------------------------------------------------
     3vs8
34                   |   -0.112    -0.829     0.604          0.74
66                   |   -0.125    -0.516     0.266          1.17
67                   |   -0.295    -0.616     0.026          1.27
 Sub-total           |
  D+L pooled SMD     |   -0.214    -0.449     0.020          3.18
--------------------+-------------------------------------------------
```

2vs14				
35	0.050	-0.224	0.324	1.34
36	-0.129	-0.399	0.141	1.34
68	-0.128	-0.394	0.138	1.35
69	-0.017	-0.277	0.243	1.36
Sub-total				
D+L pooled SMD	-0.056	-0.190	0.077	5.39
2vs16				
42	0.410	0.151	0.668	1.36
70	0.612	0.367	0.856	1.38
Sub-total				
D+L pooled SMD	0.515	0.317	0.713	2.74
4vs12				
44	0.047	-0.933	1.027	0.51
46	0.000	-0.877	0.877	0.59
Sub-total				
D+L pooled SMD	0.021	-0.632	0.674	1.09
3vs12				
47	-0.360	-1.108	0.388	0.71
52	-0.097	-0.856	0.662	0.70
Sub-total				
D+L pooled SMD	-0.230	-0.763	0.302	1.40
1vs3				
54	-0.061	-0.284	0.162	1.40
Sub-total				
D+L pooled SMD	-0.061	-0.284	0.162	1.40
2vs3				
54	0.299	0.078	0.520	1.41
56	0.683	0.392	0.973	1.32
66	0.110	-0.273	0.494	1.18
67	0.330	0.012	0.648	1.28
68	0.445	0.180	0.710	1.35
69	0.454	0.190	0.718	1.35
Sub-total				
D+L pooled SMD	0.400	0.263	0.537	7.88
2vs4				
55	0.368	0.144	0.591	1.40
57	0.677	0.390	0.963	1.32
58	0.944	0.673	1.214	1.34
62	0.452	0.216	0.689	1.39
71	0.548	0.061	1.034	1.03
Sub-total				
D+L pooled SMD	0.593	0.375	0.812	6.49
4vs5				
57	-0.425	-0.706	-0.144	1.33
Sub-total				
D+L pooled SMD	-0.425	-0.706	-0.144	1.33
4vs6				
58	-0.508	-0.722	-0.294	1.41
Sub-total				
D+L pooled SMD	-0.508	-0.722	-0.294	1.41
3vs4				
61	1.110	0.334	1.887	0.68
Sub-total				
D+L pooled SMD	1.110	0.334	1.887	0.68

3vs10				
61	0.666	-0.072	1.404	0.72
Sub-total				
D+L pooled SMD	0.666	-0.072	1.404	0.72
4vs10				
61	-0.444	-1.170	0.282	0.73
62	0.041	-0.186	0.269	1.40
Sub-total				
D+L pooled SMD	-0.074	-0.479	0.331	2.13
2vs11				
63	0.494	0.250	0.737	1.38
64	0.342	0.091	0.592	1.37
Sub-total				
D+L pooled SMD	0.420	0.245	0.594	2.75
7vs11				
63	-0.164	-0.366	0.039	1.43
64	-0.286	-0.487	-0.085	1.43
Sub-total				
D+L pooled SMD	-0.225	-0.368	-0.083	2.86
2vs8				
66	-0.019	-0.312	0.275	1.31
67	0.015	-0.304	0.334	1.28
Sub-total				
D+L pooled SMD	-0.003	-0.219	0.213	2.59
3vs14				
68	-0.564	-0.833	-0.294	1.34
69	-0.471	-0.734	-0.208	1.35
Sub-total				
D+L pooled SMD	-0.516	-0.704	-0.328	2.70
5vs16				
70	0.167	-0.034	0.368	1.43
Sub-total				
D+L pooled SMD	0.167	-0.034	0.368	1.43
Overall				
D+L pooled SMD	0.139	0.054	0.224	100.00

Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
1vs2	6.85	4	0.144	41.6%	0.0103
1vs4	0.53	1	0.465	0.0%	0.0000
3vs5	2.28	1	0.131	56.2%	0.0294
2vs5	4.58	3	0.205	34.5%	0.0089
2vs6	0.40	2	0.820	0.0%	0.0000
3vs7	18.58	2	0.000	89.2%	0.7349
2vs7	7.37	5	0.195	32.1%	0.0097
7vs9	1.13	2	0.569	0.0%	0.0000
4vs7	0.01	1	0.942	0.0%	0.0000
2vs10	4.47	2	0.107	55.3%	0.0191
7vs10	0.00	0	.	.%	0.0000
3vs9	0.00	0	.	.%	0.0000
2vs9	0.74	2	0.690	0.0%	0.0000
9vs12	0.00	0	.	.%	0.0000
2vs12	0.00	0	.	.%	0.0000
3vs8	0.52	2	0.771	0.0%	0.0000
2vs14	1.22	3	0.748	0.0%	0.0000
13vs15	0.00	0	.	.%	0.0000
2vs16	1.24	1	0.265	19.4%	0.0040
4vs12	0.00	1	0.944	0.0%	0.0000
3vs12	0.23	1	0.628	0.0%	0.0000
1vs3	0.00	0	.	.%	0.0000
2vs3	7.09	5	0.214	29.5%	0.0086
2vs4	11.98	4	0.018	66.6%	0.0398
4vs5	0.00	0	.	.%	0.0000
4vs6	0.00	0	.	.%	0.0000
3vs4	0.00	0	.	.%	0.0000
3vs10	0.00	0	.	.%	0.0000
4vs10	1.56	1	0.211	36.0%	0.0424
2vs11	0.73	1	0.393	0.0%	0.0000
7vs11	0.71	1	0.400	0.0%	0.0000
2vs8	0.02	1	0.879	0.0%	0.0000
3vs14	0.23	1	0.630	0.0%	0.0000
5vs16	0.00	0	.	.%	0.0000
Overall	574.86	80	0.000	86.1%	0.1214

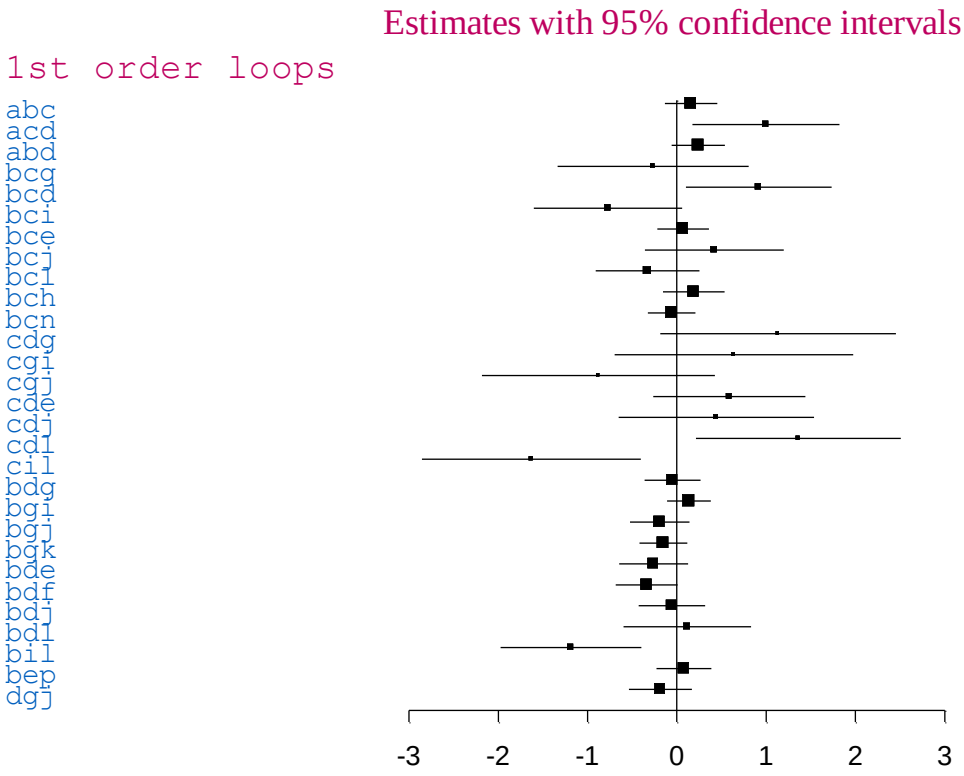
** I-squared: the variation in SMD attributable to heterogeneity. Note: between group heterogeneity not calculated; only valid with inverse variance method

```
Significance test(s) of SMD=0

1vs2                    z=  4.29     p = 0.000
1vs4                    z=  0.66     p = 0.508
3vs5                    z=  0.69     p = 0.491
2vs5                    z=  5.34     p = 0.000
2vs6                    z=  5.08     p = 0.000
3vs7                    z=  0.33     p = 0.743
2vs7                    z=  6.94     p = 0.000
7vs9                    z=  2.67     p = 0.008
