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REVIEW ARTICLE

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A systematic review and network meta-analysis of antimanic drugs for the treatment of acute mania used in Japan

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Abstract

This review aimed to clarify whether antimanic agents used in Japan are superior to placebo for the treatment of acute mania, based on reports of randomized controlled trials (RCTs) conducted in Japan and other East Asian countries. A literature search was conducted using the MEDLINE, PubMed, and Ichushi databases from their dates of inception to July 31, 2021, for studies written in English or Japanese with a primary diagnosis of bipolar I disorder, comparing any of the following active drugs to treat acute mania in adults: aripiprazole, carbamazepine, chlorpromazine, haloperidol, lithium, olanzapine, sultopride, timiperone, and zotepine. A random-effects network meta-analysis was performed within a frequentist framework. The quality of each included study was evaluated using the revised Cochrane risk-of-bias tool for randomized trials. The outcomes adopted were the response rate for efficacy and dropout rate for tolerability during 3 weeks from baseline. Eleven RCTs, totaling 1148 participants, were reviewed. The pooled odds ratio (OR) (±95% confidence interval [CI]) was calculated. Timiperone (OR = 4.53, CI 1.09–18.80), sultopride (OR = 3.76, CI 1.08–13.05), and aripiprazole (OR = 1.99, CI 1.22–3.24) were significantly more effective than placebo. Olanzapine (OR = 0.51, CI 0.29–0.90) was significantly superior in acceptability to placebo. The results showed no significant differences from placebo for carbamazepine, chlorpromazine, haloperidol, lithium, and olanzapine. These results suggest that noninferiority trials alone cannot always confirm the antimanic drug efficacy and that direct placebo-controlled trials are necessary to verify the antimanic efficacy of the drugs.

KEYWORDS
acute mania, antimanic drug, Japan, network meta-analysis, systematic review

INTRODUCTION

Before the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH-GCP) system was introduced, clinical trials for new drug approval in Japan had some unique characteristics, such as hesitation to use placebo, noninferiority designs using active controls, and traditional clinical guidelines for efficacy evaluation. The hesitation to use placebo as a control group came from the ethical consideration that it is preferable to use an established, active, approved drug as a control group. For this reason, until the ICH-GCP came into effect, the approval of antimanic drugs was mainly based on noninferiority clinical trials, in which one of the active approved drugs is used as a control agent.[1]

The progress of clinical trials in Japan is very slow for several reasons. One is the universal health insurance system, which in principal applies to all Japanese people. Because most medical costs

are covered by medical insurance, patients usually are not interested in participating in clinical trials. This often delays trials and produces the problem of "drug lags" between Japan and other countries.[1] The development of antimanic agents was no exception: numerous clinical trials were suspended due to insufficient enrollment or even did not start. The insufficient evidence for treatment with antimanic agents may derive from these situations.

The rapid assimilation of Japanese clinical trials into those of Western countries was largely due to the enactment of an ordinance of the Standards for the Conduct of Clinical Studies (Ministry of Health and Welfare Ordinance No. 28 dated March 27, 1997) in compliance with the ICH-GCP, an international guideline for pharmaceutical research and development. Before the deregulation process specified in Notifications No. 256 of the Pharmaceutical and Medical Safety Bureau (PMSB) and No. 265 of the Evaluation and Licensing Division, PMSB, both dated March 18, 1998, the data attached to applications for approval to manufacture and market drugs had to be in Japanese.[2] As a result, many randomized controlled trials (RCTs) from Japan conducted during the 20th century were not compared against placebo, not published in English, and not included in international meta-analyses.

Pharmacotherapy for acute mania has greatly progressed since the beginning of the 2000s. However, fewer drugs are approved in Japan than in other countries, and the majority are old antipsychotics, with concerns about their adverse effects on extrapyramidal symptoms and cognitive functions.[3] Even the treatment guidelines of the Japanese Society of Mood Disorders (JSMD) do not highly recommend these approved typical antipsychotics. They are classified as third-line "other recommended treatment." According to the JSMD guideline for the treatment of mania,[4,5] the most recommended treatment is a combination of lithium and atypical antipsychotics (olanzapine, aripiprazole, quetiapine, risperidone) when the manic condition is intermediate or severe, and lithium monotherapy in mild manic conditions. However, quetiapine and risperidone are unapproved for mania in Japan due to the lack of Japanese clinical trials for this purpose.

