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Review

REVIEW

Mood Stabilizers and Antipsychotics for Acute Mania: Systematic Review and Meta-Analysis of Augmentation Therapy vs Monotherapy From the Perspective of Time to the Onset of Treatment Effects

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Abstract

Background: Existing meta-analytic evidence on bipolar mania treatment has revealed that augmentation therapy (AUG) with antipsychotics and mood stabilizers is more effective than monotherapy. However, the speed of the onset of treatment effects and subsequent changes in risk/benefit are unclear.

Methods: We searched the Cochrane CENTRAL, MEDLINE, and EMBASE databases until January 2021. Our primary outcomes were response and tolerability. We set 3 time points: 1, 3, and 6 weeks after randomization.

Results: Seventeen studies compared AUG therapy and MS monotherapy (comparison 1), and 8 studies compared AUG therapy and antipsychotics monotherapy (comparison 2). In comparison 1, AUG therapy resulted in significantly more responses than monotherapy, with an odds ratio of 1.45 (95% confidence interval [CI]: 1.17 to 1.80) at 3 weeks and 1.59 (95% CI: 1.28 to 1.99) at 6 weeks. Significant improvement was observed in the first week with a standardized mean difference of –0.25 (95% CI: –0.38 to –0.12). In comparison 2, AUG therapy was significantly more effective than monotherapy, with an odds ratio of 1.73 (95% CI: 1.25 to 2.40) at 3 weeks and 1.74 (95% CI: 1.11 to 2.73) at 6 weeks. Significant improvement was observed in the first week with an standardized mean difference of –0.23 (95% CI: –0.39 to –0.07). Regarding tolerability, there was no significant difference between AUG therapy and monotherapy at 3 and 6 weeks in both comparisons.

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Conclusions: Early AUG therapy should be considered, as it has shown efficacy from weeks 1 to 6, although attention to side effects is necessary for acute mania treatment.

Keywords: Antipsychotics, bipolar disorder, manic state, mood stabilizers, systematic review and meta-analysis

Introduction

Significant changes have occurred in the treatment of bipolar disorder (BD) over the past 20 years, with second-generation antipsychotics (SGA) in large measure taking the place of traditional mood stabilizers (MS) (Rhee *et al.*, 2020). Due to the risks of mortality and marked impairment in social or occupational functioning, manic episodes often require prompt hospitalization to protect the individual from negative consequences and control impulsivity, aggression, irritability, agitation, and psychotic symptoms (Tohen and Grundy, 1999). Given the severe impact and rapid onset of manic symptoms in many patients, prompt and effective symptom control is a primary treatment goal (Oral 2005; Garlow 2008).

Pharmacological treatment is the standard of care for adults with acute manic episodes. Almost all guidelines for the treatment of acute mania in BD recommend monotherapy with antipsychotics (AP) or MS as the first option, and augmentations of AP and MS are required for an immediate effect (Grunze *et al.*, 2009; Goodwin *et al.*, 2016; Malhi *et al.*, 2020). In Japanese guidelines, lithium monotherapy is recommended for mild manic conditions, and augmentation of lithium and AP (olanzapine, aripiprazole, quetiapine, and risperidone) is recommended for intermediate or severe manic conditions (Kanba *et al.*, 2013). As rapid control is often required in clinical settings, a combination of 2 MS or augmentation of an MS and an AP is widely used by Japanese experts (Sakurai *et al.*, 2020). In clinical practice, however, many cases of BD are treated with polypharmacy, and an evidence-practice gap exists, which should be filled by considering the type of BD and history of suicide attempts (Fornaro *et al.*, 2016).

To date, 3 meta-analyses (Scherk *et al.*, 2007; Smith *et al.*, 2007; Ogawa *et al.*, 2014) have shown that adding AP to MS is more effective than MS alone. These include 8, 6, and 19 randomized controlled trials (RCTs) published in 2014, respectively, but several RCTs on this topic have been conducted since then. Therefore, an update on this topic is required. In previous meta-analyses, assessing the effects of acute mania at 3 weeks was common. In practice, however, even faster improvement in the manic state (e.g., 1 week into treatment) is required. In addition, evidence of its efficacy and safety needs to be examined after 3 weeks. Therefore, the purpose of the present study was to update the evidence and compare the efficacy and safety of augmentation therapy for MS and AP and their monotherapies over several treatment periods. We examined the speed of onset of treatment effects and subsequent changes in risk/benefit over several time points. We performed subgroup analyses for each AP to allow more precise clinical decision-making. "Combination therapy" refers to the concomitant use of drugs in the same category, while "augmentation therapy" refers to the concomitant use of drugs in different categories. However, in previous studies, these terms have often been used in a confusing manner. Because this study focuses on the combination of MS and AP, the terminology is unified as augmentation (AUG).

MATERIALS AND METHODS

This study was conducted as part of the development of an updated version of the Guidelines for the Treatment of Bipolar Disorder by the Japanese Society of Mood Disorders (Kanba *et al.*, 2013). The key clinical questions agreed to in advance for the development of these Japanese guidelines are provided in the table (supplementary file 1). A few modifications have been made to this study. In the guidelines, the search was limited to SGA, but in this study, the search was broader and included first-generation APs. Also, there was no restriction for age. Initially, lamotrigine was included but was then excluded because it is not indicated for acute manic phase treatment in Japan or worldwide.

Criteria for Considering Studies for This Review

All double-blind RCTs comparing the AUG of AP and MS with monotherapy in the acute treatment of bipolar mania were included. Essentially, all participants were diagnosed with manic BD using the following operationalized criteria: Feighner criteria (Feighner *et al.*, 1972), Research Diagnostic Criteria (Spitzer *et al.*, 1978), DSM-III, DSM-III-R, DSM-IV, DSM-5 (American Psychiatric Association), and ICD-10 (World Health Organization). Patients with mixed BD and schizoaffective disorder were included. Patients with bipolar depression were excluded from this study. Three MS were included: lithium carbonate, sodium valproate, and carbamazepine. The AP included amisulpride, aripiprazole, asenapine, chlorpromazine, clozapine, flupentixol, fluphenazine, haloperidol, levomepromazine, olanzapine, paliperidone, perazine, perphenazine, prochlorperazine quetiapine, risperidone, sulpiride, ziprasidone, zotepine, and zuclopenthixol. Age was not restricted. Electronic searches of Cochrane CENTRAL (until January 7, 2021), MEDLINE (until January 7, 2021), and EMBASE (until January 11, 2021) were conducted. The search terms for each database are listed in the supplementary Data (supplementary file 2). This is an update of Ogawa *et al.* (2014)'s previous meta-analysis comparing AUG therapy with either monotherapy. In the previous version, the search period was July 1, 2014. To prevent search omissions, we added EMBASE to the search and conducted the search for the entire period.