4vs7                    z=  1.68     p = 0.094
2vs10                   z=  6.02     p = 0.000
7vs10                   z=  0.35     p = 0.726
3vs9                    z=  2.44     p = 0.015
2vs9                    z=  2.33     p = 0.020
9vs12                   z=  2.22     p = 0.027
2vs12                   z=  5.06     p = 0.000
3vs8                    z=  1.79     p = 0.073
2vs14                   z=  0.83     p = 0.408
13vs15                  z=  1.15     p = 0.249
2vs16                   z=  5.11     p = 0.000
4vs12                   z=  0.06     p = 0.950
3vs12                   z=  0.85     p = 0.397
1vs3                    z=  0.54     p = 0.590
2vs3                    z=  5.72     p = 0.000
2vs4                    z=  5.33     p = 0.000
4vs5                    z=  2.96     p = 0.003
4vs6                    z=  4.65     p = 0.000
3vs4                    z=  2.80     p = 0.005
3vs10                   z=  1.77     p = 0.077
4vs10                   z=  0.36     p = 0.720
2vs11                   z=  4.71     p = 0.000
7vs11                   z=  3.10     p = 0.002
2vs8                    z=  0.03     p = 0.977
3vs14                   z=  5.38     p = 0.000
5vs16                   z=  1.63     p = 0.104
Overall                 z=  3.21     p = 0.001
```

Coherence for Continuous Response Outcome Excluding Studies with Combination Strategy

Evaluation of coherence within first order closed loops



Code	Name	Code	Name
a	Aripiprazole	h	Lamotrigine
b	Placebo	i	Divalproex
c	Lithium	j	Risperidone
d	Haloperidol	k	Asenapine
e	Quetiapine	l	Carbamazepine
f	Ziprasidone	n	Topiramate
g	Olanzapine	p	Paliperidone

----- Evaluating the coherence of the network ------

Nr of treatments: 14
Nr of all possible first order loops (triangles): 1680
Nr of available first order loops: 29

1 : Evaluation of the loop abc
Direct comparisons in the loop:
ab bc ac
5 6 1

Meta-analysis for the ab arm
mean(se)= -0.302(0.07)
Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the ac arm
mean(se)= -0.061(0.114)
Indirect comparison for the ac arm
Mean(se)= 0.098(0.097)

Incoherence within the loop: Mean(se)= 0.16(0.15)

2 : Evaluation of the loop acd
Direct comparisons in the loop:
ac cd ad
1 1 2

Meta-analysis for the ac arm
mean(se)= -0.061(0.114)
Meta-analysis for the cd arm
mean(se)= 1.11(0.396)
Meta-analysis for the ad arm
mean(se)= 0.051(0.078)
Indirect comparison for the ad arm
Mean(se)= 1.049(0.412)

Incoherence within the loop: Mean(se)= 0.998(0.419)

3 : Evaluation of the loop abd
Direct comparisons in the loop:
ab bd ad
5 5 2

Meta-analysis for the ab arm
mean(se)= -0.302(0.07)
Meta-analysis for the bd arm
mean(se)= 0.593(0.11)
Meta-analysis for the ad arm
mean(se)= 0.051(0.078)
Indirect comparison for the ad arm
Mean(se)= 0.291(0.131)

Incoherence within the loop: Mean(se)= 0.24(0.152)

4 : Evaluation of the loop bcg
Direct comparisons in the loop:
bc cg bg
6 3 6

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the cg arm
mean(se)= -0.173(0.537)
Meta-analysis for the bg arm
mean(se)= 0.493(0.074)
Indirect comparison for the bg arm
Mean(se)= 0.227(0.541)

Incoherence within the loop: Mean(se)= -0.266(0.546)

5 : Evaluation of the loop bcd
Direct comparisons in the loop:
bc cd bd
6 1 5

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the cd arm
mean(se)= 1.11(0.396)
Meta-analysis for the bd arm
mean(se)= 0.593(0.11)
Indirect comparison for the bd arm

Mean(se)= 1.511(0.402)

Incoherence within the loop: Mean(se)= 0.917(0.417)

6 : Evaluation of the loop bci
Direct comparisons in the loop:
bc ci bi
6 1 3

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the ci arm
mean(se)= -1.008(0.413)
Meta-analysis for the bi arm
mean(se)= 0.162(0.07)
Indirect comparison for the bi arm
Mean(se)= -0.608(0.418)

Incoherence within the loop: Mean(se)= -0.77(0.424)

7 : Evaluation of the loop bce
Direct comparisons in the loop:
bc ce be
6 2 4

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the ce arm
mean(se)= 0.098(0.106)
Meta-analysis for the be arm
mean(se)= 0.429(0.077)
Indirect comparison for the be arm
Mean(se)= 0.498(0.125)

Incoherence within the loop: Mean(se)= 0.069(0.147)

8 : Evaluation of the loop bcj
Direct comparisons in the loop:
bc cj bj
6 1 3

