Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis

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Summary

Background Conventional meta-analyses have shown inconsistent results for efficacy of pharmacological treatments for acute mania. We did a multiple-treatments meta-analysis, which accounted for both direct and indirect comparisons, to assess the effects of all antimanic drugs.

Methods We systematically reviewed 68 randomised controlled trials (16 073 participants) from Jan 1, 1980, to Nov 25, 2010, which compared any of the following pharmacological drugs at therapeutic dose range for the treatment of acute mania in adults: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, quetiapine, risperidone, topiramate, and ziprasidone. The main outcomes were the mean change on mania rating scales and the number of patients who dropped out of the allocated treatment at 3 weeks. Analysis was done by intention to treat.

Findings Haloperidol (standardised mean difference [SMD] –0·56 [95% CI –0·69 to –0·43]), risperidone (–0·50 [–0·63 to –0·38]), olanzapine (–0·43 [–0·54 to –0·32], lithium (–0·37 [–0·63 to –0·11]), quetiapine (–0·37 [–0·51 to –0·23]), aripiprazole (–0·37 [–0·51 to –0·23]), carbamazepine (–0·36 [–0·60 to –0·11], asenapine (–0·30 [–0·53 to –0·07]), valproate (–0·20 [–0·37 to –0·04]), and ziprasidone (–0·20 [–0·37 to –0·03]) were significantly more effective than placebo, whereas gabapentin, lamotrigine, and topiramate were not. Haloperidol had the highest number of significant differences and was significantly more effective than lithium (SMD –0·19 [95% CI –0·36 to –0·01]), quetiapine (–0·19 [–0·37 to 0·01]), aripiprazole (–0·19 [–0·36 to –0·02]), carbamazepine (–0·20 [–0·36 to –0·01]), asenapine (–0·26 [–0·52 to 0·01]), valproate (–0·36 [–0·56 to –0·15]), ziprasidone (–0·36 [–0·56 to –0·15]), lamotrigine (–0·48 [–0·77 to –0·19]), topiramate (–0·63 [–0·84 to –0·43]), and gabapentin (–0·88 [–1·40 to –0·36]). Risperidone and olanzapine had a very similar profile of comparative efficacy, being more effective than valproate, ziprasidone, lamotrigine, topiramate, and gabapentin. Olanzapine, risperidone, and quetiapine led to significantly fewer discontinuations than did lithium, lamotrigine, placebo, topiramate, and gabapentin.

Interpretation Overall, antipsychotic drugs were significantly more effective than mood stabilisers. Risperidone, olanzapine, and haloperidol should be considered as among the best of the available options for the treatment of manic episodes. These results should be considered in the development of clinical practice guidelines.

Funding None.

Introduction

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 recurring illness, and one of the leading causes of worldwide disability, especially in those aged 15–44 years.[1] Mood stabilisers and antipsychotic drugs have long been the mainstay of treatment of acute mania with and without psychotic features.[2] These medicines have been shown to be individually more effective than placebo, but guidelines have not usually attempted to rank the effectiveness of these drugs.[3–7]

We report a systematic review of randomised controlled trials that compared efficacy and acceptability of antimanic drugs, either against placebo or against one another, in the treatment of acute mania. We used the method of multiple-treatments meta-analysis, to allow the integration of data from direct and indirect comparisons.[8,9] We had previously compared the effectiveness of antidepressants in unipolar depression in this way.[10] This method comprehensively synthesises data to provide a clinically useful summary that can guide treatment decisions.

For the **trial protocol** see http://cebmh.warne.ox.ac.uk/cebmh/downloads/MTM%20acute%20mania_protocol_To%20be%20published_1.pdf

See Online for webappendix

For the **overall dataset** see http://www.psychiatry.ox.ac.uk/research/researchunits/octumi/downloads/MTMacutemania

Methods

Study protocol

At the beginning of this project, we drafted a study protocol and subsequently made it freely available to the public on our institutional website before doing the final analyses (webappendix p 1). Furthermore, with the publication of this Article, the overall dataset will be in the public domain for anyone who would be interested to use it.

Search strategy and selection criteria

We searched Medline, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), PsycINFO, the

Cochrane Central Register of Controlled Trials, and the trial databases of the main regulatory agencies to identify relevant studies published between Jan 1, 1980, and Nov 25, 2010. The webappendix (p 7) shows full details of the review methods and the search strategy. All relevant authors and principal manufacturers were contacted to supplement incomplete reports of the original papers or to provide new data for unpublished studies. The Cochrane risk-of-bias method was used to assess study quality.[11,12]

We included all randomised, double-blind trials comparing one active antimanic drug at a therapeutic dose with another active antimanic drug or with placebo as oral therapy for adults with acute mania. Combination and augmentation studies were also included. The participants were both men and women, aged 18 years or older, and with a primary diagnosis of bipolar I disorder (manic or mixed episode) according to standardised diagnostic criteria. Both fixed-dose and flexible-dose designs were allowed.