Types of Outcome Measures

The following outcomes were predetermined by agreement with the guidelines committee (supplementary file 1):

1. Response defined by each study;
2. Remission defined by each study;
3. Improvement of manic symptoms on a continuous scale;
4. Dropout from the study due to side effects;
5. Incidence of side effects;
6. Dropout from the study due to any reason; and
7. Incidence of depressive symptoms

To date, there is no evidence on the duration of AUG therapy for mania. Because we were interested in the differences in the number of days until the outcome occurred, we collected data at 3 time points:1 week (hyper-acute phase), 3 weeks (2 to 4 weeks is acceptable) (acute phase), and 6 weeks (over 5 weeks is acceptable) (sub-acute phase) after randomization. Our primary

benefit outcome was the response defined by each study, and the primary harm outcome was dropout due to side effects. All other outcomes were considered secondary outcomes.

Selection of Studies and Data Extraction

Two authors independently examined the titles and abstracts of all publications obtained using the search strategy described above. If either review author decided to include, the full paper was obtained as secondary screening and examined by the 2 review authors to identify studies that met the review criteria. If there was disagreement regarding the eligibility of the study, a third review author was consulted. Two independent review authors extracted data from each trial and assessed the risk of bias using Cochrane Collaboration's risk of bias tool. This tool includes random sequence generation, allocation concealment, the integrity of blinding of participants and study personnel, the integrity of blinding of outcome assessments, completeness of outcome data, selective reporting, and other biases. Disagreements were resolved in consultation with a third reviewer.

Data Analysis

A pairwise meta-analysis was performed to compare all AUG therapies with monotherapies. Two comparisons were performed. Comparison 1: MS + AP AUG therapy vs MS alone; Comparison 2: MS + AP AUG therapy vs AP alone. A random-effects model was used to integrate the data using Review Manager (RevMan) 5.4. Results of dichotomous outcomes were presented as odds ratios (OR), and continuous outcomes were presented as standardized mean differences (SMD) with 95% confidence intervals (CI). For studies that did not describe the SD of the data, Furukawa's method was used to impute the missing SD (Furukawa *et al.*, 2006). In cases where only the continuous outcome was presented and the results for the binary outcome were not stated, the mean and SD of the continuous outcome were used to calculate the approximation for the binary outcome (Furukawa *et al.*, 2005). Heterogeneity was first checked by visual inspection of the forest plots and then examined using the I^2 statistic. For publication bias, when the number of studies was more than 10, funnel plots were created using RevMan 5.4, and Egger's test and meta-regression were conducted using STATA/SE 17.0.

Sensitivity Analysis and Meta-Regression

Sensitivity analysis was performed, excluding studies with different definitions of response or remission. Studies that started prescribing MS and AP simultaneously at the start of treatment were excluded. A meta-regression analysis was performed for age and year of publication.

Subgroup Analysis

The results were presented separately for each drug subgroup. The participants' medical conditions might include mixed episodes as well as manic episodes. We also performed subgroup analyses for each episode. Heterogeneity was examined using I^2 statistics.

RESULTS

The flow diagram of the study is shown in Figure 1. We found 15 studies (Delbello *et al.*, 2002; Sachs *et al.*, 2002; Tohen *et al.*, 2002; Yatham *et al.*, 2003; Sachs *et al.*, 2004; Yatham *et al.*, 2007; Tohen *et al.*, 2008; Vieta *et al.*, 2008; Houston *et al.*, 2009; Berwaerts *et al.*, 2011; Sachs *et al.*, 2012a. 2012b; Szegedi *et al.*, 2012; Loze *et al.*, 2013; Sahraian *et al.*, 2018) comparing AUG therapy and MS monotherapy and 6 studies (Biederman *et al.*, 1979; Möller *et al.*, 1989; Chou *et al.*, 1999; Müller-Oerlinghausen *et al.*, 2000; Bourin *et al.*, 2014; Moosavi *et al.*, 2014) comparing AUG therapy and AP monotherapy. In addition, 2 studies (Garfinkel *et al.*, 1980; Xu *et al.*, 2015) compared AUG therapy, MS monotherapy, and AP