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the cj arm
mean(se)= 0.666(0.377)
Meta-analysis for the bj arm
mean(se)= 0.646(0.107)

Indirect comparison for the bj arm
Mean(se)= 1.067(0.383)

Incoherence within the loop: Mean(se)= 0.42(0.397)

9 : Evaluation of the loop bcl
Direct comparisons in the loop:
bc cl bl
6 2 1

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the cl arm
mean(se)= -0.23(0.272)
Meta-analysis for the bl arm
mean(se)= 0.497(0.098)
Indirect comparison for the bl arm
Mean(se)= 0.17(0.28)

Incoherence within the loop: Mean(se)= -0.327(0.297)

10 : Evaluation of the loop bch
Direct comparisons in the loop:
bc ch bh
6 3 2

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the ch arm
mean(se)= -0.214(0.12)
Meta-analysis for the bh arm
mean(se)= -0.003(0.11)
Indirect comparison for the bh arm
Mean(se)= 0.186(0.137)

Incoherence within the loop: Mean(se)= 0.189(0.176)

11 : Evaluation of the loop bcn
Direct comparisons in the loop:
bc cn bn
6 2 4

Meta-analysis for the bc arm
mean(se)= 0.4(0.067)
Meta-analysis for the cn arm
mean(se)= -0.516(0.096)
Meta-analysis for the bn arm

mean(se)= -0.056(0.068)
Indirect comparison for the bn arm
Mean(se)= -0.116(0.117)

Incoherence within the loop: Mean(se)= -0.059(0.136)

12 : Evaluation of the loop cdg
Direct comparisons in the loop:
cd dg cg
1 2 3

Meta-analysis for the cd arm
mean(se)= 1.11(0.396)
Meta-analysis for the dg arm
mean(se)= -0.149(0.089)
Meta-analysis for the cg arm
mean(se)= -0.173(0.537)
Indirect comparison for the cg arm
Mean(se)= 0.962(0.406)

Incoherence within the loop: Mean(se)= 1.135(0.673)

13 : Evaluation of the loop cgi
Direct comparisons in the loop:
cg gi ci
3 3 1

Meta-analysis for the cg arm
mean(se)= -0.173(0.537)
Meta-analysis for the gi arm
mean(se)= -0.196(0.073)
Meta-analysis for the ci arm
mean(se)= -1.008(0.413)
Indirect comparison for the ci arm
Mean(se)= -0.369(0.542)

Incoherence within the loop: Mean(se)= 0.639(0.681)

14 : Evaluation of the loop cgj
Direct comparisons in the loop:
cg gj cj
3 1 1

Meta-analysis for the cg arm
mean(se)= -0.173(0.537)
Meta-analysis for the gj arm
mean(se)= -0.039(0.11)

Meta-analysis for the cj arm
mean(se)= 0.666(0.377)
Indirect comparison for the cj arm
Mean(se)= -0.212(0.548)

Incoherence within the loop: Mean(se)= -0.878(0.665)

15 : Evaluation of the loop cde
Direct comparisons in the loop:
cd de ce
1 1 2

Meta-analysis for the cd arm
mean(se)= 1.11(0.396)
Meta-analysis for the de arm
mean(se)= -0.425(0.143)
Meta-analysis for the ce arm
mean(se)= 0.098(0.106)
Indirect comparison for the ce arm
Mean(se)= 0.686(0.421)

Incoherence within the loop: Mean(se)= 0.588(0.434)

16 : Evaluation of the loop cdj
Direct comparisons in the loop:
cd dj cj
1 2 1

Meta-analysis for the cd arm
mean(se)= 1.11(0.396)
Meta-analysis for the dj arm
mean(se)= -0.002(0.111)
Meta-analysis for the cj arm
mean(se)= 0.666(0.377)
Indirect comparison for the cj arm
Mean(se)= 1.108(0.411)

Incoherence within the loop: Mean(se)= 0.442(0.558)

17 : Evaluation of the loop cdl
Direct comparisons in the loop:
cd dl cl
1 2 2

Meta-analysis for the cd arm
mean(se)= 1.11(0.396)
Meta-analysis for the dl arm

mean(se)= 0.021(0.333)
Meta-analysis for the cl arm
mean(se)= -0.23(0.272)
Indirect comparison for the cl arm
Mean(se)= 1.131(0.518)

Incoherence within the loop: Mean(se)= 1.361(0.585)

18 : Evaluation of the loop cil
Direct comparisons in the loop:
ci il cl
1 1 2

Meta-analysis for the ci arm
mean(se)= -1.008(0.413)
Meta-analysis for the il arm
mean(se)= -0.851(0.384)
Meta-analysis for the cl arm
mean(se)= -0.23(0.272)
Indirect comparison for the cl arm
Mean(se)= -1.859(0.564)

Incoherence within the loop: Mean(se)= -1.629(0.626)

19 : Evaluation of the loop bdg
Direct comparisons in the loop:
bd dg bg
5 2 6

Meta-analysis for the bd arm
mean(se)= 0.593(0.11)
Meta-analysis for the dg arm
mean(se)= -0.149(0.089)
Meta-analysis for the bg arm
mean(se)= 0.493(0.074)
Indirect comparison for the bg arm
Mean(se)= 0.445(0.142)

Incoherence within the loop: Mean(se)= -0.049(0.16)

20 : Evaluation of the loop bgi
Direct comparisons in the loop:
bg gi bi
6 3 3

Meta-analysis for the bg arm
mean(se)= 0.493(0.074)

Meta-analysis for the gi arm
mean(se)= -0.196(0.073)