Outcome measures

Acute treatment was defined as a 3-week treatment in both the efficacy and acceptability analyses. Mean change scores on the Young Mania Rating Scale (YMRS)[13] and dropout rates (treatment discontinuation) were chosen as primary outcomes to represent, respectively, the most sensible and sensitive estimates of acute treatment efficacy and acceptability. 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 of the total number of patients randomly assigned to each treatment group. As a secondary analysis, we also estimated the proportion of patients who responded to treatment.

We did sensitivity analyses according to the following variables: (1) exclusion of studies adopting combination or augmentation treatment strategies and (2) splitting of risperidone and paliperidone. Furthermore, To investigate the effect of sponsorship on outcome estimate, we did a meta-regression analysis.

Data extraction

We used the data that have been extracted for the previous Cochrane reviews carried out by the members of our review team (JG, JR, AC, and GG). Concerning the updated search, three reviewers (AC, JR, RB, and CB) independently reviewed references and abstracts. If all 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 (JG or GG). The same reviewers (AC, JR, RB, and CB) independently read each article, assessed the completeness of the data abstraction, and confirmed the quality rating. As for previous Cochrane systematic reviews, we used a structured data abstraction form to ensure consistency of appraisal for every study. Information extracted included study characteristics (such as lead author, publication year, journal, study setting, and sponsorship), participant characteristics (such as diagnostic criteria, mean baseline score, and age), intervention details (such as dose ranges, mean doses of study drugs, and concomitant or rescue medications, or both) and outcome measures.

Statistical analysis

According to study protocol, only randomised trials contributing to both primary outcomes were included in

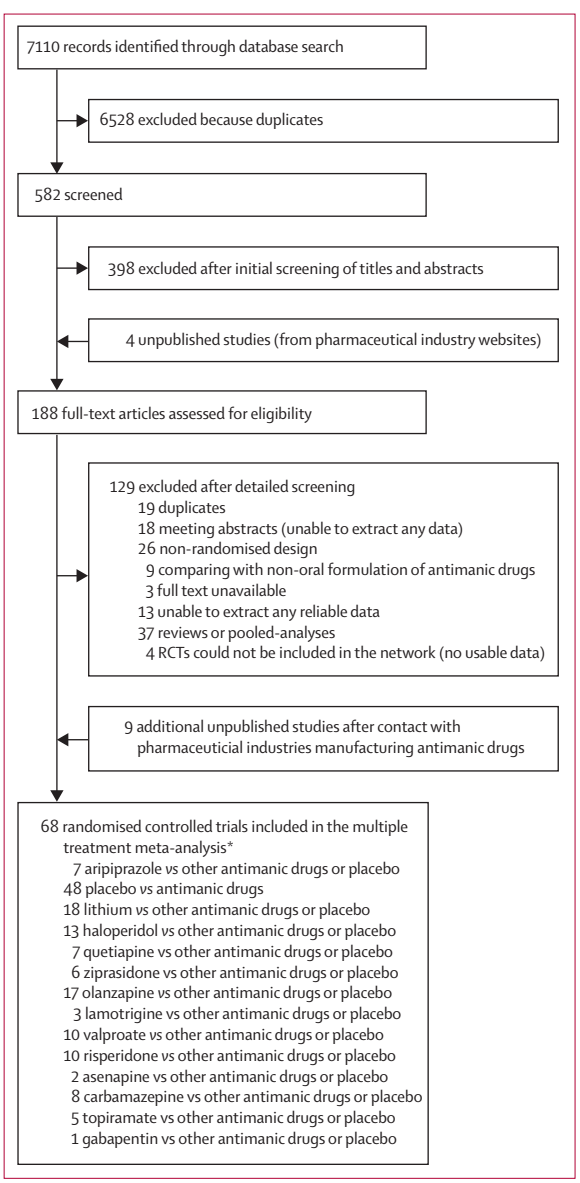

Figure 1: **Included and excluded studies**
*68 randomised trials correspond to 155 groups because three-group or four-group studies were included in this multiple-treatments meta-analysis.

the multiple-treatments meta-analysis. A priori, because paliperidone is the main active metabolite of risperidone, we decided to combine data for these two drugs for the primary analyses. Dichotomous outcomes were analysed with the total number of randomly assigned participants as the denominator. For the secondary analysis of efficacy measured as a binary outcome, outcomes for the missing participants were imputed, assuming that all missing participants did not respond to treatment. When data for drop-outs were carried forward and included in the assessment (last observation carried forward, LOCF), they were analysed with data as they were reported in the primary studies.