The purposes of this paper are to introduce RCTs that have been conducted in Japan but not published in English, clarify the efficacy of approved drugs against placebo obtained from a network meta-analysis, and discuss how the results of the current network meta-analysis are being applied to the current therapeutic guidelines for manic state in Japan.

METHODS

Review inclusion criteria

This review protocol was not registered. The inclusion criteria were randomized, double-blind trials comparing one active antimanic drug used in Japan with another active antimanic drug used in Japan or placebo as acute antimanic therapy for East Asian adults with a primary diagnosis of bipolar I disorder (manic or mixed episode) according to standardized diagnostic criteria. The participants were mainly Japanese. However, in the placebo-controlled clinical trials conducted to obtain approval of antimanic drugs in Japan, other East Asian patients are also included, therefore studies involving East Asian populations such as Korean, Chinese, and Taiwanese people were also included in this review, considering the similarity of common pharmacokinetic- and pharmacodynamic-related gene polymorphisms.[6] Only RCT articles written in English or Japanese were included.

The target drugs were nine antimanic drugs approved in Japan (excluding sodium valproate from 10 approved drugs) and zotepine (not approved as an antimanic but as an antipsychotic agent). The nine antimanic agents (approved year in parenthesis) were chlorpromazine (1955), levomepromazine (1959), haloperidol (1964), carbamazepine (1980), lithium (1980), timiperone (1987), sultopride (1989), sodium valproate (2002), olanzapine (2010), and aripiprazole (2012). No companies selling sodium valproate in Japan intended to conduct an RCT to obtain a new indication for the treatment of manic state because many generic drugs of this compound were already on the market as antiepileptic drugs when its antimanic effects first attracted attention in Japan. Therefore, the Japanese Society of Clinical Psychopharmacology submitted the "public knowledge-based application" to obtain approval of this compound as an anti-manic indication to the Ministry of Health and Welfare in Japan, based on its approval in France (1966) and the approval of sodium divalproex (comprising valproic acid and sodium valproate) in the United States (1995). It was approved by the Ministry of Health and Welfare in Japan in 2002 without Japanese RCT data. The antipsychotic agent zotepine was included in this analysis because (1) a noninferiority trial in the treatment of mania (Harada,[7]) showed its favorable effects and (2) the JSMD guidelines for the treatment of bipolar disorder recommend zotepine along with chlorpromazine, sultopride, haloperidol, levomepromazine, and timiperone for the third-line "other recommended treatment" of manic episodes.[4,5]

Search strategy

An electronic search was performed of MEDLINE, PubMed, and Ichushi (Japanese medical bibliographic database) from their dates of inception to July 31, 2021, to identify relevant studies. The search terms were bipolar disorder, mania, manic, or acute mania; and aripiprazole, carbamazepine, chlorpromazine, haloperidol, levomepromazine, lithium, olanzapine, sultopride, timiperone, or zotepine; and randomized controlled trial, RCT, randomized, double-blind, or blind; and Japan, Japanese, Korea, Korean, China, Chinese, Taiwan, Taiwanese, Asia, or Asian. K.I. and T.I. independently performed the literature search and reviewed all identified publications. Any disagreement was resolved by discussion with another reviewer.

Outcome measures

Acute treatment was defined as 3 weeks in both the efficacy and acceptability analyses. The proportion of patients who responded to