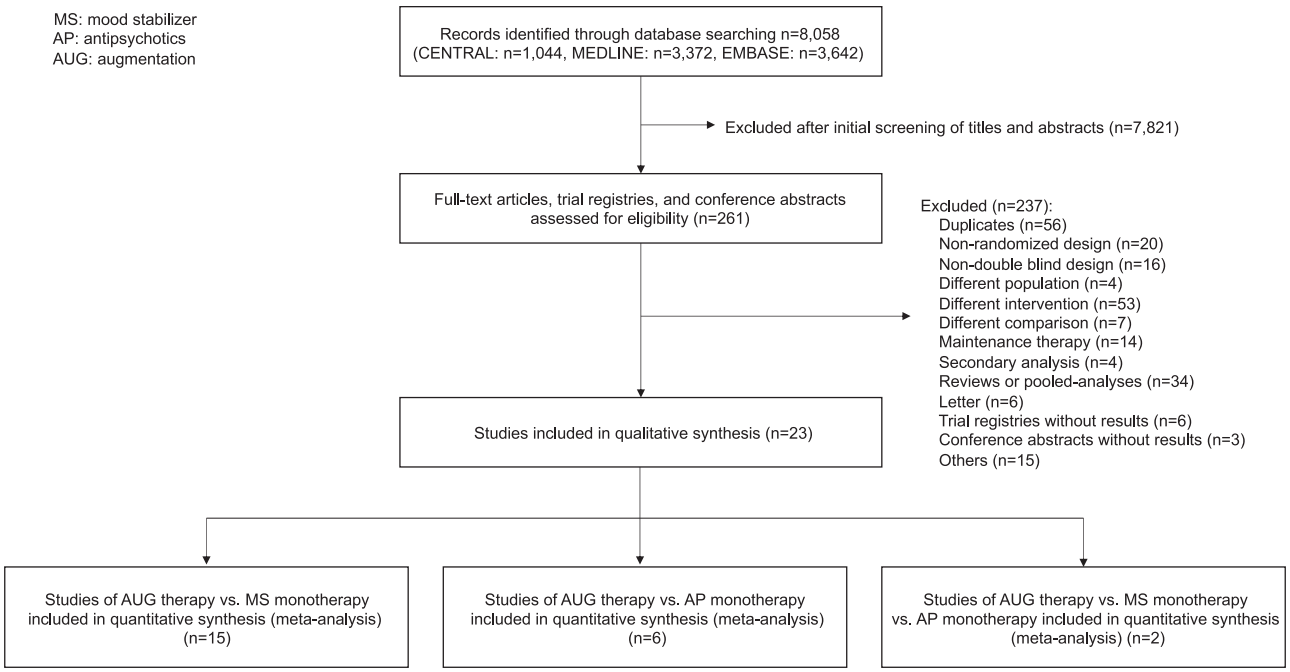

Figure 1. Study flow diagram.

monotherapy in 3 arms. We divided these 2 studies into 2 comparisons and added them to each comparison. Details of the included studies are presented in Table 1A (AUG vs MS monotherapy) and 1B (AUG vs AP monotherapy). One study (Sachs *et al.*, 2002) comparing AUG therapy and AP monotherapy had 3 arms: haloperidol, risperidone, and placebo. The number of participants in the placebo arm was divided in half, and each group was compared with haloperidol and risperidone. Finally, we included 17 studies (n = 3658 in total) to compare AUG therapy and MS monotherapy and 8 studies (n = 730 in total) to compare AUG therapy and AP monotherapy. Compared with a previous meta-analysis by Ogawa *et al.* (2014), 5 new studies (3 and 2 more studies to compare AUG therapy and MS therapy and AUG therapy and AP monotherapy, respectively) were included in this study. In all studies included in this review, the response to manic symptoms was defined as the total number of patients who had a reduction in manic severity by at least 50% of the baseline value of the Young Mania Rating Scale (Young *et al.*, 1978). As for remission of manic symptoms, the definition was a Young Mania Rating Scale score of 12 or less, except in 1 study (Moosavi *et al.*, 2014), which defined remission as the absence of any DSM-IV manic symptom criterion.

Comparison 1: AUG Therapy vs MS Monotherapy

***Study Characteristics*—**Seventeen RCTs were included in this analysis. Ten studies were conducted in settings where lithium or valproate was used without strictly separating them. Most of them used SGAs in AUG arms. Two trials used haloperidol (Garfinkel *et al.*, 1980; Sachs *et al.*, 2002). Except for 1 study on adolescents (Delbello *et al.*, 2002), all the remaining studies were on adults. For weeks 3 and 6, both binary and continuous outcomes, or one of them, are shown. Since no binary outcome was described at week 1, we only showed a continuous outcome. Forest plots of the main results are shown (Figure 2–4). All forest plots are shown in supplementary file 3 (page 1–5; comparison 1.1–1.15).

Primary outcomes

Response defined by each study (Figure 2)—Thirteen studies reported outcomes at 3 weeks. AUG therapy was significantly more effective than monotherapy, with an OR of 1.45 (13 studies, 95% CI: 1.17 to 1.80). Moderate heterogeneity was also observed ($I^2 = 38\%$). At 6 weeks, the efficacy of the AUG treatment persisted, with an OR of 1.59 (10 studies, 95% CI: 1.28 to 1.99), with no heterogeneity.

Dropout from the study due to side effects (Figure 3)—For the 3-week outcome, 6 studies were included in the analysis. No significant difference was observed between AUG therapy and monotherapy (6 studies, OR: 1.56; 95% CI: 0.90 to 2.71). The direction of the point estimates varied among studies. For week 6, as with the results for week 3, there were no significant differences between the 2 therapies (9 studies, OR: 1.61, 95% CI: 0.97 to 2.67).

Secondary Outcomes

Benefit outcomes—As for remission, AUG therapy was significantly more effective than monotherapy at both 3 and 6 weeks, with an OR of 1.43 (95% CI: 1.11 to 1.83) and 1.48 (95% CI: 1.17 to 1.86), respectively. As for the improvement of manic symptoms on a continuous scale, AUG therapy was significantly more effective than monotherapy at 1, 3, and 6 weeks, with an SMD of –0.25 (12 studies, 95% CI: –0.38 to –0.12), –0.26 (15 studies, 95% CI: –0.38 to –0.15), and –0.30 (11 studies, 95% CI: –0.41 to –0.19), respectively (Figure 4). The efficacy of the drug was observed in the first week and gradually increased over time.

Harm outcomes—The incidence of side effects was significantly higher in the AUG therapy both at 3 and 6 weeks, with OR of 2.17 (4 studies, 95% CI: 1.54 to 3.07) and 1.49 (6 studies, 95% CI: 1.09 to 2.03), respectively. As for dropouts from the study due to any reason, there was no significant difference between AUG therapy and monotherapy both at 3 and 6 weeks, with an OR of 0.80 (6 studies, 95% CI: 0.47 to 1.36) and 1.02 (11 studies, 95% CI: 0.83 to 1.26), respectively. Additionally, there was no significant difference both at 3 and 6 weeks in the incidence of depressive symptoms with an OR of 0.83 (2 studies, 95% CI: 0.39 to 1.74) and 0.96 (7 studies, 95% CI: 0.57 to 1.63), respectively.

***Publication Bias*—**No publication bias was observed in any comparison. Funnel plots are shown in supplementary File 3 (pages 46–51).

***Sensitivity Analysis and Meta-Regression*—**Few studies mentioned details about treatment before randomization, but in 2 studies (Tohen *et al.*, 2008; Xu *et al.*, 2015), no psychotropic medications were prescribed before randomization. In other words, in these 2 studies, the patient may have already received some treatment before randomization. When these 2 studies were excluded, the results were similar to when they were included with OR: 1.41 (95% CI: 1.17 to 1.68) and 1.65 (95% CI: 1.32 to 2.06) for response at 3 and 6 weeks, respectively, and with OR 1.39 (95% CI: 0.73 to 2.62) and 1.71 (95% CI: 0.98 to 2.99) for dropout due to side effects at 3 and 6 weeks, respectively. In the meta-regression analysis, the effect sizes were significantly related to the publication year in the responses at 3 and 6 weeks, and the reported effect sizes were smaller over the years in the cumulative meta-analysis. However, age was not related to the effect size (supplementary File 3, pages 53–55).