Meta-analysis for the bi arm
mean(se)= 0.162(0.07)
Indirect comparison for the bi arm
Mean(se)= 0.298(0.104)

Incoherence within the loop: Mean(se)= 0.135(0.125)

21 : Evaluation of the loop bgj
Direct comparisons in the loop:
bg gj bj
6 1 3

Meta-analysis for the bg arm
mean(se)= 0.493(0.074)
Meta-analysis for the gj arm
mean(se)= -0.039(0.11)
Meta-analysis for the bj arm
mean(se)= 0.646(0.107)
Indirect comparison for the bj arm
Mean(se)= 0.455(0.133)

Incoherence within the loop: Mean(se)= -0.192(0.171)

22 : Evaluation of the loop bgk
Direct comparisons in the loop:
bg gk bk
6 2 2

Meta-analysis for the bg arm
mean(se)= 0.493(0.074)
Meta-analysis for the gk arm
mean(se)= -0.225(0.073)
Meta-analysis for the bk arm
mean(se)= 0.42(0.089)
Indirect comparison for the bk arm
Mean(se)= 0.268(0.104)

Incoherence within the loop: Mean(se)= -0.152(0.137)

23 : Evaluation of the loop bde
Direct comparisons in the loop:
bd de be
5 1 4

Meta-analysis for the bd arm

mean(se)= 0.593(0.11)
Meta-analysis for the de arm
mean(se)= -0.425(0.143)
Meta-analysis for the be arm
mean(se)= 0.429(0.077)
Indirect comparison for the be arm
Mean(se)= 0.169(0.181)

Incoherence within the loop: Mean(se)= -0.26(0.197)

24 : Evaluation of the loop bdf
Direct comparisons in the loop:
bd df bf
5 1 3

Meta-analysis for the bd arm
mean(se)= 0.593(0.11)
Meta-analysis for the df arm
mean(se)= -0.508(0.109)
Meta-analysis for the bf arm
mean(se)= 0.423(0.083)
Indirect comparison for the bf arm
Mean(se)= 0.085(0.155)

Incoherence within the loop: Mean(se)= -0.338(0.176)

25 : Evaluation of the loop bdj
Direct comparisons in the loop:
bd dj bj
5 2 3

Meta-analysis for the bd arm
mean(se)= 0.593(0.11)
Meta-analysis for the dj arm
mean(se)= -0.002(0.111)
Meta-analysis for the bj arm
mean(se)= 0.646(0.107)
Indirect comparison for the bj arm
Mean(se)= 0.591(0.156)

Incoherence within the loop: Mean(se)= -0.055(0.19)

26 : Evaluation of the loop bdl
Direct comparisons in the loop:
bd dl bl
5 2 1

Meta-analysis for the bd arm
mean(se)= 0.593(0.11)
Meta-analysis for the dl arm
mean(se)= 0.021(0.333)
Meta-analysis for the bl arm
mean(se)= 0.497(0.098)
Indirect comparison for the bl arm
Mean(se)= 0.614(0.351)

Incoherence within the loop: Mean(se)= 0.117(0.365)

27 : Evaluation of the loop bil
Direct comparisons in the loop:
bi il bl
3 1 1

Meta-analysis for the bi arm
mean(se)= 0.162(0.07)
Meta-analysis for the il arm
mean(se)= -0.851(0.384)
Meta-analysis for the bl arm
mean(se)= 0.497(0.098)
Indirect comparison for the bl arm
Mean(se)= -0.689(0.39)

Incoherence within the loop: Mean(se)= -1.186(0.402)

28 : Evaluation of the loop bep
Direct comparisons in the loop:
be ep bp
4 1 2

Meta-analysis for the be arm
mean(se)= 0.429(0.077)
Meta-analysis for the ep arm
mean(se)= 0.167(0.103)
Meta-analysis for the bp arm
mean(se)= 0.516(0.091)
Indirect comparison for the bp arm
Mean(se)= 0.596(0.128)

Incoherence within the loop: Mean(se)= 0.079(0.157)

29 : Evaluation of the loop dgj
Direct comparisons in the loop:
dg gj dj
2 1 2

Meta-analysis for the dg arm
mean(se)= -0.149(0.089)
Meta-analysis for the gj arm
mean(se)= -0.039(0.11)
Meta-analysis for the dj arm
mean(se)= -0.002(0.111)
Indirect comparison for the dj arm
Mean(se)= -0.187(0.141)

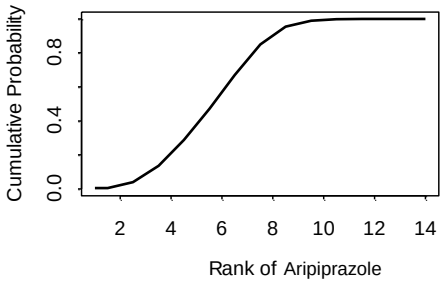
Incoherence within the loop: Mean(se)= -0.185(0.18)

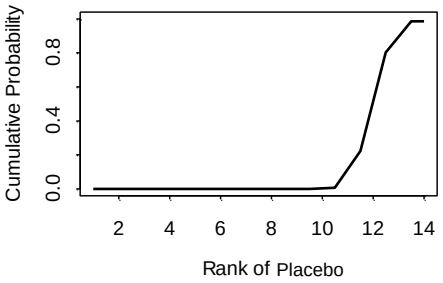
Appendix 10

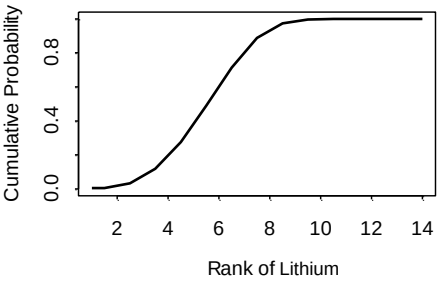
SUCRAs and rankograms

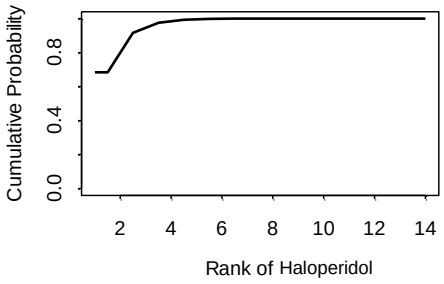
Bayesian posterior probabilities can be used to rank the treatments for each outcome. For example one can estimate for each treatment what is the probability to be the best (most effective or most acceptable) and also calculate the probability to be the second best, third best and so on. Plots of these rank probabilities (rankograms) are useful, but unlikely to provide a ranking measure when many treatments are competing. Another way would be to estimate the cumulative probabilities, i.e. the probability of each treatment to be the best, among the best two options, among the best three options etc. These probabilities can be plotted against the possible ranks. These plots are presented below together with the rankograms. Obviously, the larger the surface below the cumulative ranking curve, the more probable are the lowest ranks, i.e. the more effective or acceptable the treatment. The surface below the cumulative ranking curve (SUCRA) can be quantified. The following tables show the mean SUCRA values together with the 95% CrI for each outcome and model.