We produced 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, and sponsorship). For every pair-wise comparison between antimanic drugs, the standardised mean difference Hedges's adjusted g (SMD) was calculated as the effect size for continuous outcomes and the odds ratio (OR) was calculated for dichotomous outcomes, both with a 95% CI. We first did pair-wise meta-analyses by synthesising studies that compared the same interventions using a random-effects model[14] to incorporate the assumption that the different studies were estimating different, yet related, treatment effects.[15] We used visual inspection of the forest plots to investigate the possibility of statistical heterogeneity. This inspection was supplemented with, mainly, the I^2 statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error.[15] We calculated 95% CIs for I^2 tests, and we used a p value from a standard test for heterogeneity to assess evidence of its presence.[16]

For more on the **Bayesian models fitted and R functions** see http://www.mtm.uoi.gr/howtodoanmtm.html

For more on the **STATA software** see http://www.stata.com

For more on **R 2.11.1** see http://www.r-project.org

For more on **WinBUGS 1.4.3** see http://www.mrc-bsu.cam.ac.uk/bugs

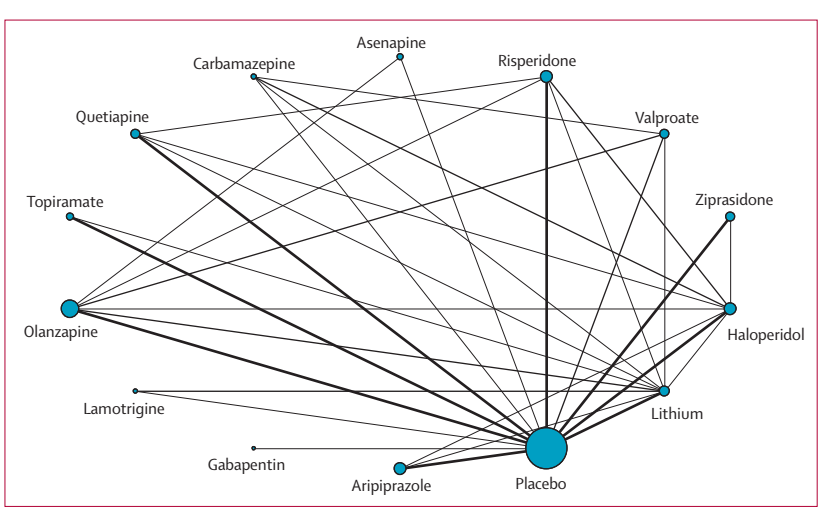

Figure 2: **Network of eligible comparisons for the multiple-treatments meta-analysis for efficacy**
The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomised participants (sample size). The networks of eligible comparisons for acceptability analysis dropout rate) and for efficacy as binary outcome are similar (webappendix pp 26–27).

Second, we did a random-effects multiple-treatments meta-analysis within a Bayesian framework[17,18] and we summarised the results using effect sizes and their credible intervals (CrI). The model fitted is the group-based model as described by Salanti and colleagues.[9] We calculated the probability for each antimanic drug to be the most effective (first-best) regimen, the second-best, the third-best, and so on, and presented the results graphically with rankograms.[19] To estimate inconsistency, we calculated the difference between indirect and direct estimates whenever indirect estimates could be constructed with a single common comparator.[20] Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CI excluding 0. We also fitted the model with and without the consistency assumptions and we compared the two models in terms of fit and parsimony.[21] In case of significant inconsistency, we investigated the distribution of clinical and methodological variables that we suspected might be potential sources of either heterogeneity or inconsistency in every comparison-specific group of trials.

Finally, we looked at comparative efficacies between the antimanic drugs and expressed these using placebo as reference. We present the results using several numerical and graphical methods.[19] Analyses were done in STATA 10.0 (pairwise meta-analysis and I^2 calculations), in R 2.11.1 (estimation of consistency, rankograms, and SUCRA graphs), and WinBUGS 1.4.3 (multiple-treatments meta-analysis models).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In total, we included 68 trials in the multiple-treatments meta-analysis (figure 1, webappendix pp 15–20 for references to included studies and study characteristics). 14 treatments were analysed: aripiprazole, asenapine, carbamazepine, valproate, gabapentin, haloperidol, lamotrigine, lithium, olanzapine, paliperidone, quetiapine, risperidone, topiramate, ziprasidone, and placebo. Most trials (54 [79%] of 68) 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 antimanic 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. Overall, 16 073 patients were randomly assigned to one of the 14 antimanic 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 (38%) of the 68 included studies. In terms of clinical characteristics, most 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; webappendix p 19). The overall quality of studies was rated as good, even though some studies did not record details about randomisation and allocation concealment and there were only few randomised trials at low risk of bias in every question-based entry (webappendix p 21).

Figure 2 shows the network of eligible comparisons for primary efficacy outcome of the multiple-treatments meta-analysis (the networks for dropouts and for efficacy