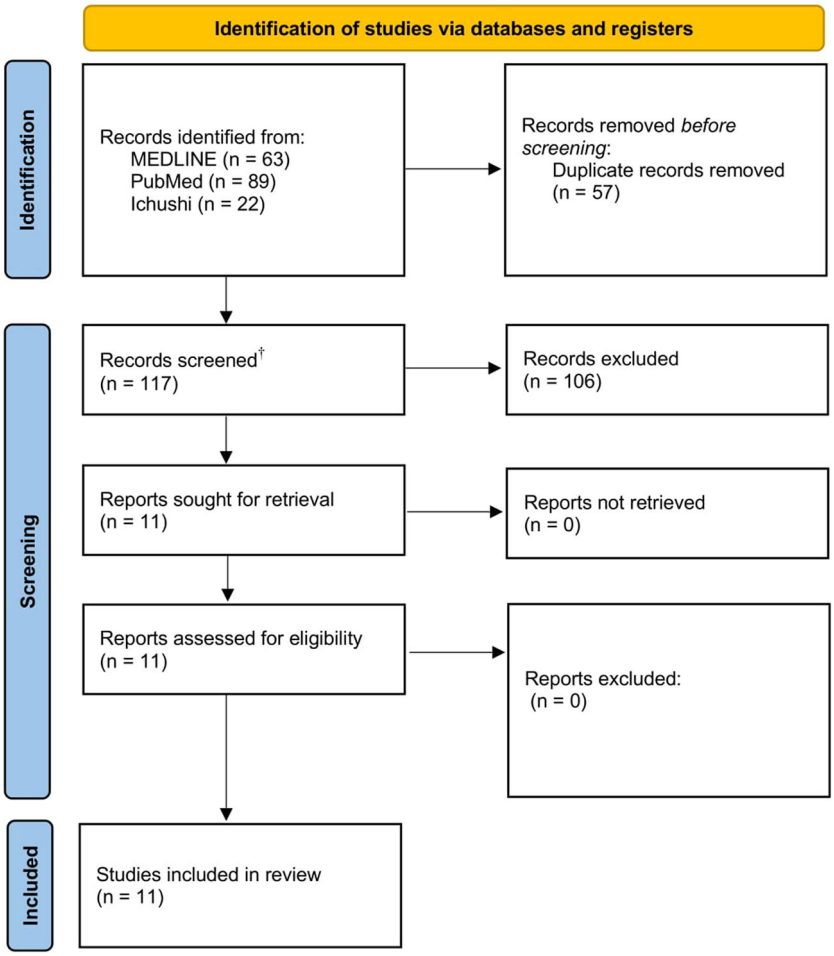

FIGURE 1 Flowchart of the literature search. †Trials that were presented in both Japanese and English were counted as one.

treatment and the rates of dropout (treatment discontinuation) were chosen as outcomes to represent, respectively, the most sensible and sensitive estimates of acute treatment efficacy and acceptability. The response to treatment was defined as the proportion of patients who showed moderate or marked improvement on the Clinical Psychopharmacology Research Group (CPRG) Rating Scales for Mania[8] or ≥50% reduction from baseline in total score on the Yang Mania Rating Scale (YMRS).[9] Treatment discontinuation 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 group.

Data extraction

K.I. and T.I. obtained the full text of all remaining articles and used the same eligibility criteria to determine which, if any, to exclude at this stage. We independently extracted the data and performed checks together to ensure their accuracy. The variables recorded were participant characteristics, diagnostic criteria for bipolar I disorder (manic or mixed episode), study design, details of the treatment component, treatment duration, control intervention, and outcome measures. No data required for meta-analysis were missing in the articles. The quality of each included study was evaluated by K.I. and T.I. using the revised Cochrane risk-of-bias tool for randomized trials.[10]

Statistical analysis

We produced descriptive statistics for trial and study population characteristics across all eligible trials. For every pair-wise comparison between antimanic drugs, the odds ratio (OR) was calculated for dichotomous outcomes, with a 95% confidential interval (CI). We conducted a random-effects network meta-analysis using the frequentist approach. We obtained the odds ratio for active treatments vs. placebo from dichotomous data. The network heterogeneity (heterogeneity standard deviation) and local heterogeneity (I^2) were calculated for all the investigated outcomes. We also used funnel plots to explore potential publication bias. Analyses used the netmeta package[11] in R (version 4.1.0).[12] Since the RCTs included in this study were nine two-arm studies (eight comparative studies and one crossover study) and one three-arm comparative RCT, the data analysis was performed by setting the "arm" to three groups and leaving the third arm blank for the two-arm RCTs. For a trial of a 3-weekly crossover design,[13] the results at the end of the initial