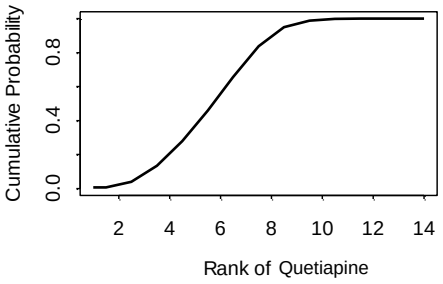
Continuous efficacy data
SUCRAS (1)

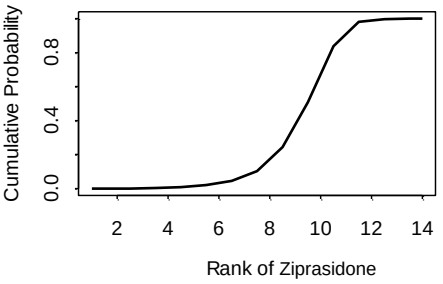


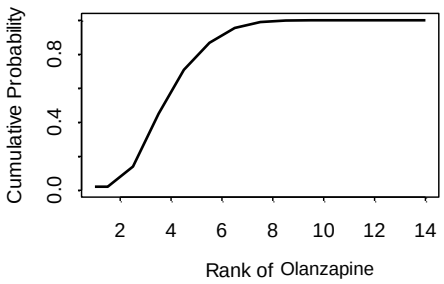


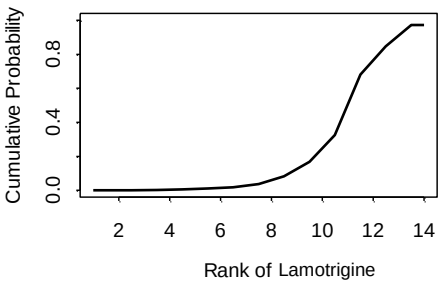


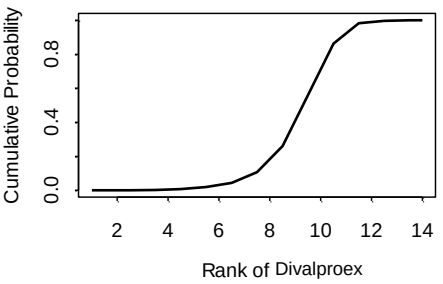




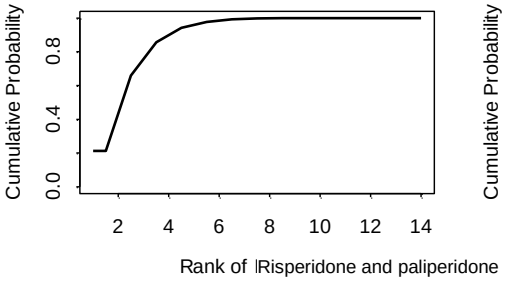


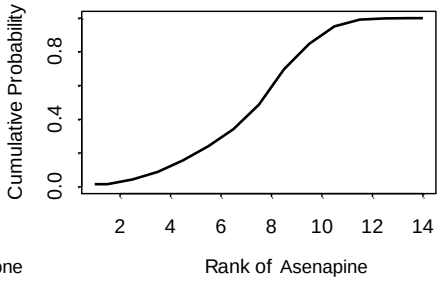


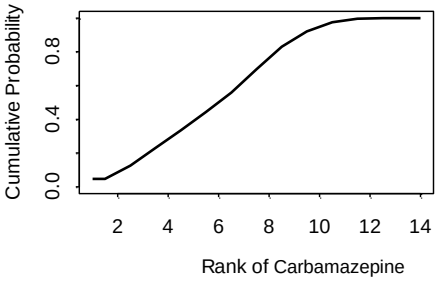


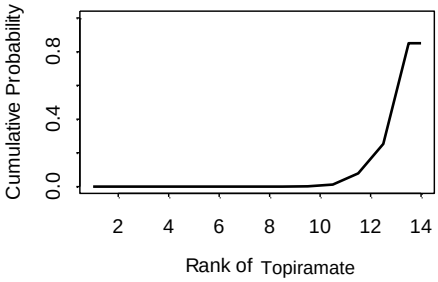


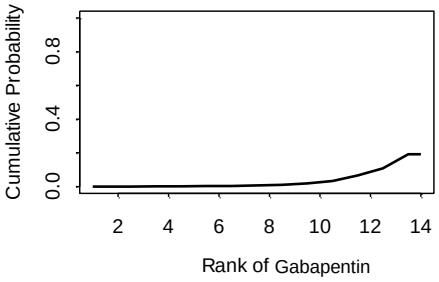
Continuous efficacy data
SUCRAS (2)



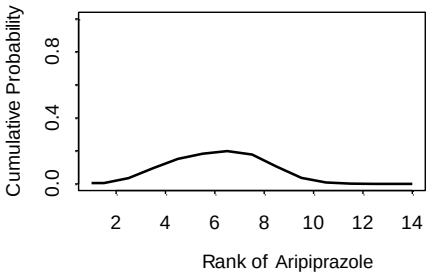


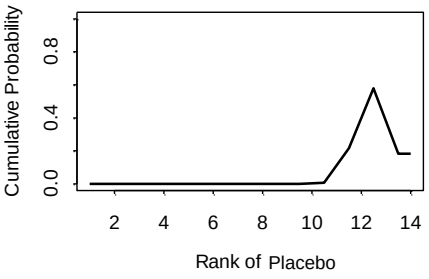


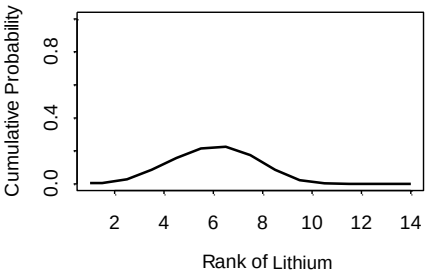


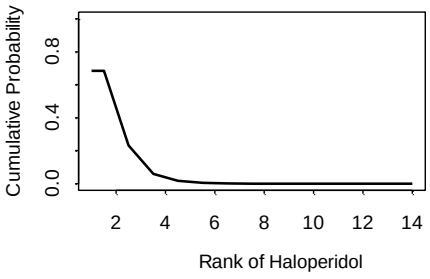


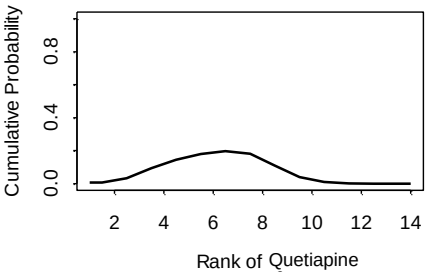
Continuous efficacy data
Rankograms (1)

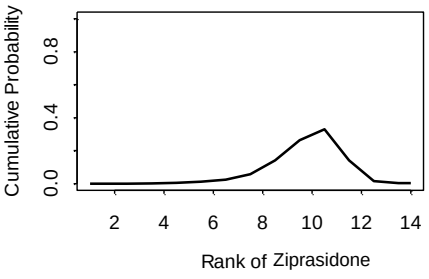


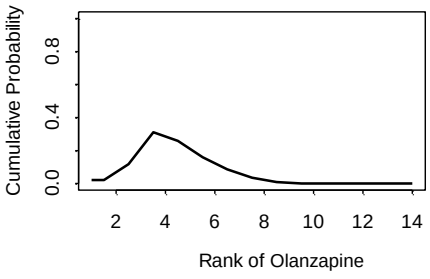


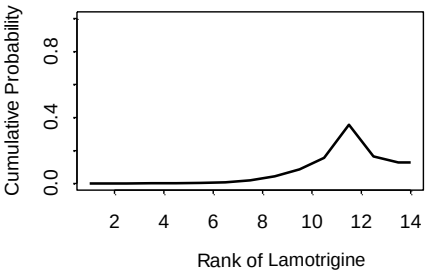


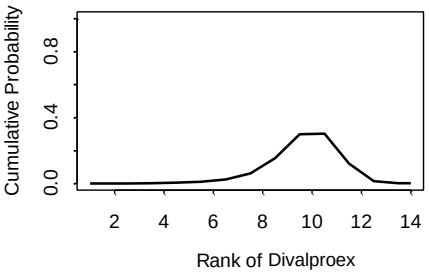




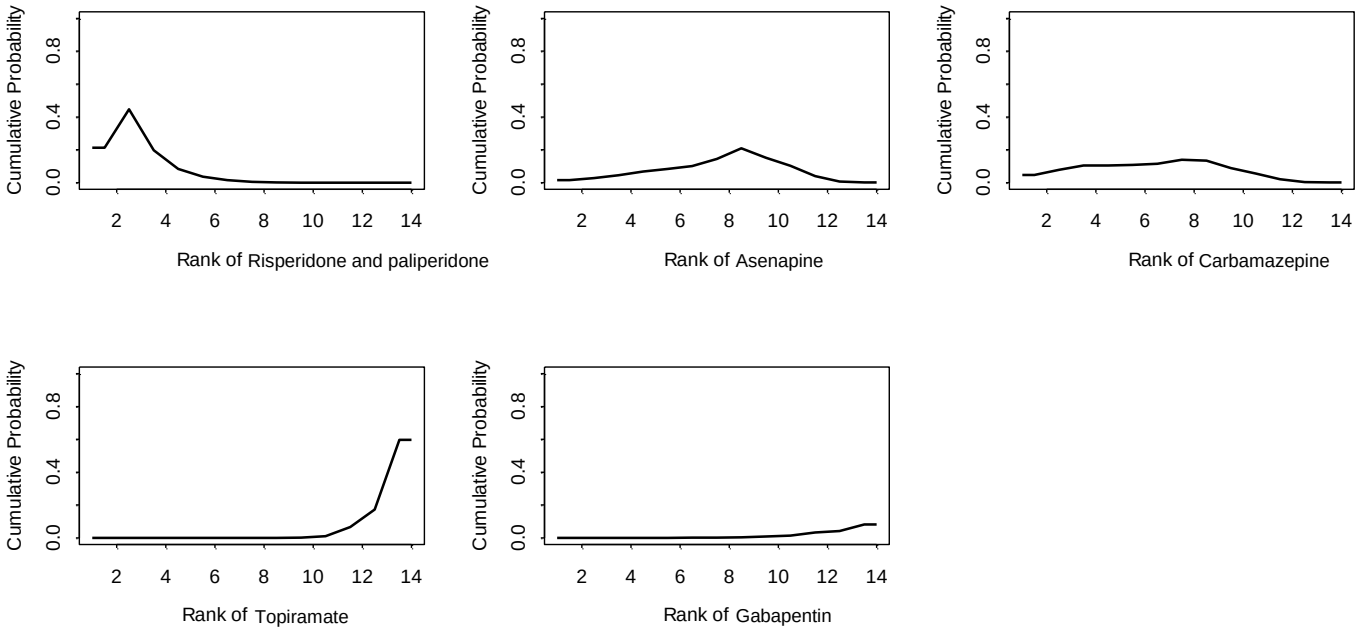




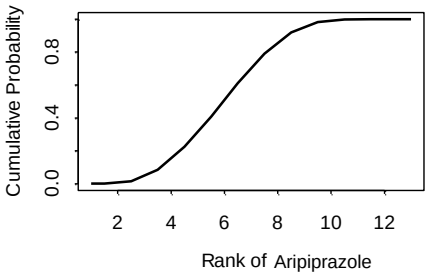


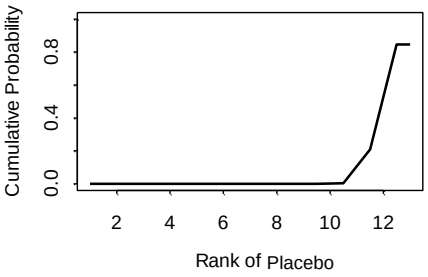


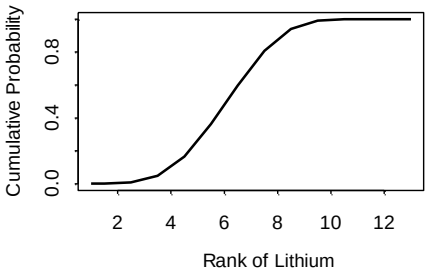
Continuous efficacy data
Rankograms (2)

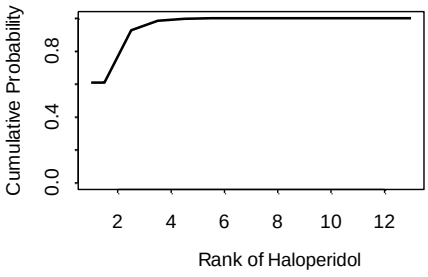


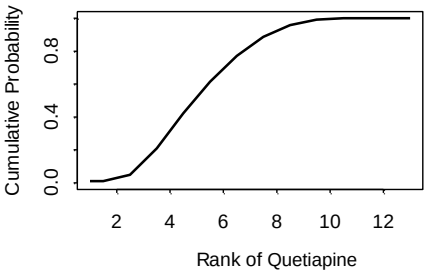
Continuous efficacy data
SUCRAs (excluding combination studies) (1)

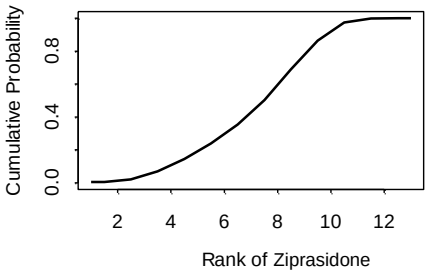


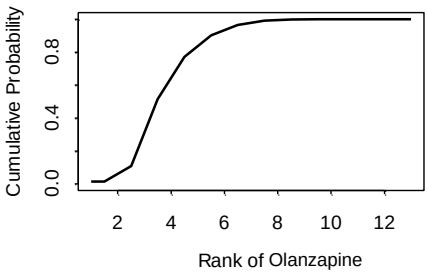


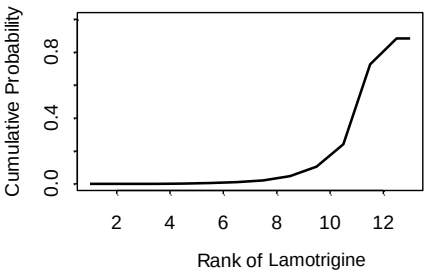


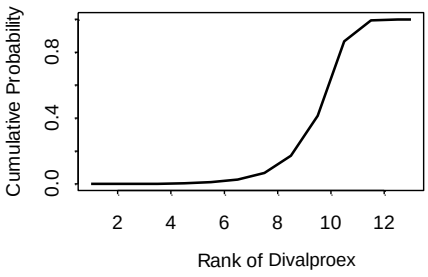




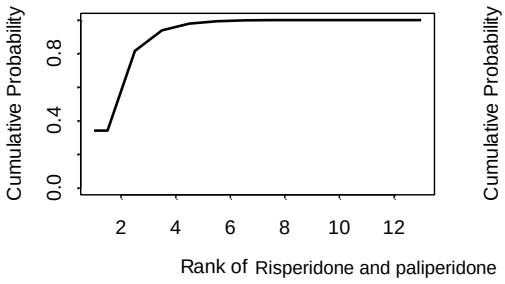


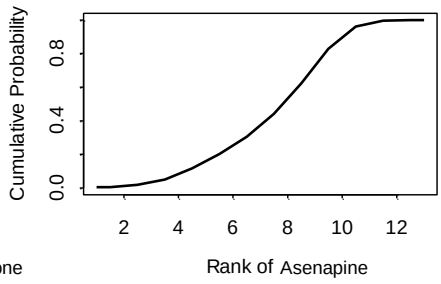


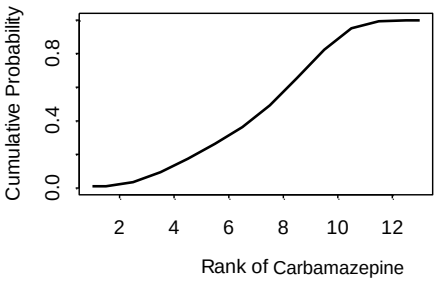


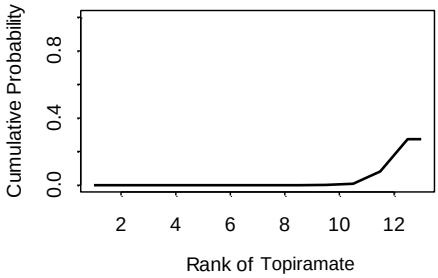


Continuous efficacy data SUCRAs (excluding combination studies) (2)

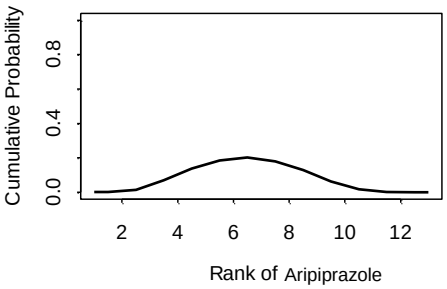


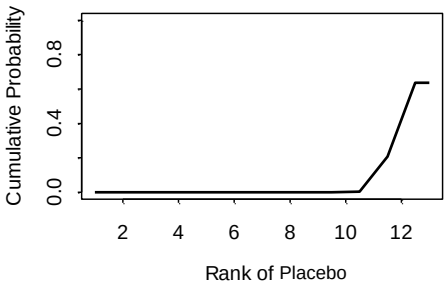


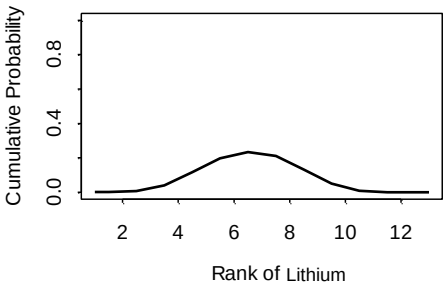


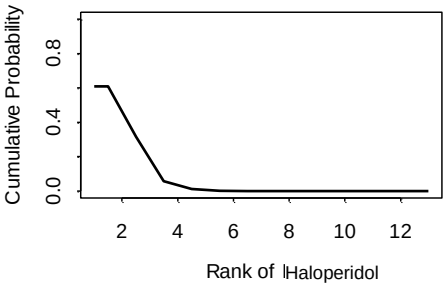


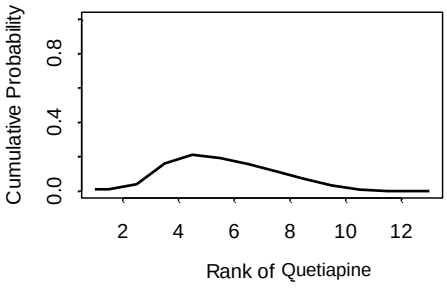
Continuous efficacy data
Rankograms (excluding combination studies) (1)

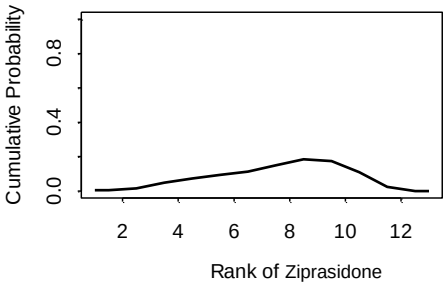


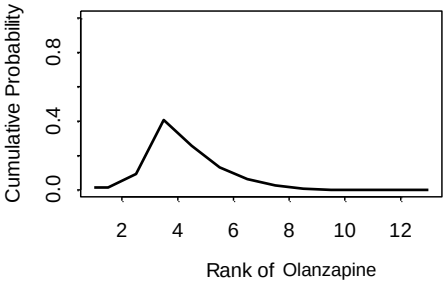


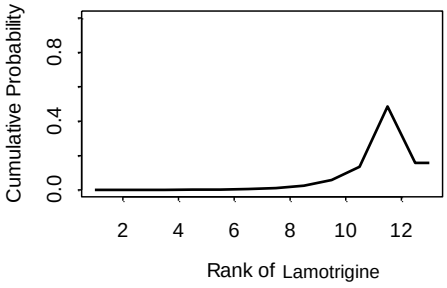


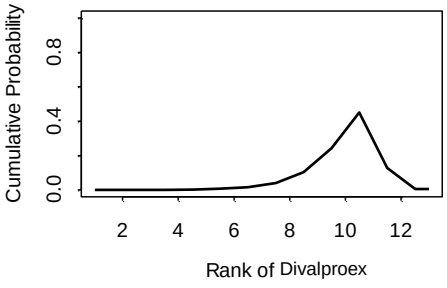




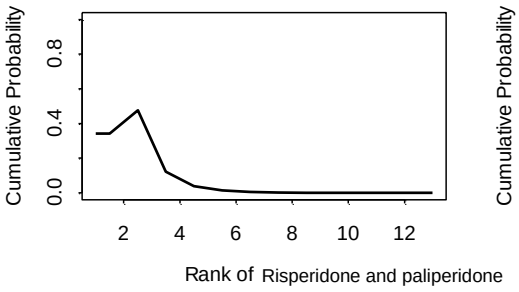


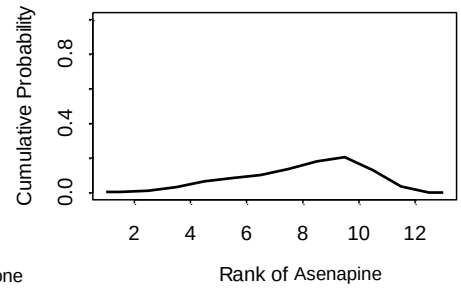


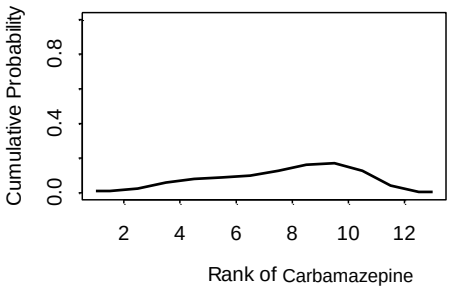


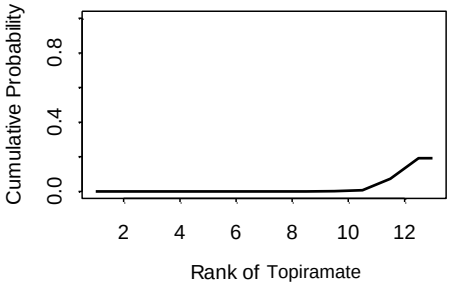


Continuous efficacy data
Rankograms (excluding combination studies) (2)

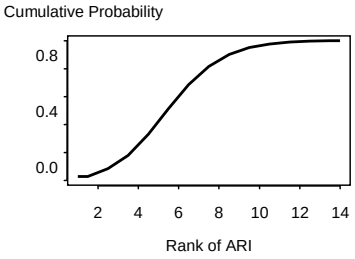


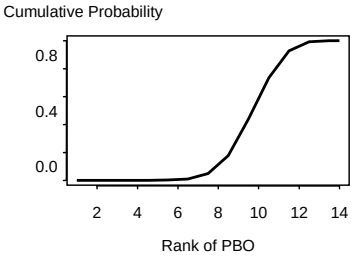


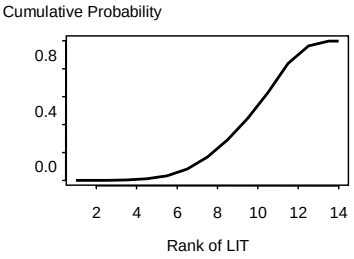


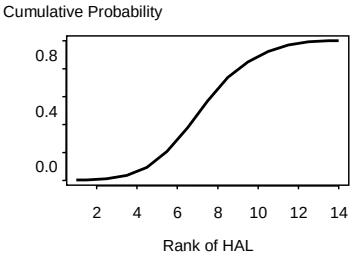


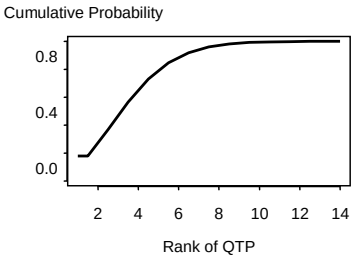
Acceptability (dropout) data-SUCRAs

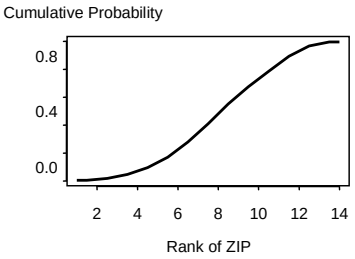


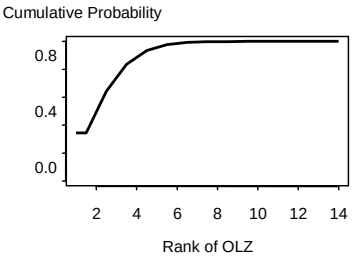


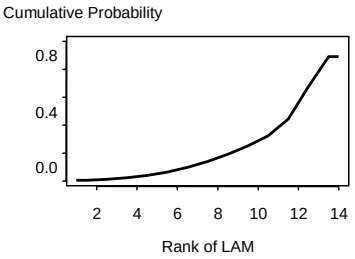


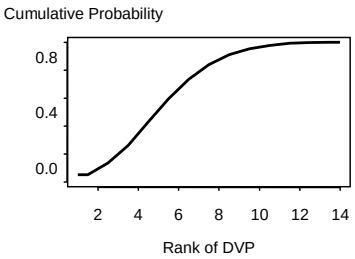


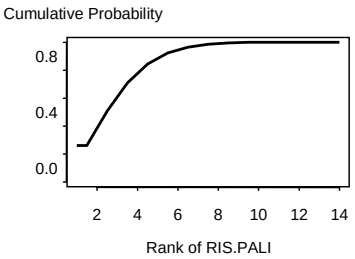


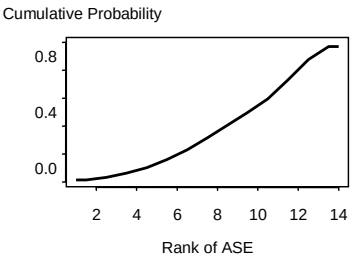


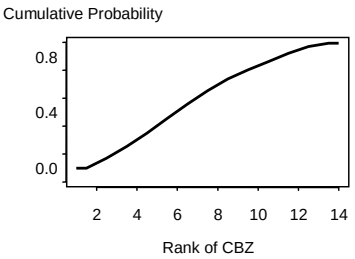


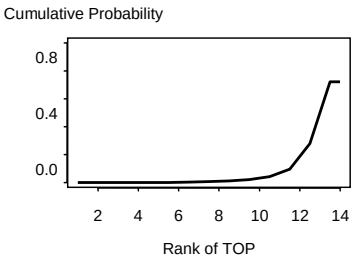


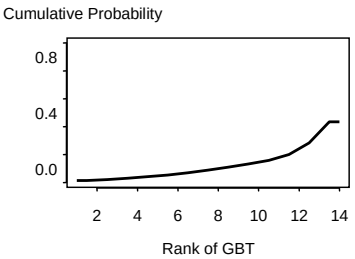




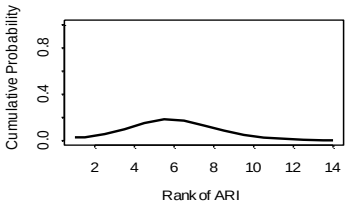


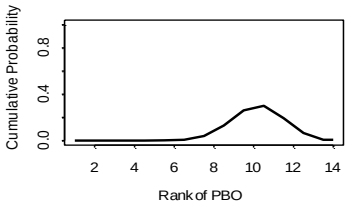


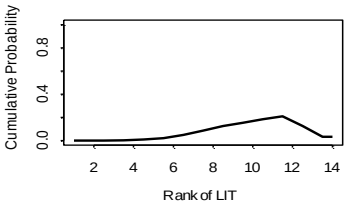


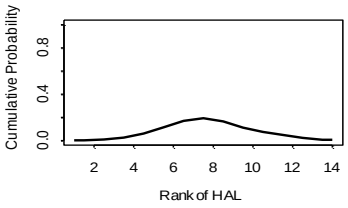


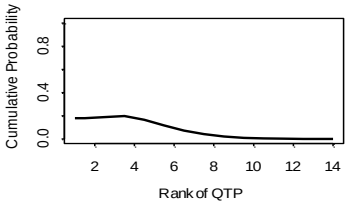
Acceptability (dropout) data - Rankograms

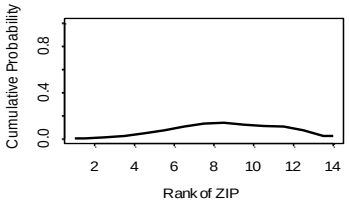


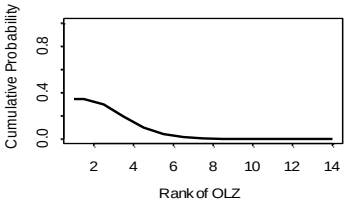


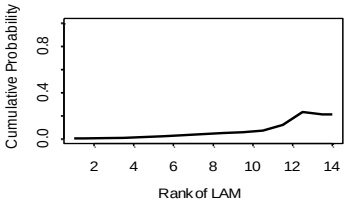


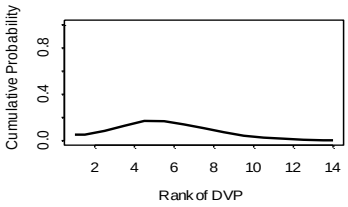


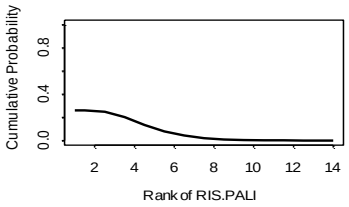


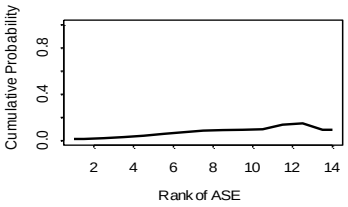


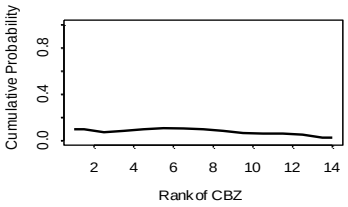


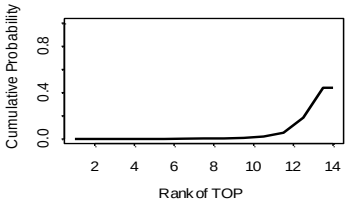


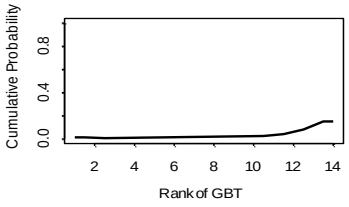




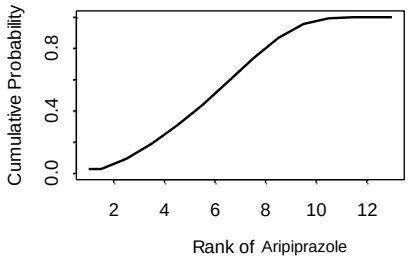


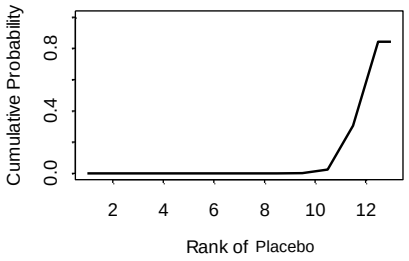


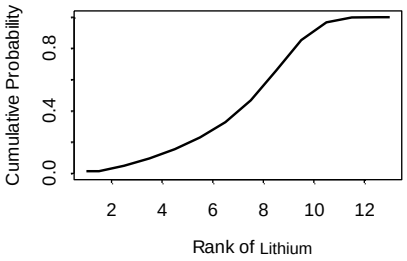


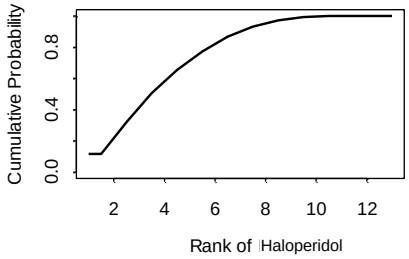