	Number of studies	Overall number of patients	Efficacy		Acceptability
			Standardised mean difference (95% CI)	Response rate OR (95% CI)	Dropout rate OR (95% CI)
Aripiprazole *vs*					
Haloperidol	2	679	0·05 (–0·10 to 0·20)	1·16 (0·76 to 1·77)	0·58 (0·25 to 1·35)
Lithium	1	315	–0·06 (–0·28 to 0·16)	1·09 (0·70 to 1·70)	1·07 (0·69 to 1·66)
Placebo	6	1959	–0·31 (–0·42 to –0·20)	1·75 (1·37 to 2·24)	0·86 (0·62 to 1·19)
Asenapine *vs*					
Olanzapine	2	774	0·22 (0·08 to 0·37)	0·68 (0·46 to 1·03)	2·04 (1·49 to 2·86)
Placebo	2	582	–0·42 (–0·59 to –0·24)	2·04 (1·20 to 3·45)	0·80 (0·56 to 1·14)
Carbamazepine *vs*					
Valproate	1	30	0·85 (0·10 to 1·60)	0·41 (0·09 to 1·92)	1·00 (0·16 to 5·88)
Haloperidol	3	70	–0·09 (–0·56 to 0·38)	0·80 (0·12 to 5·56)	0·81 (0·06 to 10·00)
Lithium	2	67	0·23 (–0·30 to 0·76)	..	0·81 (0·08 to 8·33)
Placebo	1	443	–0·50 (–0·69 to –0·30)	3·12 (2·08 to 4·76)	0·71 (0·49 to 1·04)
Gabapentin *vs*					
Placebo	1	118	0·32 (–0·08 to 0·72)	..	1·75 (0·83 to 3·70)
Haloperidol *vs*					
Aripiprazole	2	679	–0·05 (–0·20 to 0·10)	0·86 (0·56 to 1·32)	1·72 (0·74 to 4·00)
Carbamazepine	3	70	0·09 (–0·38 to 0·56)	1·25 (0·18 to 8·44)	1·23 (0·10 to 15·43)
Lithium	2	44	–1·11 (–1·89 to –0·33)	..	0·98 (0·09 to 11·11)
Olanzapine	2	578	–0·15 (–0·32 to 0·03)	1·14 (0·76 to 1·70)	1·86 (0·81 to 4·30)
Placebo	6	1285	–0·58 (–0·77 to –0·39)	2·27(1·54 to 3·33)	0·72 (0·50 to 1·06)
Quetiapine	1	201	–0·42 (–0·71 to –0·14)	1·71 (0·98 to 3·00)	0·52 (0·28 to 0·98)
Risperidone	3	433	0·02 (–0·17 to 0·21)	0·95 (0·60 to 1·51)	1·36 (0·72 to 2·57)
Ziprasidone	1	350	–0·51 (–0·72 to –0·29)	2·05 (1·33 to 3·14)	0·83 (0·55 to 1·28)
Lamotrigine *vs*					
Lithium	3	303	0·21 (–0·02 to 0·50)	0·76 (0·18 to 3·23)	1·01 (0·26 to 3·85)
Placebo	2	331	0·01 (–0·21 to 0·22)	..	1·25 (0·81 to 1·96)
Lithium *vs*					
Aripiprazole	1	315	0·06 (–0·16 to 0·28)	0·92 (0·59 to 1·43)	0·93 (0·60 to 1·45)
Carbamazepine	2	86	–0·23 (–0·76 to 0·30)	..	1·23 (0·12 to 12·54)
Valproate	2	132	–1·01 (–1·82 to –0·20)	1·86 (0·31 to 11·16)	1·71 (0·75 to 3·89)
Haloperidol	2	44	1·11 (0·33 to 1·89)	..	1·02 (0·09 to 11·32)
Lamotrigine	3	303	–0·21 (–0·50 to 0·02)	1·31 (0·31 to 5·58)	0·99 (0·26 to 3·79)
Olanzapine	3	210	–0·17 (–1·21 to 0·86)	0·76 (0·17 to 3·28)	2·16 (0·92 to 5·03)
Placebo	7	1366	–0·40 (–0·54 to –0·26)	2·33 (1·39 to 3·85)	0·91 (0·61 to 1·35)
Quetiapine	2	360	0·11 (–0·20 to 0·43)	0·68 (0·31 to 1·50)	2·24 (1·05 to 4·77)
Risperidone	1	30	0·67 (–0·07 to 1·40)	..	0·46 (0·04 to 5·75)
Topiramate	2	563	–0·52 (–0·70 to –0·33)	..	1·01 (0·58 to 1·76)