TABLE 1 Description of included studies

Study	Total participants	Region	Age (years)	% of female	Evaluation of outcome (weeks)	Intervention	Maximum dose (mg/day)	N[a]	Number of responders	Number of dropouts	Results	ClinicalTrials.gov identifier
Takahashi and colleagues[8,23]	77	Japan	13–65	48.1	3	LIT	1800	38 (1)	21	1	LIT > CPZ	
						CPZ	450	39 (3)	18	5		
Okuma and colleagues[19,20]	60	Japan	14–65	46.7	3	CBZ	900	32 (unknown)	17	6	CBZ≒CPZ	
						CPZ	450	28 (unknown)	12	5		
Inanaga and colleagues[24]	53	Japan	15–60	47.2	1	TIM	24	23 (0)	17	6	TIM≒HAL	
						HAL	70	30 (0)	17	7		
Kudo and colleagues[17]	77	Japan	13–64	42.9	3	SUL	1800	40 (1)	29	8	SUL≒HAL	
						HAL	18	37 (1)	22	6		
[21,22]	101	Japan	13–65	52.5	3	CBZ	1200	50 (1)	30	8	CBZ = LIT	
						LIT	1200	51 (3)	24	12		
Harada and colleagues[7]	88	Japan	16–65	54.5	4	ZTP	300	46 (3)	34	6	ZTP > LIT	
						LIT	1200	42 (2)	26	13		
Niufan and colleagues[18]	140	China	≥18	52.9	4	OLZ	20	69 (0)	60	6	OLZ > LIT	NCT00485680
						LIT	1500	71 (0)	52	15		
Chan and colleagues[15]	41	Taiwan	20–65	56.8[b]	4	ZTP[c]	450	21 (0)	16	2	ZTP≒HAL	
						HAL[c]	25	20 (0)	14	4		
Jeong and colleagues[25]	42	Korea	≥18	64.3	3	ARI	33	28 (0)	20	2	ARI≒HAL	
						HAL	12	14 (0)	11	1		
Katagiri and colleagues[13]	221	Japan	20–65	54.8	3	OLZ	20	104 (9)	53	32	OLZ≒HAL > PBO	NCT00129220
						HAL	10	20 (8)	13	12		
						PBO	–	97 (1)	43	45		
Kanba and colleagues[16]	247	Japan, other areas[e]	18–64	58.7	3	ARI	24	122 (15)	64	56	ARI > PBO	NCT00606281
						PBO		125 (13)	44	66		

Abbreviations: ARI, aripiprazole; CBZ, carbamazepine; CPZ, chlorpromazine; HAL, haloperidol; LIT, lithium carbonate; OLZ, olanzapine; PBO, placebo; SUL, sultopride; TIM, timiperone; ZTP, zotepine.

[a]Numbers in parentheses are those with mixed episodes.

[b]Including four dropouts before baseline assessment whose sex is not shown.

[c]Combination therapy with either LIT or sodium valproate (VPA).

[d]Combination therapy with VPA.

[e]Korea, China, Taiwan, Hong Kong, Malaysia, Philippine.

3-week period were included. Throughout the process, we adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) 2020 statement.[14]

RESULTS

In total, 11 trials were included in this network meta-analysis (Figure 1)[7,8,13,15–23,24,25] Of the 11 trials, only one was a three-grouped study,[13] and the remaining 10 were two-grouped. Two trials had a combination design, in which the antimanic drugs of interest were added to lithium and/or valproic acid.[15,25] Six trials conducted before 2000 used the CPRG Rating Scale for Mania[7,8,17,19–23,24] and the remaining five trials used the YMRS to assess response. According to our assessment, we identified potential risks of bias in all but three studies due to the lack of research registration (Table 1 and Figure 2). Other risks of bias included the involvement of pharmaceutical companies.

Table 1 summarizes the characteristics of the studies. Overall, 1148 participants were randomly assigned to one of the nine antimanic treatments or placebo and were included in this network meta-analysis. For a trial of a 3-weekly crossover design,[13] the results at the end of the initial 3-week period were included. For the three trials for which the results at week 3 were not available,[7,15,18] the results at week 4 were used. A trial in which the observation period was 1 week with injectable timiperone, the approved form for acute mania in Japan,[24] was also included in the analysis.

Figure 3 shows the network of eligible comparisons for response rate of the multiple-treatments meta-analysis (the networks for dropouts were essentially the same). No controlled trials including levomepromazine were found.

Figure 4 shows the forest plots of network meta-analysis results for response rate and dropout rate with placebo as the reference compound. Timiperone, sultopride, and aripiprazole were significantly more effective than placebo, whereas lithium, chlorpromazine, zotepine, carbamazepine, olanzapine, and haloperidol were not.