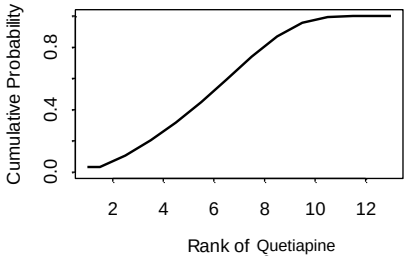
Binary efficacy data
SUCRAs (1)

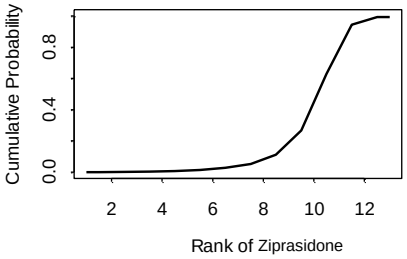


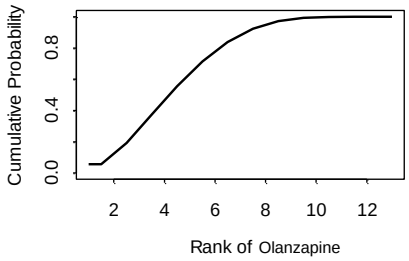


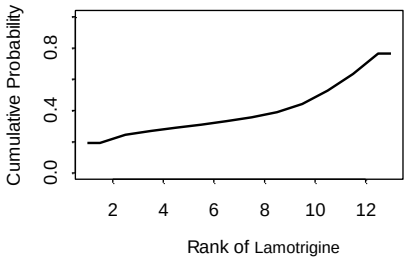


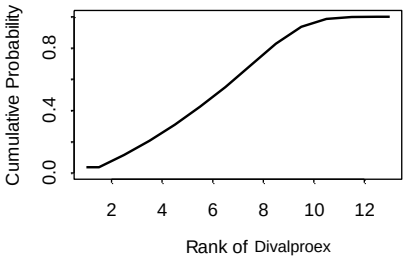




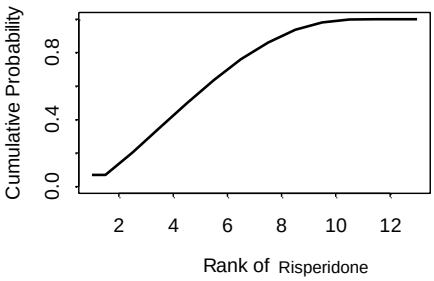


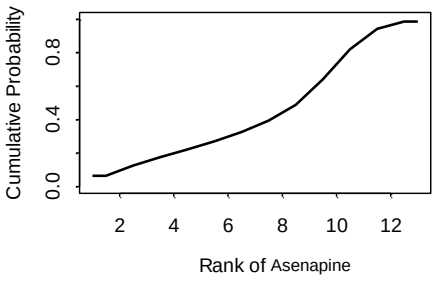


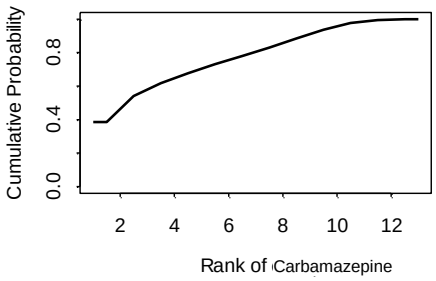


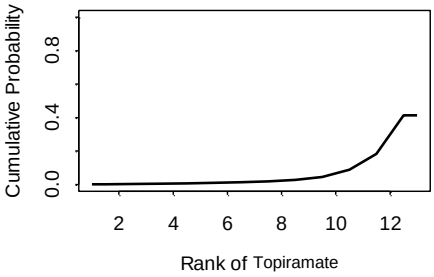


Binary efficacy data
SUCRAs (2)

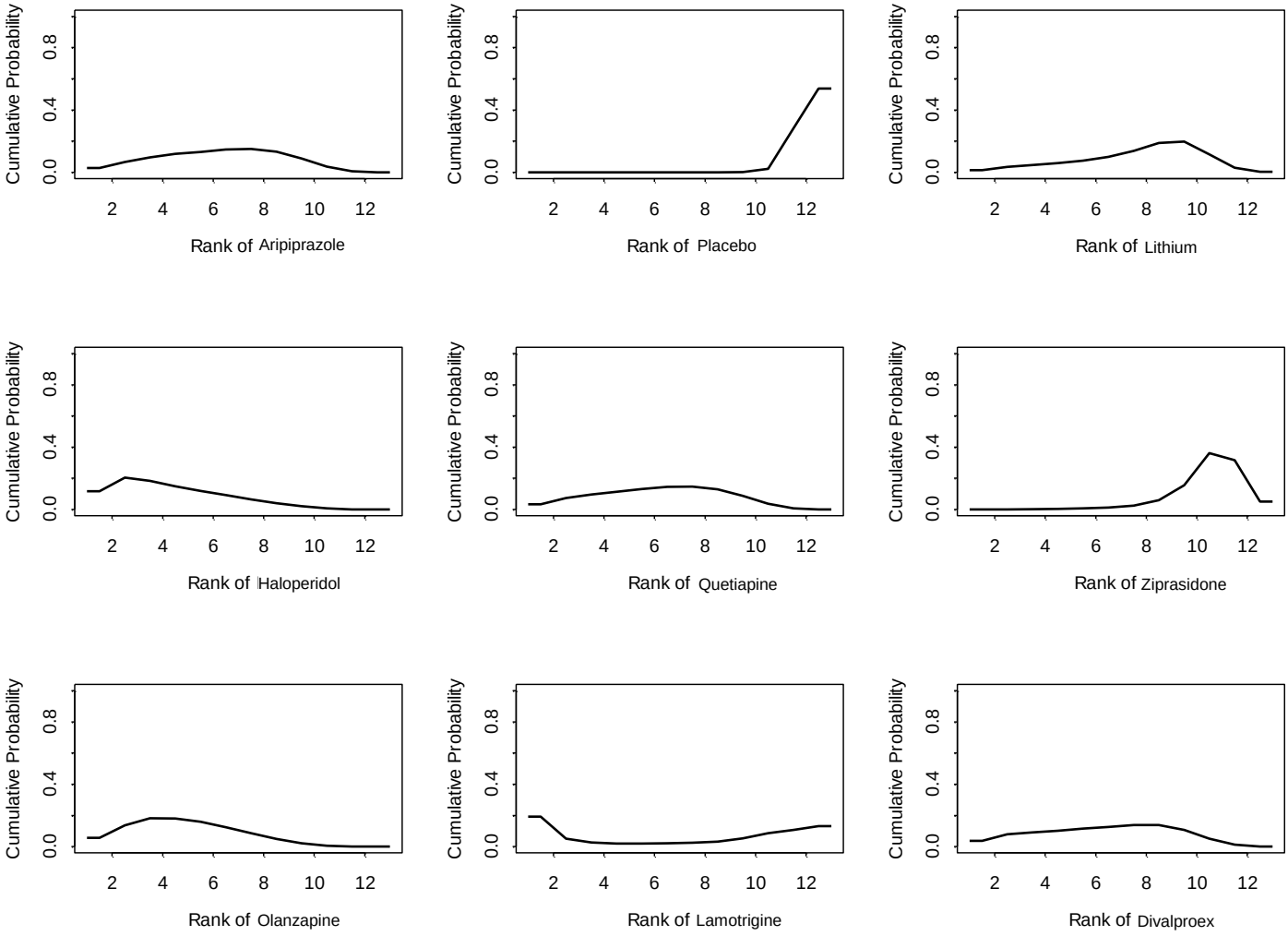




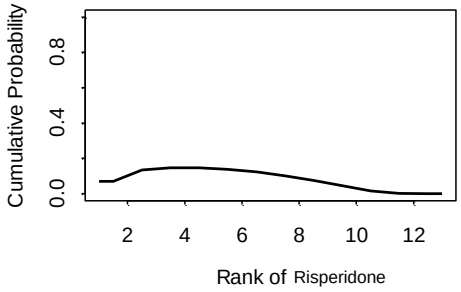


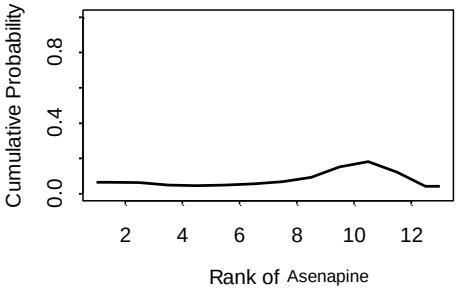


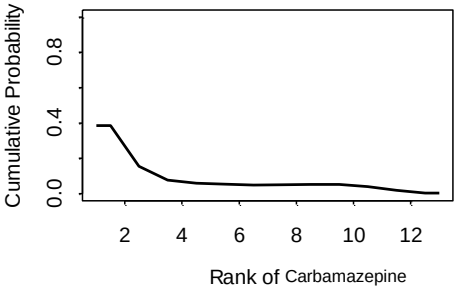
Binary efficacy data
Rankograms (1)

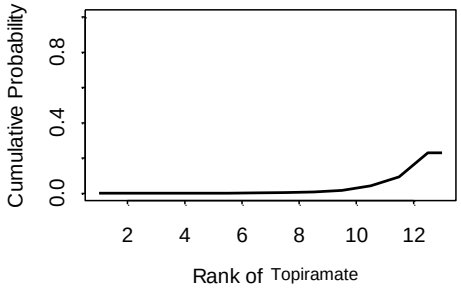


Binary efficacy data
Rankograms (2)









- **Continuous Response**

1.1 Comparing SUCRAs values

Drug	Split			Combined	
	Mean	*95% CrI*		*Mean*	*95% CrI*
Aripiprazole	0.635	[0.3571,0.8571]		0.646	[0.3846,0.9231]
Placebo	0.144	[0.07143,0.2143]		0.155	[0.07692,0.2308]
Lithium	0.636	[0.4286,0.8571]		0.653	[0.3846,0.9231]
Haloperidol	0.948	[0.7857,1]		0.966	[0.8462,1]
Quetiapine	0.599	[0.3571,0.8571]		0.642	[0.3846,0.9231]
Ziprasidone	0.343	[0.2143,0.6429]		0.365	[0.2308,0.6154]
Olanzapine	0.777	[0.5714,0.9286]		0.779	[0.5385,0.9231]
Lamotrigine	0.227	[0,0.5]		0.242	[0,0.5385]
Divalproex	0.355	[0.2143,0.6429]		0.372	[0.2308,0.6154]
Risperidone	0.945	[0.7857,1]		0.895	[0.6923,1]
Asenapine	0.514	[0.2143,0.8571]		0.527	[0.2308,0.9231]
Carbamazepine	0.613	[0.2857,1]		0.628	[0.3077,1]
Topiramate	0.085	[0,0.2143]		0.092	[0,0.2308]
Gabapentin	0.031	[0,0.2857]		0.034	[0,0.3077]
Paliperidone	0.647	[0.2857,1]		-	-

- **Continuous Response with No Combo**

2.2 Comparing SUCRA values

Drug	Split			Combined	
	Mean	*95% CrI*		*Mean*	*95% CrI*
Aripiprazole	0.556	[0.3077,0.8462]		0.586	[0.3333,0.8333]
Placebo	0.081	[0,0.1538]		0.088	[0,0.1667]
Lithium	0.544	[0.3077,0.7692]		0.576	[0.3333,0.8333]
Haloperidol	0.935	[0.7692,1]		0.960	[0.8333,1]
Quetiapine	0.607	[0.3077,0.8462]		0.659	[0.3333,0.9167]
Ziprasidone	0.468	[0.1538,0.8462]		0.489	[0.1667,0.8333]
Olanzapine	0.746	[0.4615,0.9231]		0.772	[0.5,0.9167]
Lamotrigine	0.157	[0,0.3846]		0.170	[0,0.4167]
Divalproex	0.277	[0.1538,0.5385]		0.296	[0.1667,0.5833]
Risperidone	0.921	[0.6923,1]		0.922	[0.75,1]
Asenapine	0.438	[0.1538,0.8462]		0.462	[0.1667,0.8333]
Carbamazepine	0.460	[0.1538,0.8462]		0.488	[0.1667,0.9167]
Topiramate	0.028	[0,0.1538]		0.030	[0,0.1667]
Gabapentin	-	-		-	-
Paliperidone	0.780	[0.3077,1]		-	-

- **Binary Response**

3.2 Comparing SUCRAs values

Drug	Split			Combined	
	Mean	*95% CrI*		*Mean*	*95% CrI*
Aripiprazole	0.574	[0.2308,0.9231]		0.599	[0.25,1]
Placebo	0.087	[0,0.1538]		0.098	[0,0.1667]
Lithium	0.473	[0.1538,0.9231]		0.484	[0.1667,0.9161]
Haloperidol	0.766	[0.3846,1]		0.761	[0.3333,1]
Quetiapine	0.552	[0.2308,0.9231]		0.605	[0.25,1]
Ziprasidone	0.245	[0.07692,0.5385]		0.254	[0.08333,0.5833]
Olanzapine	0.717	[0.3846,1]		0.718	[0.3333,1]
Lamotrigine	0.380	[0,1]		0.396	[0,1]
Divalproex	0.596	[0.2308,0.9231]		0.590	[0.25,1]
Risperidone	0.826	[0.3846,1]		0.691	[0.3333,1]
Asenapine	0.466	[0.07692,1]		0.454	[0.8333,1]
Carbamazepine	0.781	[0.2308,1]		0.780	[0.25,1]
Topiramate	0.076	[0,0.4615]		0.068	[0,0.4167]
Gabapentin	-	-		-	-
Paliperidone	0.460	[0.1538,0.9231]		-	-

- **Binary Drop**

4.2 Comparing SUCRAs values

Drug	Split			Combined	
	Mean	*95% CrI*		*Mean*	*95% CrI*
Aripiprazole	0.627	[0.2857,0.9286]		0.650	[0.3077,1]
Placebo	0.314	[0.1429,0.5]		0.333	[0.1538,0.5385]
Lithium	0.327	[0.07143,0.6429]		0.343	[0.07692,0.6923]
Haloperidol	0.499	[0.1429,0.7857]		0.520	[0.1538,0.8462]
Quetiapine	0.782	[0.4286,1]		0.811	[0.4615,1]
Ziprasidone	0.434	[0.07143,0.8571]		0.453	[0.07692,0.8462]
Olanzapine	0.879	[0.6429,1]		0.902	[0.6923,1]
Lamotrigine	0.231	[0,0.7857]		0.243	[0,0.7692]
Divalproex	0.656	[0.2857,1]		0.682	[0.3077,1]
Risperidone	0.848	[0.5,1]		0.860	[0.5385,1]
Asenapine	0.369	[0,0.9286]		0.383	[0,0.9231]
Carbamazepine	0.582	[0.07143,1]		0.601	[0.07692,1]
Topiramate	0.086	[0,0.2857]		0.091	[0,0.3077]
Gabapentin	0.122	[0,0.8571]		0.126	[0,0.8462]
Paliperidone	0.740	[0.2143,1]		-	-

Appendix 11

Meta-regression analysis

Meta-regression analysis for Continuous and Dropouts response