***Subgroup Analysis*—**In all comparisons, the results are presented separately for each drug subgroup. As for the response, which is our primary outcome, there was a significant difference in quetiapine with an OR of 1.81 (2 studies, 95% CI: 1.19 to 2.76) at week 3 and in olanzapine with an OR of 1.73 (3 studies, 95% CI: 1.07 to 2.77) and quetiapine with an OR of 2.40 (2 studies, 95% CI: 1.39 to 4.12) at week 6. Owing to the small number of studies on individual drugs, it was not possible to present further details of the profiles of each drug. There was nothing noteworthy regarding the heterogeneity of the drugs. Details of the other outcomes are shown in supplementary File 3 (pages 9–21). The results for the 3 subgroups, "manic only," "manic or mixed," and "mixed only" are shown in supplementary File 3 (pages 33–40). No notable differences were observed between the subgroups.

Comparison 2: AUG Therapy vs AP Monotherapy

***Study Characteristics*—**Eight RCTs were included in this analysis. Haloperidol was used in 5 studies, and haloperidol and perazine were used in 1 study. The remaining 3 studies used olanzapine, risperidone, and quetiapine. Forest plots of the main results are shown in Figures 5–7. All forest plots are shown in supplementary file 3 (page 6–8; comparison 2.1–2.13).

Table 1A. Characteristics of included studies

Comparison 1. MS plus AP augmentation therapy versus MS monotherapy

Study, year, area	Population	Study duration (weeks)	Mood stabilizers, mean dose (range)	Antipsychotics, mean dose (range)	N	YMRS Baseline mean (SD)	Mean age (SD)	Prior treatment before randomization
Berwaerts 2011 Cross-continental	DSM-IV, bipolar I, manic or mixed	6	lithium/valproate	paliperidone 8.1 (3–12) mg	150	27.0 (5.5)	40.0 (10.9)	MS
			lithium/valproate	placebo	150	27.0 (5.0)	40.0 (11.2)	MS
Delbello 2002 North America	DSM-IV, bipolar I, manic or mixed	6	valproate	quetiapine 432.0mg	15	33.9	14.1 (2.0)	MS
			valproate	placebo	15	30.7	14.5 (2.0)	MS
Garfinkel 1980 North America	Feighner, manic only	3	lithium	haloperidol 24.2mg	7	NA	37 (6.1)	others
			lithium	placebo	7	NA	41.5 (5.8)	others
Houston 2009 North America	DSM-IV, bipolar I, mixed only	6	valproate	olanzapine 14.6 (5–20) mg	101	21.4 (4.8)	38.6 (11.2)	MS
			valproate	placebo	101	20.4 (4.0)	38.5 (11.1)	MS
Loze 2013 Cross-continental	DSM-IV, bipolar I, manic or mixed	12	lithium/valproate	aripiprazole (10–30) mg	181	NA	44.4 (12.1)	MS
			lithium/valproate	placebo	189	NA	44.9 (13.0)	MS
NCT00183443 North America	DSM-IV, bipolar I, manic only	12	valproate	quetiapine (up to 800) mg	26	NA	33.1 (9.8)	others
			valproate	placebo	24	NA	39.5 (11.6)	others
Sachs 2002 North America	DSM-IV, bipolar I, manic or mixed	3	lithium/valproate Li: 1041mg/ Va: 1436mg	haloperidol 6.2mg	53	27.3 (6.1)	(median) 44.0	MS
			lithium/valproate Li: 1052mg/ Va: 1418mg	risperidone 3.8mg	52	28 (5.5)	(median) 41.0	MS
			lithium/valproate Li: 1077mg/ Va: 1312mg	placebo	51	28 (6.1)	(median) 42.1	MS
Sachs 2004 North America	DSM-IV, bipolar I, manic or mixed	3	lithium/valproate	quetiapine 504 (200–800) mg	91	31.5	39.6	MS
			lithium/valproate	placebo	100	31.1	41.3	MS
Sachs 2012 North America	DSM-IV, bipolar I, manic or mixed	3	lithium/valproate Li: 1012mg/ Va: 1296mg	ziprasidone 90.1 (20–80) mg	458	27.2 (5.6)	41.4 (11.1)	MS
			lithium/valproate	placebo	222	26.0 (5.3)	41.5 (10.3)	MS
Sahraian 2018 Asia	DSM-IV, bipolar I, manic only	8	lithium 725mg	aripiprazole 16.3 (up to 20) mg	29	25.4 (4.9)	34.1 (11.6)	MS
			lithium 700mg	placebo	27	26.3 (3.3)	39.4 (14.2)	MS
Szegedi 2012 Cross-continental	DSM-IV, bipolar I, manic or mixed	12	lithium/valproate	asenapine 11.8 (10–20) mg	159	28.0 (5.7)	39.6 (11.7)	MS
			lithium/valproate	placebo	167	28.2 (5.8)	39.0 (12.0)	MS
Tohen 2002 North America	DSM-IV, bipolar I, manic or mixed	6	lithium/valproate	olanzapine 10.4 (5–20) mg	229	22.3 (5.4)	40.7 (11.2)	MS
			lithium/valproate	placebo	115	22.7 (5.2)	40.4 (10.8)	MS
Tohen 2008 Cross-continental	DSM-IV, bipolar I, manic or mixed	6	carbamazepine 617.5mg	olanzapine 26.9 (fixed 30) mg	58	27.9 (6.5)	40.1 (10.7)	none