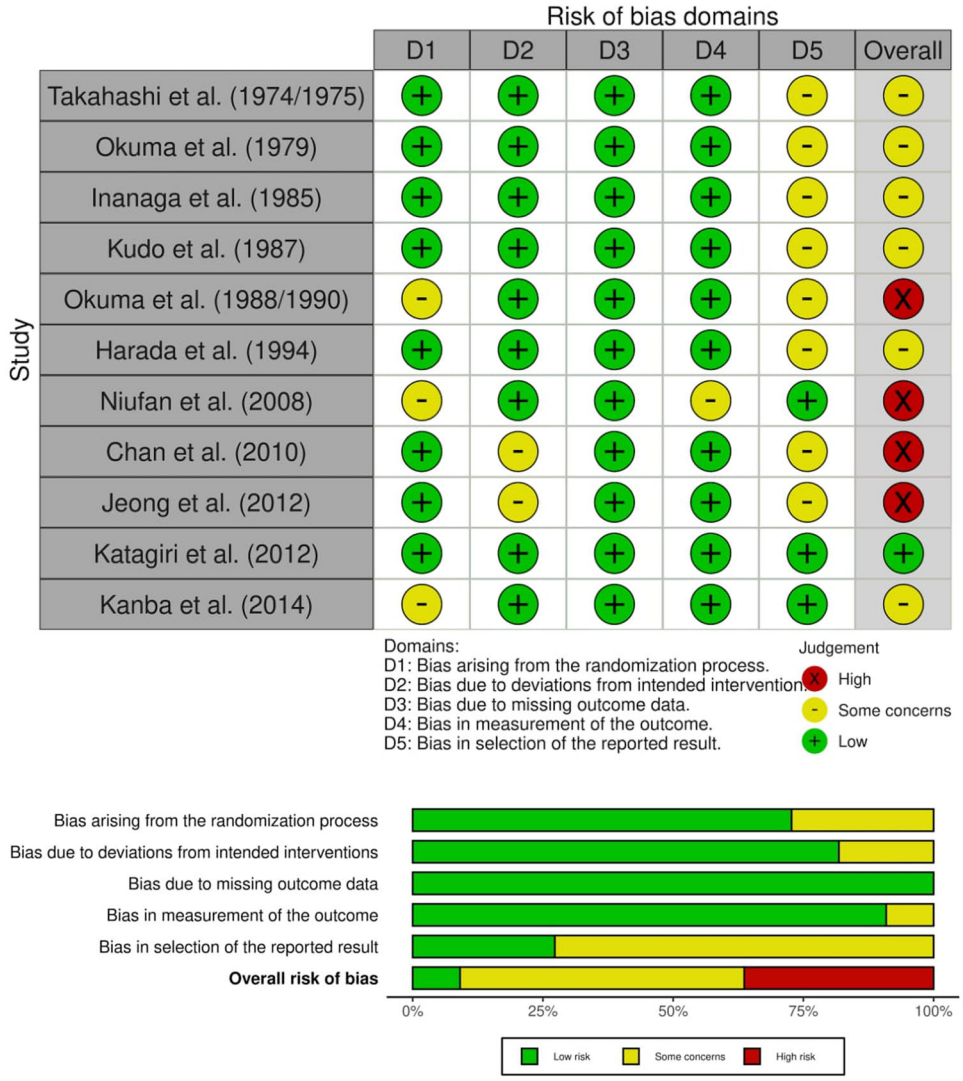

FIGURE 2 Risk of bias

Olanzapine was significantly superior in acceptability to placebo, whereas lithium was significantly inferior to zotepine and olanzapine. For dropouts, only olanzapine was significantly better than placebo. Neither statistical heterogeneity (I^2) nor publication bias (funnel plots) was evaluated because of the lack of studies with identical comparisons.

Figure 5 presents all antimanic drugs, ordered by their overall rank in terms of both efficacy and acceptability. In head-to-head comparisons, timiperone and sultopride had the highest number of significant differences compared with other antimanic drugs and were significantly more effective than lithium and chlorpromazine.