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	Number of studies	Overall number of patients	Efficacy		Acceptability
			Standardised mean difference (95% CI)	Response rate OR (95% CI)	Dropout rate OR (95% CI)
(Continued from previous page)					
Olanzapine *vs*					
Asenapine	2	774	−0·22 (−0·37 to −0·08)	1·46 (0·97 to 2·18)	0·49 (0·35 to 0·67)
Valproate	3	787	−0·20 (−0·34 to −0·05)	1·29 (0·80 to 2·10)	0·95 (0·68 to 1·34)
Haloperidol	2	578	0·15 (−0·03 to 0·32)	0·88 (0·59 to 1·32)	0·54 (0·23 to 1·23)
Lithium	2	210	0·17 (−0·86 to 1·21)	1·32 (0·30 to 5·88)	0·46 (0·20 to 1·09)
Placebo	9	2040	−0·44 (−0·56 to −0·32)	1·89 (1·45 to 2·50)	0·60 (0·44 to 0·82)
Risperidone	1	329	−0·04 (−0·25 to 0·18)	1·20 (0·78 to 1·86)	0·55 (0·33 to 0·90)
Ziprasidone	1	29	..	..	3·03 (0·48 to 20·00)
Placebo *vs*					
Aripiprazole	6	1959	0·31 (0·20 to 0·42)	0·57 (0·45 to 0·73)	1·16 (0·84 to 1·61)
Asenapine	2	582	0·42 (0·24 to 0·59)	0·49 (0·29 to 0·83)	1·25 (0·88 to 1·78)
Carbamazepine	1	443	0·50 (0·30 to 0·69)	0·32 (0·21 to 0·48)	1·40 (0·96 to 2·03)
Valproate	6	1229	0·16 (0·03 to 0·30)	0·46 (0·31 to 0·68)	1·26 (0·97 to 1·63)
Gabapentin	1	118	−0·32 (−0·72 to 0·08)	..	0·57 (0·27 to 1·20)
Haloperidol	6	1285	0·58 (0·39 to 0·77)	0·44 (0·30 to 0·65)	1·38 (0·94 to 2·01)
Lamotrigine	2	331	−0·01 (−0·22 to 0·21)	..	0·80 (0·51 to 1·24)
Lithium	7	1366	0·40 (0·26 to 0·54)	0·43 (0·26 to 0·72)	1·10 (0·74 to 1·63)
Olanzapine	9	2040	0·44 (0·32 to 0·56)	0·53 (0·40 to 0·69)	1·67 (1·22 to 2·29)
Quetiapine	6	1423	0·37 (0·24 to 0·51)	0·51 (0·40 to 0·64)	1·67 (1·14 to 2·45)
Risperidone	8	2167	0·50 (0·33 to 0·67)	0·47 (0·31 to 0·71)	1·85 (1·38 to 2·48)
Topiramate	5	1375	−0·06 (−0·17 to 0·06)	1·29 (0·72 to 2·29)	0·62 (0·47 to 0·82)
Ziprasidone	5	1567	0·24 (0·01 to 0·49)	0·68 (0·49 to 0·94)	1·08 (0·71 to 1·65)
Quetiapine *vs*					
Haloperidol	1	201	0·42 (0·14 to 0·71)	0·58 (0·33 to 1·02)	1·92 (1·02 to 3·57)
Lithium	2	360	−0·11 (−0·43 to 0·20)	1·47 (0·67 to 3·23)	0·45 (0·21 to 0·95)
Placebo	6	1423	−0·37 (−0·51 to −0·24)	1·96 (1·56 to 2·50)	0·60 (10·41 to 0·88)
Risperidone	1	388	0·17 (−0·03 to 0·37)	0·80 (0·53 to 1·19)	1·05 (0·64 to 1·71)
Risperidone *vs*					
Haloperidol	3	433	−0·02 (−0·21 to 0·17)	1·05 (0·66 to 1·67)	0·73 (0·39 to 1·39)
Lithium	1	30	−0·67 (−1·40 to 0·07)	..	2·17 (0·17 to 25·00)
Olanzapine	1	329	0·04 (−0·18 to 0·25)	0·83 (0·54 to 1·28)	1·82 (1·11 to 3·03)
Placebo	8	2167	−0·50 (−0·67 to −0·33)	2·13 (1·41 to 3·22)	0·54 (0·40 to 0·72)
Quetiapine	1	388	−0·17 (−0·37 to 0·03)	1·25 (0·84 to 1·89)	0·95 (0·58 to 1·56)
Topiramate *vs*					
Lithium	2	563	0·52 (0·33 to 0·70)	..	0·99 (0·57 to 1·72)
Placebo	5	1375	0·06 (−0·06 to 0·17)	0·78 (0·44 to 1·39)	1·61 (1·22 to 2·13)
Valproate *vs*					
Carbamazepine	1	30	−0·85 (−1·60 to −0·10)	2·41 (0·52 to 11·10)	1·00 (0·17 to 5·98)
Lithium	2	132	1·01 (0·20 to 1·82)	0·54 (0·09 to 3·22)	0·58 (0·26 to 1·33)
Olanzapine	3	787	0·20 (0·05 to 0·34)	0·78 (0·48 to 1·25)	1·05 (0·75 to 1·47)
Placebo	6	1229	−0·16 (−0·30 to −0·03)	2·17 (1·47 to 3·23)	0·79 (0·61 to 1·03)
Ziprasidone *vs*					
Haloperidol	1	350	0·51 (−0·29 to −0·72)	0·49 (0·32 to 0·75)	1·20 (0·78 to 1·82)
Olanzapine	1	29	..	..	0·33 (0·05 to 2·10)
Placebo	5	1567	−0·24 (−0·49 to −0·01)	1·47 (1·06 to 2·04)	0·93 (0·61 to 1·41)

OR=odds ratio. For efficacy as continuous outcome (standardised mean difference), positive values favour the first treatment. For efficacy (response rate), ORs higher than 1 favour the first treatment. For dropout rate, ORs lower than 1 favour the first treatment.