Table 1A. Continued

Comparison 1. MS plus AP augmentation therapy versus MS monotherapy

Study, year, area	Population	Study duration (weeks)	Mood stabilizers, mean dose (range)	Antipsychotics, mean dose (range)	N	YMRS Baseline mean (SD)	Mean age (SD)	Prior treatment before randomization
Vieta 2008 Europe	DSM-IV, bipolar I, manic or mixed	6	carbamazepine 717.3mg	placebo	60	26.6 (5.6)	41.3 (11.4)	none
			lithium/valproate Li: 1160mg/ Va: 1225mg	aripiprazole 19.0 (15–30) mg	253	23.2 (5.7)	42.2 (11.6)	MS
			lithium/valproate Li: 985mg/ Va: 1179mg	placebo	131	23.0 (4.9)	41.7 (12.1)	MS
Xu 2015 Asia	DSM-IV, bipolar I, manic only	4	valproate 1080mg	olanzapine 13.1 (5–20) mg	37	34.3 (6.1)	31.7 (8.2)	none
			valproate 1530mg	placebo	38	34.4 (9.1)	30.2 (7.8)	none
Yatham 2003 Cross-continental	DSM-IV, manic or mixed	3	lithium/valproate/ carbamazepine	risperidone 4.0 (1–6) mg	75	29.3 (5.8)	37.0	MS
			lithium/valproate/ carbamazepine	placebo	76	28.3 (6.0)	42.0	MS
Yatham 2007 Cross-continental	DSM-IV, bipolar I, manic only	6	lithium/valproate	quetiapine 423 (up to 800) mg	106	32.3	38.9	MS
			lithium/valproate	placebo	105	32.6	40.1	MS

DSM; Diagnostic and Statistical Manual of Mental Disorders, ICD; International Statistical Classification of Diseases and Related Health Problems, RDC; Research Diagnostic Criteria, MS; mood stabilizer, AP; antipsychotics, YMRS; Young Mania Rating Scale, Li; lithium, Va; valproate, NA; not applicable

Primary Outcomes

Response defined by each study (*Figure 5*)—Four studies reported outcomes at 3 weeks. AUG therapy was significantly more effective than monotherapy, with an OR of 1.73 (4 studies, 95% CI: 1.25 to 2.40). Heterogeneity was not observed ($I^2=0\%$). At 6 weeks, the efficacy of the AUG treatment persisted, with an OR of 1.74 (2 studies, 95% CI: 1.11 to 2.73), with no heterogeneity.

Dropout from the study due to side effects (*Figure 6*)—Three studies were included in the analysis. There was no significant difference between the AUG therapy and monotherapy (OR: 2.19; 95% CI: 0.48 to 10.09). Heterogeneity was not observed ($I^2=0\%$). For week 6, 3 studies reported; however, 2 had zero events in any arm. There was no significant difference between AUG therapy and monotherapy (OR: 0.47; 95% CI: 0.17 to 1.27) in only 1 study (Bourin *et al.*, 2014).

Secondary Outcomes

Benefit outcomes—As for remission, AUG therapy was significantly more effective than monotherapy both at 3 and 6 weeks, with an OR of 1.71 (4 studies, 95% CI: 1.21 to 2.42) and 1.73 (2 studies, 95% CI: 1.12 to 2.67), respectively. As for the improvement of manic symptoms on a continuous scale, AUG therapy was significantly more effective than monotherapy at 1 and 3 weeks, with an SMD of –0.23 (4 studies, 95% CI: –0.39 to –0.07) and –0.40 (4 studies, 95% CI: –0.64 to –0.16), respectively. At 6 weeks, the difference was no longer significant (SMD, –0.20, 95% CI: –0.86, 0.46); however, only 1 old first-generation AP study was included in this comparison, and it was not possible to conclude on ineffectiveness (Figure 7).

Harm outcomes—The incidence of side effects was not reported at 3 weeks and was significantly higher in the AUG therapy at 6 weeks with an OR of 1.84 (2 studies, 95% CI: 1.23 to 2.75). As for dropouts from the study for any reason, there was no significant difference between AUG therapy and monotherapy both at 3 and 6 weeks, with an OR of 1.29 (3 studies, 95% CI: 0.53 to 3.19) and 0.85 (2 studies, 95% CI: 0.28 to 2.60), respectively. There was no significant difference at 6 weeks in the incidence of depressive symptoms with an OR of 2.13 (1 study, 95% CI: 0.19 to 23.69).

Sensitivity Analysis—In 2 studies (Biederman *et al.*, 1979; Xu *et al.*, 2015), patients were not treated with any MS or AP before randomization. When these 2 studies were excluded, the results were similar to when they were included with OR 1.73 (95% CI: 1.22 to 2.44) and 1.81 (95% CI: 1.12 to 2.93) for response at 3 and 6 weeks, respectively. Due to the small number of included studies, no meta-regression analysis was performed. One study (Moosavi *et al.*, 2014) with a different definition of remission was excluded from the analysis; however, the results were the same.

Subgroup Analysis—In all comparisons, the results are presented separately for each AP subgroup (supplementary File 3, page 22–27) and MS subgroup (supplementary File 3, page 28–32). No apparent heterogeneity was observed in the AP subgroup. In most comparisons, as the number of included studies was only 1, we do not know anything definitive about the differences by the AP subgroup. Similarly, in the MS subgroup, no apparent heterogeneity was observed between lithium and valproic acid. Only 1 study on carbamazepine showed no differences from lithium or valproate. The results for the 3 subgroups, "manic

Table 1B. Characteristics of included studies

Comparison 2. MS plus AP augmentation therapy versus AP monotherapy

Study, year, area	Population	Study duration (weeks)	Mood stabilizers, mean dose (range)	Antipsychotics, mean dose (range)	N	YMRS Baseline mean (SD)	Mean age (SD)	Prior treatment before randomization
Biederman 1979 Asia	RDC, schizoaffective, manic only	5	lithium 1440mg	haloperidol 28.0mg	21	NA	32.3	Only short courses of AP were permitted
			placebo	haloperidol 35.0mg	18	NA	29.6	Only short courses of AP were permitted
Bourin 2014 Cross-continental	DSM-IV, bipolar I, manic or mixed	6	lithium 1085.5mg	quetiapine 623.1 (400–800) mg	173	29.9 (5.4)		AP
			placebo	quetiapine 669.1 (400–800) mg	183	30.0 (5)		AP
Chou 1999 North America	DSM-III-R, bipolar I, manic only	3	lithium	haloperidol 15.9mg	22	NA	34.6 (11.5)	others
			placebo	haloperidol 14.5mg	19	NA	34.6 (11.5)	others
Garfinkel 1980 North America	Feighner, manic only	3	lithium	haloperidol 24.2mg	7	NA	37.0 (6.1)	others
			placebo	haloperidol 28.0mg	7	NA	37.0 (5.3)	others
Moller 1989 Europe	ICD-9 and RDC, mania or schizomanic syndrome	3	carbamazepine 600mg	haloperidol 24.0mg	11	NA	34.0 (13.2)	others
			placebo	haloperidol 24.0mg	9	NA	32.8 (13.6)	others
Moosavi 2014 Asia	DSM-IV, bipolar I, manic only	7	valproate (800–1200) mg	risperidone	25	NA	24.0 (1.1)	others
			placebo	risperidone	23	NA	26.0 (1.3)	others
Muller-Oerlinghausen 2000 Europe	ICD-10, manic only	3	valproate	haloperidol/perazine 8.2mg	69	30.9 (8.1)	39.0 (12.0)	AP
			placebo	haloperidol/perazine 10.4mg	67	30.9 (8.4)	37.0 (11.0)	AP
Xu 2015 Asia	DSM-IV, bipolar I, manic only	4	valproate 1080mg	olanzapine 13.1mg	37	34.3 (6.1)	31.7 (8.2)	none
			placebo	olanzapine 16.3mg	39	34.6 (7.0)	30.9 (9.1)	none