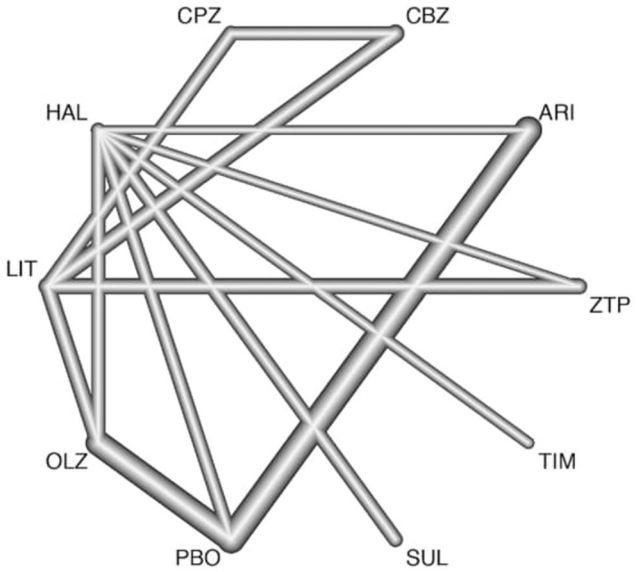

FIGURE 3 Network of eligible comparisons for the multiple-treatments meta-analysis for response rate. The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of every node is proportional to the number of randomized participants (sample size). ARI, aripiprazole; CBZ, carbamazepine; CPZ, chlorpromazine; HAL, haloperidol; LIT, lithium carbonate; OLZ, olanzapine; PBO, placebo; SUL, sultopride; TIM, timiperone; ZTP, zotepine

DISCUSSION

In the present network meta-analysis, three drugs—timiperone, sultopride, and aripiprazole—were significantly more effective than placebo. Other drugs approved for acute mania in Japan such as haloperidol, olanzapine, carbamazepine, lithium, and chlorpromazine were not shown to be significantly more effective than placebo.

Lithium is an effective maintenance treatment for bipolar disorder. However, evidence assessing the efficacy of lithium in the treatment of acute mania is less robust. A recent systematic review of lithium for acute mania concluded that more, rigorously designed, large-scale studies are needed to definitively conclude whether lithium is superior to other interventions in treating acute mania.[26] The JSMD guidelines for the treatment of bipolar disorder cite for intermediate or severe manic episodes lithium and atypical anti-psychotic drugs (olanzapine, aripiprazole, quetiapine, risperidone) in combination as the most recommended treatment.[4,5]

In the direct placebo-controlled trials, olanzapine showed a significant reduction in the total YMRS score compared to placebo, although the response rate used in the present network meta-analysis did not show a significant difference. The observations of the present network meta-analysis study show results not always consistent with existing knowledge of acute mania.[4,5]

In the previous meta-analysis of antimanic drugs for acute mania conducted by Cipriani and colleagues,[27] a total of 68 RCTs were included with 16,073 participants. In their meta-analysis, lithium, carbamazepine, olanzapine, aripiprazole, haloperidol, valproic acid, quetiapine, and risperidone showed significantly higher response rates versus placebo, and significantly lower dropout rates versus placebo were observed in olanzapine, quetiapine, and risperidone. The critical difference between their study and our current study is that theirs contained only the antimanic drugs for which at least one