Sponsored drugs often appear to be more efficacious and acceptable when a company decides to fund a drug then it intends to have high efficacy or/ and acceptability. Through meta-regression we want to "uncover" the true relative effectiveness of each drug taking into consideration its sponsorship status (that is, whether it is sponsored or not compared to the baseline). After applying meta-regression we expect the efficacy of sponsored drugs to decrease compared to placebo and dropout rate to increase.

- ***Continuous Response***

The meta-regression model is the below

$$\Theta_{k1,i}^{obs} = \Theta_{k1,i}^{*} + b\left(sp_{1,i} - sp_{k,i}\right)$$

where

$\Theta_{k1,i}^{obs} = SMD_{k1,i}^{obs}=\left(\bar{X}_{k,i} - \bar{X}_{1,i}\right)/SD_i$ is the observed (unadjusted) standardized mean difference when we compare the $k-th$ drug with the first drug (which is supposed to be the baseline treatment) independently of the sponsorship status.

$sp_k = \left\{ \begin{array}{l} 1,\ \text{there is sponsorship for the } k\text{-}th \text{ drug} \\ 0,\ \text{there is no sponsorship for the } k\text{-}th \text{ drug} \end{array} \right\}$ is the covariate we examine for publication bias and

$\Theta_{k1,i}^{*}$ is the (adjusted for the sponsorship standardized mean difference) efficacy of the $k-th$ drug in comparison with the first drug according to the sponsorship status of the $k-th$ drug, sp_k. So, $\Theta_{1k} < 0$ means that the $k-th$ drug is better; the lower the effect size Θ_1k thebetter for drug k

Running WinBUGS in 100000 iterations and excluding the results from the first 10001 iterations we estimated that $b = 0.03293$ with 95% CrI $[-0.0975, 0.1786]$. The positive sign of this regression coefficient implies that the difference between the mean response of the $k-th$ treatment's effect and the mean response of the baseline treatment's effect tends to increase, when the $k-th$ treatment is sponsored.

The SMDs after adjusting for sponsorship compared to placebo are

	Adjusted		Unadjusted	
SMD	**mean**	**95% CrI**	**mean**	**95% CrI**
Aripiprazole	-0.3386	[-0.5341, -0.1349]	-0.3710	[-0.5082, -0.2329]
Lithium	-0.3766	[-0.5061, -0.2474]	-0.3742	[-0.503, -0.247]
Haloperidol	-0.5615	[-0.6889, -0.4325]	-0.5592	[-0.6862, -0.431]
Quetiapine	-0.3458	[-0.5274,-0.1591]	-0.3691	[-0.5133, -0.2281]
Ziprasidone	-0.1631	[-0.384, 0.06193]	-0.1962	[-0.3664, -0.03014]
Olanzapine	-0.4077	[0.2354, 0.5684]	-0.4346	[-0.5433, -0.3235]
Lamotrigine	-0.0509	[-0.3485, 0.2461]	-0.0777	[-0.3381,0.1824]
Divalproex	-0.1831	[-0.3668, 0.00554]	-0.2036	[-0.3698,-0.03554]
Risperidone	-0.4724	[-0.6526, -0.2876]	-0.5034	[-0.6272, -0.3807]
Asenapine	-0.2513	[-0.5719, 0.07131]	-0.3000	[-0.5315, -0.06895]
Carbamazepine	-0.3349	[-0.5961, -0.07501]	-0.3575	[-0.594, -0.1083]
Topiramate	0.1071	[-0.114, 0.3338]	0.0752	[-0.09268, 0.2418]
Gabapentin	0.3532	[-0.1722, 0.8797]	0.3224	[-0.1788, 0.823]

The relative effectiveness of the all active treatments is dropping compared to placebo after adjustment.

- ***Binary Dropout Response***

The meta-regression model is the below

$\Theta_{k1}^{obs} = \Theta_{k1}^{*} + b(sp_1 - sp_k)$

where

$\Theta_{k1}^{obs} = logit(p_k) - logit(p_1)$ is the observed (unadjusted) log odds ratio when we compare the $k-th$ drug with the first drug (reference in the trial)

$sp_k = \left\{ \begin{array}{l} 1, \text{ there is sponsorship for the } k\text{-}th \text{ drug} \\ 0, \text{ there is no sponsorship for the } k\text{-}th \text{ drug} \end{array} \right\}$ is the covariate we examine for sponsorship bias and

Θ_{k1}^{*} is the acceptability of the $k-th$ drug in comparison with the first drug of each trial according to the sponsorship status of the $k-th$ drug, sp_k.

Running WinBUGS in 100000 iterations and excluding the results from the first 10001 iterations we found that $b = -0.04628$ with 95% CI $[-0.39, 0.2744]$. The coefficient is very imprecise and centered at. The negative sign of this regression coefficient implies that the difference between the log odds of the $k-th$ treatment's effect and the log odds of the first treatment's effect tends to decrease when the $k-th$ treatment is sponsored, meaning that the acceptability of the sponsored treatment is downplayed in the observed estimates.