DSM; Diagnostic and Statistical Manual of Mental Disorders, ICD; International Statistical Classification of Diseases and Related Health Problems, RDC; Research Diagnostic Criteria, MS; mood stabilizer, AP; antipsychotics, YMRS; Young Mania Rating Scale, NA; not applicable

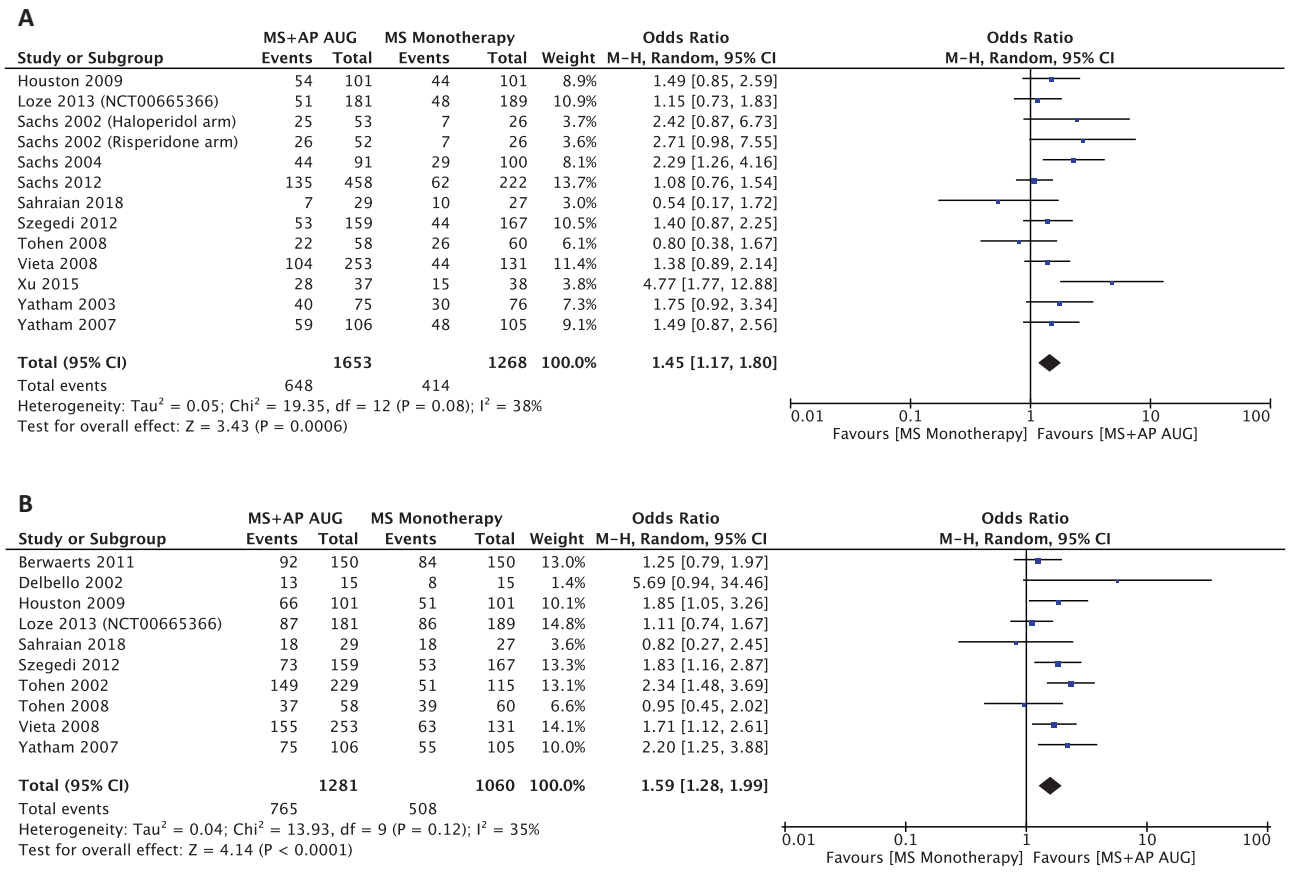

Figure 2. Response defined by each study (augmentation therapy [AUG] therapy vs MS monotherapy).

only," "manic or mixed," and "manic or schizomanic" are shown in supplementary File 3 (pages 41–45). No notable differences were observed between the subgroups.

Risk of Bias

The results of the evaluation using Cochrane's risk of bias tool are shown in supplementary File 3 (page 52). There have been no studies of notably low quality.

Discussion

The main findings of the present study, including 23 RCTs, can be summarized as follows: comparison of AUG therapy and MS monotherapy (Comparison 1) showed that AUG therapy was more effective than MS monotherapy. The effects began to appear in week 1 and continued until week 6. There was no difference in dropout rates between the 2 groups; however, the incidence of side effects was higher with AUG therapy. Comparison of AUG therapy and AP monotherapy (Comparison 2) showed that AUG therapy was more effective than AP monotherapy. The effects began to appear at week 1 and persisted for 6 weeks. There was no difference in dropout rates between the 2 groups; however, the incidence of side effects was higher in the AUG therapy group at 6 weeks.