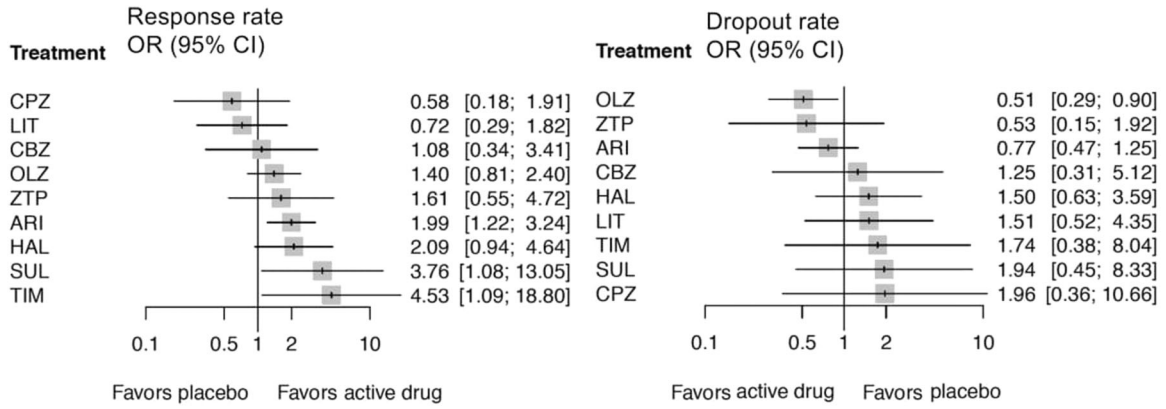

FIGURE 4 Forest plots of network meta-analysis results for response rate and dropout rate with placebo as reference compound. ARI, aripiprazole; CBZ, carbamazepine; CI, credibility interval; CPZ, chlorpromazine; HAL, haloperidol; LIT, lithium carbonate; OLZ, olanzapine; OR, odds ratio; SUL, sultopride; TIM, timiperone; ZTP, zotepine

TIM	0.90 (0.16–5.00)	1.16 (0.33–4.08)	2.27 (0.46–11.1)	3.25 (0.55–19.4)	3.42 (0.74–15.8)	1.39 (0.20–9.73)	1.74 (0.38–8.04)	1.15 (0.21–6.38)	0.89 (0.10–7.67)
1.21 (0.26–5.49)	SUL	1.29 (0.40–4.15)	2.53 (0.55–11.5)	3.62 (0.65–20.3)	3.81 (0.89–16.4)	1.55 (0.23–10.2)	0.52 (0.12–2.22)	1.29 (0.25–6.66)	0.99 (0.12–8.12)
2.17 (0.67–7.04)	1.80 (0.69–4.67)	HAL	1.96 (0.74–5.16)	2.81 (0.79–9.93)	2.95 (1.23–7.07)	1.20 (0.27–5.29)	1.50 (0.63–3.59)	1.00 (0.31–3.17)	0.76 (0.13–4.42)
2.25 (0.53–9.83)	1.89 (0.52–6.86)	1.05 (0.44–2.50)	ARI	1.43 (0.37–5.58)	1.51 (0.72–3.17)	0.61 (0.14–2.71)	0.77 (0.47–1.25)	0.51 (0.16–1.62)	0.39 (0.068–2.26)
2.81 (0.59–13.5)	2.34 (0.57–9.52)	1.30 (0.46–3.64)	1.23 (0.39–3.90)	ZTP	1.05 (0.32–3.49)	0.43 (0.11–1.64)	0.53 (0.15–1.92)	**0.35 (0.13–0.94)**	0.27 (0.053–1.40)
3.25 (0.78–13.5)	2.69 (0.77–9.39)	1.50 (0.67–3.35)	1.42 (0.70–2.90)	1.15 (0.42–3.14)	OLZ	0.41 (0.11–1.51)	**0.51 (0.29–0.90)**	**0.34 (0.13–0.85)**	0.26 (0.052–1.30)
4.20 (0.78–22.7)	3.48 (0.75–16.2)	1.94 (0.58–6.48)	1.84 (0.54–6.29)	1.49 (0.51–4.32)	1.29 (0.45–3.68)	CBZ	1.25 (0.31–5.12)	0.83 (0.33–2.10)	0.64 (0.20–2.02)
4.53 (1.09–18.8)	**3.76 (1.08–13.1)**	2.09 (0.94–4.64)	**1.99 (1.22–3.24)**	1.61 (0.55–4.72)	1.40 (0.81–2.40)	1.08 (0.34–3.41)	PBO	0.66 (0.23–1.91)	0.51 (0.094–2.76)
6.28 (1.34–29.4)	**5.21 (1.31–20.7)**	**2.90 (1.07–7.86)**	2.75 (0.99–7.66)	2.23 (0.99–5.04)	1.93 (0.87–4.28)	1.50 (0.76–2.96)	1.39 (0.55–3.50)	LIT	0.77 (0.21–2.87)
7.75 (1.40–42.9)	**6.43 (1.34–30.8)**	**3.58 (1.04–12.4)**	3.40 (0.96–12.0)	2.75 (0.92–8.26)	2.39 (0.81–7.05)	1.85 (0.85–4.01)	1.71 (0.52–5.58)	1.23 (0.59–2.58)	CPZ