Table: **Summary estimates for efficacy (standardised mean difference and response rate) and dropout rates in meta-analyses of direct comparisons between pairs of antimanic drugs or placebo**

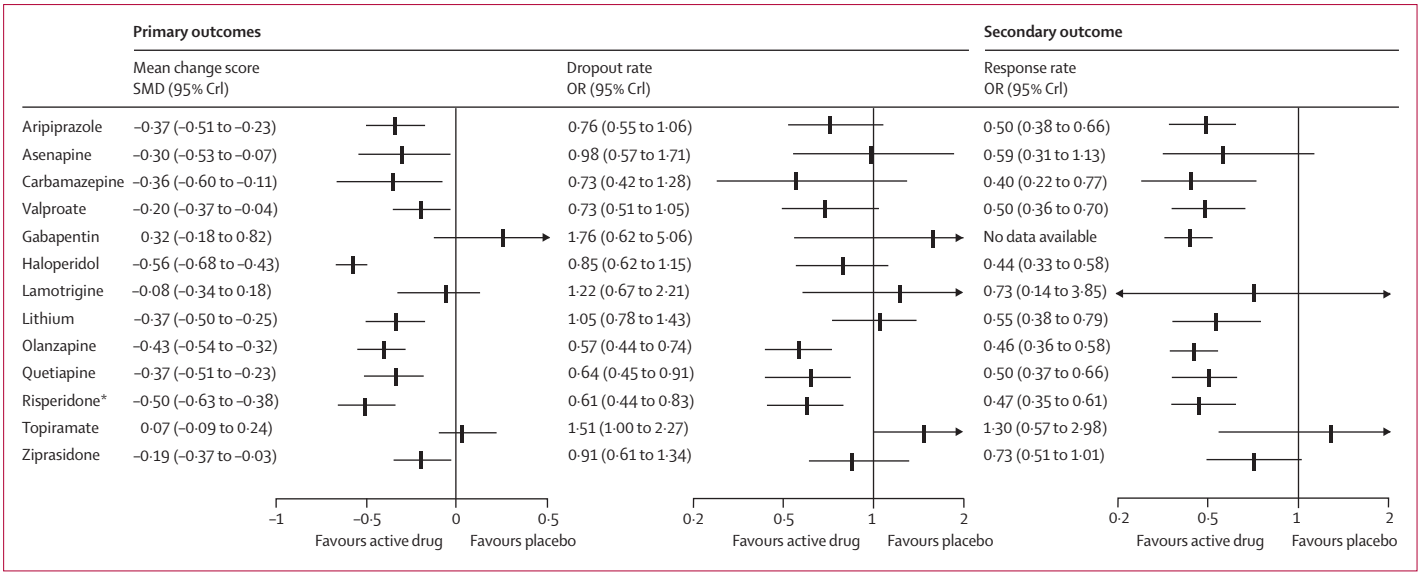

***Figure 3*: Forest plots of MTM results for efficacy outcomes and dropout rate with placebo as reference compound**
Standardised mean differences lower than 0 and ORs lower than 1 favour active compound. *As stated in the protocol, data from risperidone and paliperidone were merged. MTM= multiple-treatments meta-analysis. OR=odds ratio. CrI=credibilty interval.

as dichotomous outcome are essentially the same; webappendix pp 26–27). 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 antimanic drugs had at least one placebo-controlled randomised trial (table). 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 antimanic treatments compared with placebo, with the exception of topiramate and gabapentin (table). 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 (table). 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 (table).

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. 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 (webappendix p 28).

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 3). 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. 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 antimanic drugs, partly because it was often used as an active comparator. It was significantly more effective than lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate, ziprasidone, lamotrigine, topiramate, and gabapentin (figure 4). 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 antimanic drugs. In terms of dropout rate, haloperidol was significantly inferior to olanzapine; lithium inferior to olanzapine, risperidone, and

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)

Figure 4: **Efficacy and acceptability of all antimanic drugs according to multiple-treatments meta-analysis (primary outcomes)**
Drugs are reported in order according to efficacy ranking. 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. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values, and vice versa. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored. ARI=aripiprazole. ASE=asenapine. CBZ=carbamazepine. VAL=valproate. GBT=gabapentin. HAL=haloperidol. LAM=lamotrigine. LIT=lithium. OLZ=olanzapine. PBO=placebo. QTP=quetiapine. RIS=risperidone and paliperidone. TOP=topiramate. ZIP=ziprasidone. CrI=credibility interval. SMD=standardised mean difference.

quetiapine; lamotrigine inferior to olanzapine and risperidone; gabapentin inferior to olanzapine; topiramate inferior to many other antimanic treatments, such as haloperidol, olanzapine, risperidone, quetiapine, aripiprazole, carbamazepine, and valproate (figure 4; webappendix p 31).

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 (webappendix p 43). 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).[9] We could not identify any important variables that differed across comparison in those loops, but the number of included studies was very small in the three inconsistent loops (webappendix pp 44–46).