Previous reviews comparing AUG therapy with monotherapy showed that AUG therapy was more effective than monotherapy, and our results are in line with these findings. However, when looking at the number of weeks of outcomes, Smith (Smith *et al.*, 2007) prioritized outcomes at the longest time point of the individual RCTs and combined data from 3 to 8 weeks. In Scherk's study (Scherk *et al.*, 2007), the time points of outcome assessments were mostly 3 weeks. Ogawa et al. (Ogawa *et al.*, 2014) set the time point for the primary outcome to 3 weeks (range, 2–6 weeks) and did not distinguish the outcomes between weeks 3 and 6. Thus, previous studies have mainly focused on the results of the third week, and the results from longer studies are not shown separately. However, in the treatment of manic states, where a rapid onset of effects is expected, the implications of weeks 3 and 6 are clinically different. Treatment options should be considered earlier than for other disorders. The Canadian Network for Mood and Anxiety Treatments guideline (Yatham *et al.*, 2018) recommends that efficacy and tolerability be determined after 1–2 weeks to consider treatment options. The World Federation of Societies of Biological Psychiatry (Grunze *et al.*, 2009) guideline states that there are insufficient data on whether to use the augmentation from the beginning and that there is no statement on when to start using the augmentation. Likewise, the National Institute for Health and Care Excellence (Kendall *et al.*, 2014) and the International College of Neuropsychopharmacology (Tohen, 2017) guidelines do not state when to initiate AUG therapy. Among the above reviews, only Ogawa's study assessed outcomes at week 1, and there was a significant difference in AUG therapy vs MS monotherapy. However, since only 1 study was included in AUG therapy vs AP monotherapy, no significant difference was found. In the current study, we were able to combine the results of several studies and show the efficacy of AUG therapy in both comparison 1 and comparison 2 at week 1. Yildiz (Yildiz *et al.*, 2011) pointed out that AP have a faster onset of effect than MS do. Cipriani et al. (Cipriani *et al.*, 2011) stated that a network meta-analysis of 68 acute RCTs showed that AP were more

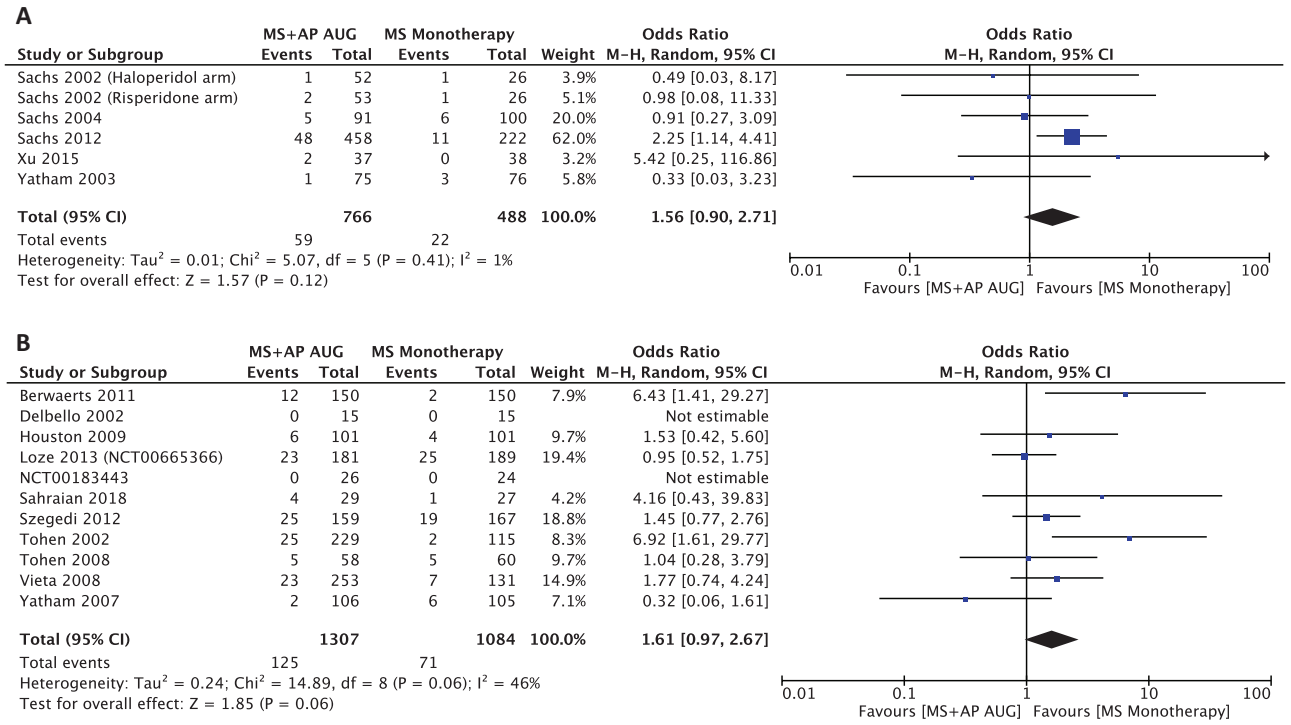

Figure 3. Dropout from the study due to side effects (augmentation therapy [AUG] vs mood stabilizer [MS] monotherapy).

effective than MS. The Canadian Network for Mood and Anxiety Treatments guideline (Yatham *et al.*, 2018) states that it does not necessarily mean that monotherapy must be administered before AUG therapy, and the decision is left to the therapist. Based on the results of this study, AUG therapy should be considered as early as possible. As for harm outcomes, Ogawa et al. (Ogawa *et al.*, 2014) pointed out that there was no difference in dropout for any reason in both comparisons 1 and 2. In our study, the results were the same; however, the incidence of side effects was higher with AUG therapy than with monotherapy. Furthermore, in this study, the effect of AUG therapy was maintained for up to 6 weeks, while the dropout rate was found to be similar to that of monotherapy, which could be a rationale for continuing the combination for up to 6 weeks. However, since the incidence of side effects was higher with AUG therapy, it is recommended that the combination be continued with careful monitoring of side effects. The more recent the year of publication, the smaller the effect size. This is similar to the trend observed in antipsychotic studies on schizophrenia (Leucht *et al.*, 2017; Leucht *et al.*, 2019). For this reason, Leucht reported an increase in placebo response over the past decades. The same may be true for BD.