Efficacy (response rate; OR with 95% CI) Acceptability (dropout rate; OR with 95% CI)

Treatment

FIGURE 5 Efficacy and acceptability of all antimanic agents according to multiple-treatments meta-analysis. Comparisons between treatments should be read from left to right: the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For efficacy, ORs higher than 1 favor the column-defining treatment. For acceptability, ORs lower than 1 favor the row-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underscored. ARI, aripiprazole; CBZ, carbamazepine; CI, credibility interval; CPZ, chlorpromazine; HAL, haloperidol; LIT, lithium carbonate; OLZ, olanzapine; OR, odds ratio; SUL, sultopride; TIM, timiperone; ZTP, zotepine

randomized placebo-controlled trial had been conducted. A 1.16- to 3.10-fold change in the calculated effect is reported, depending on whether placebo nodes are included in a network meta-analysis.[28] In the present meta-analysis, the placebo group was included in only two of the 11 trials, and their placebo response rates were relatively high, that is, 44% for Katagiri and colleagues[13] and 35% for Kanba and colleagues,[4] which could contribute to reducing the overall difference between active drugs and placebo. The present results do not always support the previous studies and clinical guidelines, implying that recent analytical techniques such as network meta-analysis would not substitute for direct placebo-controlled clinical trials and that direct comparison with placebo is necessary to verify the drugs' significant efficacy.

The results of this study must be interpreted in the context of some limitations of the analysis and the specific clinical situation. First, the limited number of clinical trials made definite conclusions about this outcome difficult. Because this study required all 11 papers to establish a network (Figure 3), it was impossible to perform subgroup analyses, such as a cumulative analysis for a wide range of study publication years. Neither statistical heterogeneity (I^2) nor publication bias (funnel plots) was evaluated because of the lack of studies with identical comparisons. Placebo-controlled trials directly demonstrating efficacy have been conducted only for aripiprazole and olanzapine, not for the other compounds. Second, most of the trials included in this study were conducted before the establishment of the World Health Organization's International Clinical Trials Registry Platform (ICTRP),[29] therefore screening for publication bias or reporting bias was not possible. Third, only RCT articles written in English or Japanese were included. RCT articles written in Korean and Chinese should have been included in addition to English and Japanese. Finally, acceptability was based on rates of dropout. Although the reasons for dropout may have included specific unwanted adverse effects, toxic effects, or loss of personal or social functioning or quality of life due to sedative effects, other reasons for dropout that are unrelated to acceptability, such as moving or loss of transport for attending the clinical study, may have also been included.

Nevertheless, this study has several strengths. First, we focused on studies conducted with genetically homogeneous Asian people, mainly Japanese, Korean, and Chinese. For example, the cytochrome P450 2D6 (CYP2D6) genotype had a substantial clinical effect on risperidone and aripiprazole exposure.[30] The proportion of poor metabolizers of CYP2D6 has been estimated at 7%–10% among European Caucasians and 1% of East Asians.[6] Considering results from similar populations to Japan is thus preferred. Second, introducing well-designed Japanese clinical trials to the world is worthwhile. These RCTs were conducted strictly to obtain approval from the Ministry of Health, Labor, and Welfare of Japan for antimanic agents. Under the approval rule in Japan until March 2000, these RCTs had to be published in Japanese, therefore most were not

published in English but exclusively in Japanese. Finally, this network meta-analysis includes all RCTs conducted in Japan to obtain approval for antimanic agents.

In conclusion, the current network meta-analysis, which included nine noninferiority trials and two direct placebo-controlled trials, found no significant differences from placebo for a total of five drugs. These results suggest that noninferiority trials alone cannot always confirm the drug efficacy and that direct placebo-controlled comparative trials are essential to verify it.

AUTHOR CONTRIBUTIONS

Kanako Ishizuka and Toshiya Inada conceived and designed the review, identified and acquired reports of trials, extracted data, analyzed and interpreted the data, and wrote the manuscript. Toshiya Inada had full access to all the data in the study and takes responsibility for the integrity of the data along with the accuracy of the data analysis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data analyzed in this study are summarized in Table 1 and the original papers are listed in the references.

ETHICS APPROVAL STATEMENT

Not applicable.

PATIENT CONSENT STATEMENT

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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