Exclusion of the studies adopting strategies for combination or augmentation treatment resulted in a total of 48 trials. The multiple-treatments meta-analysis model was refitted accordingly and no material change in either the groups of estimated SMDs or ORs was recorded (webappendix p 47). The secondary analysis including risperidone and paliperidone as separate drugs did not produce materially different results (webappendix p 67). 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 4 presents all antimanic 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 (see webappendix p 74 for the SUCRAs and

rankograms that show the distribution of the probabilities of every treatment being ranked at each of the possible 14 positions). 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 (figure 5). We ranked antimanic drugs according to these two dimensions (figure 6). 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 (webappendix p 93). 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. The three best treatments in terms of acceptability (risperidone, olanzapine, and quetiapine) and valproate scored better after adjustment for sponsorship.

Discussion

This study shows both statistically and clinically significant differences between treatments of acute mania. In terms of efficacy, haloperidol, risperidone, and olanzapine outperformed other drugs. In terms of drop-outs, olanzapine, risperidone, and quetiapine were better than haloperidol. These results have potential clinical implications that should be considered in the development of clinical practice guidelines.[2,4,22–24] Strikingly, 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.[8,17] 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

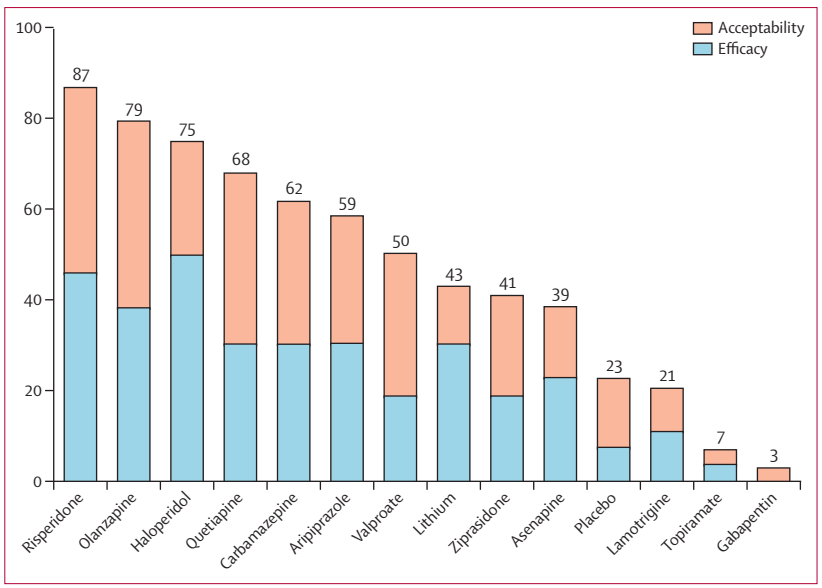

Figure 5: **Drugs ordered by their overall probability to be the best treatment in terms of both efficacy and dropout rate, showing the separate contributions to the overall scores of efficacy and dropout**
The cumulative percentages after normalisation (0–100) are shown in the key. Every drug was scored with points up to a maximum of 50 for efficacy and 50 for acceptability (overall maximum score 100), with data from rankograms and SUCRAs.

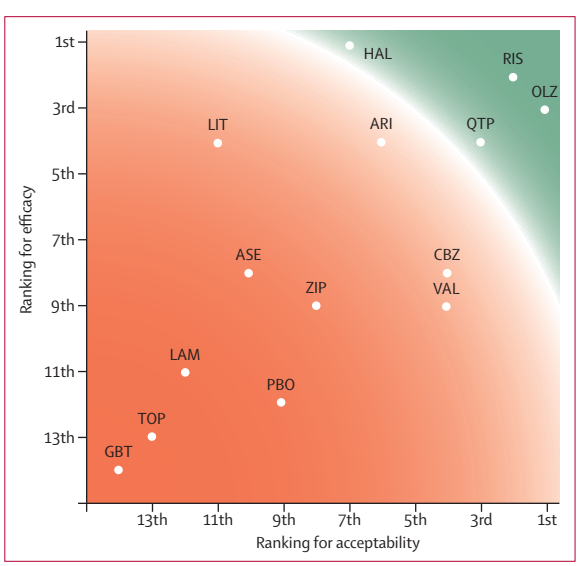

Figure 6: **Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate**
Red colour represents worst treatment and green represents best treatment in a qualitative approach. ARI=aripiprazole. ASE=asenapine. CBZ=carbamazepine. VAL=valproate. GBT=gabapentin. HAL=haloperidol. LAM=lamotrigine. LIT=lithium. OLZ=olanzapine, PBO=placebo. QTP=quetiapine. RIS=risperidone, TOP=topiramate. ZIP=ziprasidone.

versus placebo were modest. 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 drop-out rather than direct measures of patient's experience. The best treatment in terms of efficacy alone was haloperidol, although it was of low acceptability.

Despite the increasing number of randomised 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.[10,25] This low number might indicate specific difficulties associated with doing randomised 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 extrapyramidal 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 extrapyramidal side-effects are seen early in treatment even at this dose.[26] 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 extrapyramidal side-effects.[27] Haloperidol is one of the oldest available antimanic drugs and is still frequently used worldwide as standard treatment for mania, notwithstanding the known risk of inducing extrapyramidal 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 randomised trials is difficult, so those who are entered might not be fully representative of those who cannot be.[28]

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 stabilise 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[29] 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.[29] 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 stabilisers, possibly in combination and particularly with lithium, for long-term treatment.[30] Application of our results should take into account any limitations of the analysis and the specific clinical situation. However, overall, risperidone, olanzapine, and haloperidol seem to be the most effective evidence-based options for the treatment of manic episodes. Results from this study emphasise 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.