	Adjusted		Unadjusted	
OR	**mean**	**95% CrI**	**mean**	**95% CrI**
Aripiprazole	0.6930	[0.4411, 1.1525]	0.7479	[0.5464, 1.0547]
Lithium	0.9681	[0.7252, 1.3371]	0.9950	[0.7380, 1.3797]
Haloperidol	0.8217	[0.6131, 1.1370]	0.8418	[0.6266, 1.1618]
Quetiapine	0.5845	[0.3827, 0.9425]	0.6297	[0.4507, 0.9050]
Ziprasidone	0.8340	[0.5051, 1.4575]	0.8913	[0.6139, 1.3362]
Olanzapine	0.5345	[0.3642, 0.8271]	0.5760	[0.4442, 0.7599]
Lamotrigine	1.0543	[0.5559, 2.2568]	1.1392	[0.6506, 2.1810]
Divalproex	0.7082	[0.4805, 1.0889]	0.7194	[0.5081, 1.0547]
Risperidone	0.5618	[0.3630, 0.9091]	0.5981	[0.4403, 0.8319]
Asenapine	0.8460	[0.4205, 1.9650]	0.9515	[0.5659, 1.7188]
Carbamazepine	0.7294	[0.4203, 1.4029]	0.7530	[0.4403, 1.4049]
Topiramate	1.3721	[0.8271, 2.4540]	1.4605	[0.9901, 2.2482]
Gabapentin	1.4302	[0.5435, 5.2743]	1.5293	[0.6143, 5.1099]

Checking model fit using deviances

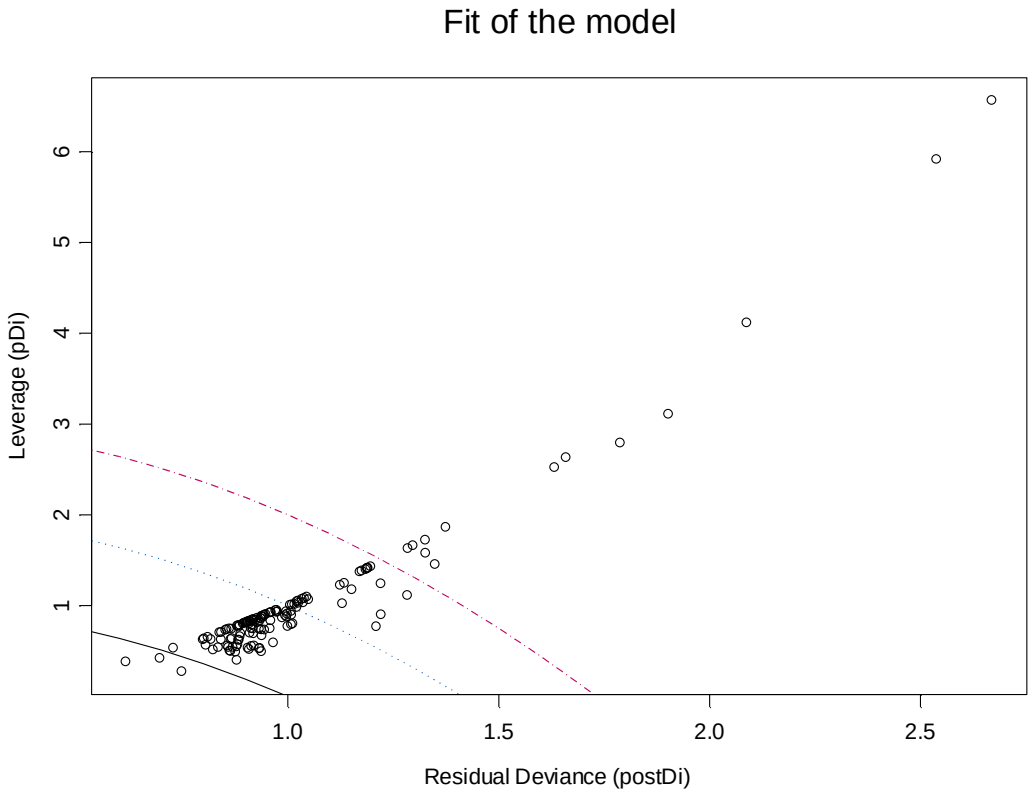
The fit of each model can be evaluated using the posterior mean of the residual deviance $\bar{D}$ and the Deviance Information Criterion (DIC). A model has good fit when the residual deviance approximates the number of data points.

References:

- Spiegelhalter DJ, Best NG, Bradley PC, van der Linde A. Bayesian measures of model complexity and fit. Journal of the Royal Statistical Society Series B 2002; 583—639.
- Dempster AP. The direct use of likelihood for significance testing. Statistics and Computing 1997; 7:247—252.

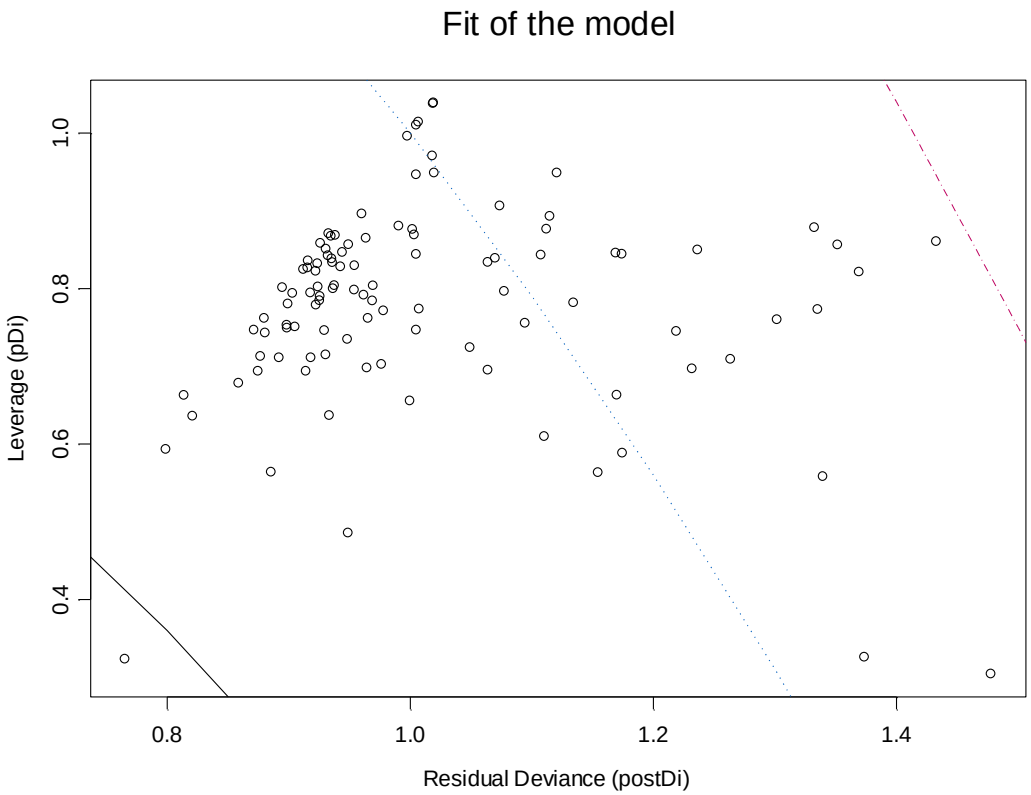
Comparison of different models can be accomplished by comparing DICs; low DIC values signify a better model when both fit and parsimony are considered. To check individual points' contributions to the DIC, for each data point, we plot the leverage (the difference between posterior residual deviance and the deviance at the posterior mean of the fitted value) against the square root of the posterior residual deviance. We identify data points as contributing to the model's poor fit if they lie outside the $x^2 + y = 3$ borders in the leverage plots.

(*Continuous response*)



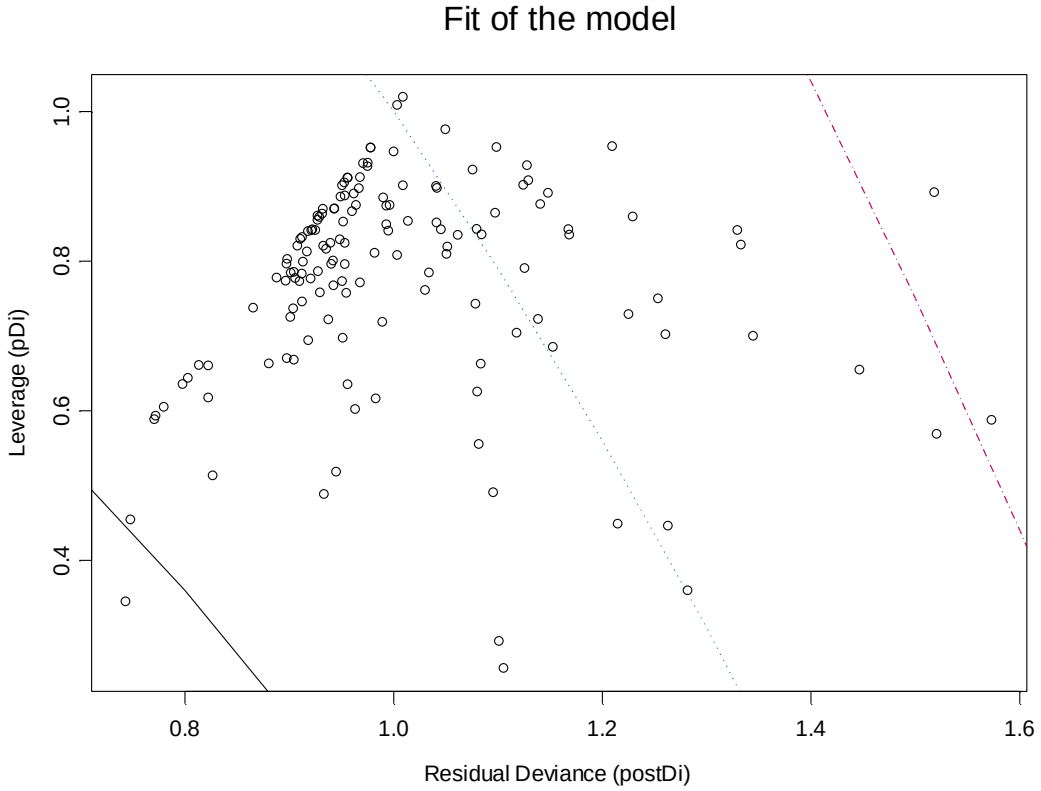
Model fit measures and diagnostics
Residual deviance: $\bar{D} = 157.52$ > 141
Data points= 141
(Note that total residual deviance should approximate the number of data points for a good fit)
Effective number of parameters: pD =141.76
DIC= 299.28

(*Binary response*)



Model fit measures and diagnostics
Residual deviance: $\bar{D} = 110.35$ > 105
Data points= 105
(Note that total residual deviance should approximate the number of data points for a good fit)
Effective number of parameters= 81.66
DIC= 192.01

(*Dropouts response*)
We have already excluded Chlorpromazine, Pimozide and Thiothixene



Model fit measures and diagnostics
Residual deviance: $\bar{D}$ =149.16 > 144
Data points= 144
(Note that total residual deviance should approximate the number of data points for a good fit)
Effective number of parameters= 111.33
DIC= 260.49