Contributors

AC, CB, GMG, and JRG conceived and designed the review and GS provided supervision. AC, JR, RB, MP, and SS identified and acquired reports of trials and extracted data. AC, RB, GMG, and JRG contacted authors of trials and pharmaceutical industries for additional information. AC, CB, GS, GMG, and JRG analysed and interpreted the data. GS and LMS provided statistical advice and input, did all the analysis related to the multiple-treatment meta-analysis, checked for statistical inconsistency, and interpreted the results. RB, JR, MP, SS, and LMS contributed to the interpretation of the data. AC and JRG drafted the report. GS and LMS helped draft the report. CB, GMG, SS, RB, JR, and MP critically reviewed the report. All authors saw and approved the final version of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interests

GMG holds or has held grants from Bailly Thomas charity, Medical Research Council, NIHR, Servier; has received honoraria from AstraZeneca, BMS, Lundbeck, Sanofi-Aventis, Servier, holds shares in P1vital ltd; has served on advisory boards for AstraZeneca, BMS, Boehringer Ingelheim, Cephalon, Janssen-Cilag, Lilly, Lundbeck, P1Vital, Servier, Shering Plough, Wyeth, and acted as an expert witness for Lilly and Servier. JRG currently receives research funding from UK Medical Research Council, UK Economic and Social Research Council, the National Institute for Health Research, and the Stanley Medical Research Institute. He was expert witness for Dr Reddys Laboratories and is Chief Investigator on the CEQUEL trial to which GlaxoSmithKline have contributed and supplied investigational drugs and placebo. AC, CB, MP, RB, JR, GS, LMS, and SS declare that they have no conflicts of interest.

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References

1 Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 1997; **349**: 1436–42.

2 NICE clinical guideline 38. Bipolar disorder: the management of bipolar disorder in adults, children 30 and adolescents, in primary and secondary care (2006). Available at http://www.nice.org.uk/CG038 (accessed July 28, 2011).

3 Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute 2 mania: a systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry* 2007; **64**: 442–55.

4 Goodwin GM; Consensus Group of the British Association for Psychopharmacology. Evidence-based guidelines for treating bipolar disorder: revised 2nd edn—recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2009; **23**: 346–88.

5 Correll CU, Sheridan EM, DelBello MP. Antipsychotic and mood stabilizer efficacy and tolerability in pediatric and adult patients with bipolar I mania: a comparative analysis of acute, randomized, placebo-controlled trials. *Bipolar Disord* 2010; **12**: 116–41.

6 Tamayo JM, Zarate CA Jr, Vieta E, Vázquez G, Tohen M. Level of response and safety of pharmacological monotherapy in the treatment of acute bipolar I disorder phases: a systematic review and meta-analysis. *Int J Neuropsychopharmacol* 2010; **13**: 813–32.

7 Yildiz A, Vieta E, Leucht S, Baldessarini RJ. Efficacy of antimanic treatments: meta-analysis of randomized, controlled trials. *Neuropsychopharmacology* 2011; **36**: 375–89.

8 Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005; **331:** 897–900.

9 Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008; **17**: 279–301.

10 Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* 2009; **373**: 746–58.

11 Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (eds). Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration, 2011. http://www.cochrane-handbook.org (accessed July 28, 2011).

12 Purgato M, Barbui C, Cipriani A. Assessing risk of bias in randomized controlled trials. *Epidemiol Psichiatr Soc* 2010; **19:** 296–97.

13 Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978; **133:** 429–35.

14 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.

15 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions version 5.0.2 (updated September, 2009). The Cochrane Collaboration, 2009. http://www.cochrane-handbook.org (accessed July 28, 2011).

16 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.

17 Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; **23**: 3105–24.

18 Ades AE, Sculpher M, Sutton A, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. *Pharmacoeconomics* 2006; **24**: 1–19.

19 Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011; **64**: 163–71.

20 Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. *J Clin Epidemiol* 2009; **62**: 857–64.

21 Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010; **29**: 932–44.

22 Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry* 2009; **10**: 85–116.

23 Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord* 2009; **11**: 225–55.

24 WHO. WHO model list of essential medicines 16th list. World Health Organization http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf (accessed Jan 19, 2011).

25 Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009; **373**: 31–41.

26 Kahn RS, Fleischhacker WW, Boter H, et al, EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 2008; **371**: 1085–97.

27 Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res* 2010; **123**: 225–33.

28 Licht RW. Limitations in randomised controlled trials evaluating drug effects in mania. *Eur Arch Psychiatry Clin Neurosci* 2001; **251**: S66–71.

29 Soares-Weiser K, Bravo Vergel Y, Beynon S, et al. A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder. *Health Technol Assess* 2007; **11**: 1–226.

30 Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* 2010; **375**: 385–95.