The limitations of the present study are as follows. First, if the difference between AUG therapy and monotherapy is strictly compared, people who have received no treatment need to be assigned to both groups from the beginning. However, in most studies, some psychotropic drugs were already administered before random assignment, and another drug was added. Therefore, it cannot be denied that they may have been affected by the medication administered before randomization. In this study, we performed a sensitivity analysis by removing 2 studies in which no psychotropic medications were prescribed before randomization, but there was no difference in the results. Second, in the previous review, the 3-week and 6-week outcomes were combined without distinction. In the current review, we separated them, thus reducing the number of studies and the types of drugs included in each analysis. This may have reduced detection power. However, the purpose of the current study was to show the results at each of these time points. It is hoped that there will be more RCTs on this topic in the future and that more studies will be included in the next systematic review. Third, in comparison 1, individual APs could be represented separately in the subgroup analysis, but MS could not, because many of the original RCTs were not limited to 1 mood stabilizer (e.g., lithium or valproate). The lithium, valproate, and carbamazepine profiles are likely to be different. Although previous studies have indicated that there are no significant differences in their efficacy and tolerability (Yildiz *et al.*, 2011), there were differences among the 3 drugs when viewed in a network meta-analysis (Cipriani *et al.*, 2011). In the future, when there are more applicable RCTs, network meta-analyses will be needed to determine differences in the effects of these drug augmentations, and it may become clear which drugs have a faster onset of effect.

The strengths of the present study would include the following. First, the number of included studies increased because we researched for all periods, including Embase. Therefore, we were able to combine outcomes that had not been meta-analyzed in previous studies. Second, we were able to show outcomes at 3 time points (hyper-acute, acute, and sub-acute phases) for the first time, to our knowledge. As a result, AUG therapy was found to be effective from the hyper-acute to sub-acute phase, indicating the effectiveness of the drugs in each phase. Patients who have passed these phases do not end their treatment but move on to the maintenance phase. In the maintenance phase, AUG therapy is more effective than monotherapy (Kishi *et al.*, 2021). We were able to show a continuous treatment path from the hyper-acute to the maintenance phase. Third, we showed not only the efficacy of adding AP to MS but also that adding MS to AP is more effective in AUG therapy from the first week. Because AP have a faster onset of effect than MS (Yildiz *et al.*, 2011),

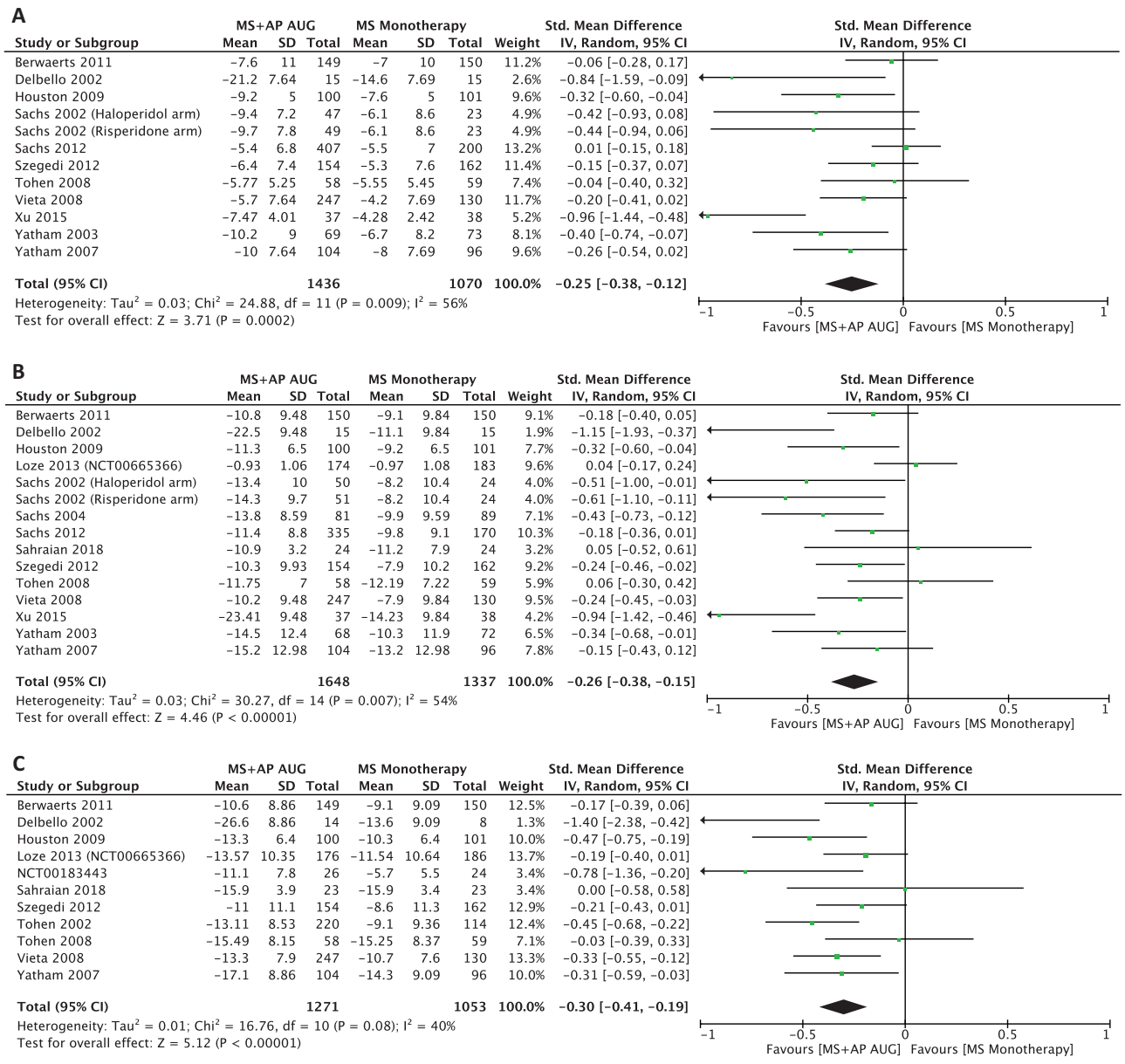

Figure 4. Improvement of manic symptoms on a continuous scale (augmentation therapy [AUG] vs mood stabilizer [MS] monotherapy).

treatment is often initiated with AP. However, if there is no immediate improvement in the symptoms with AP monotherapy, a combination of MS and AP should be considered as early as possible.

The clinical and research implications of our findings are as follows: AUG therapy should be considered early, although attention to the side effects is necessary for acute mania treatment. However, evidence on which individual MSs should be used is lacking, and it is hoped that this point will be clarified in future RCTs.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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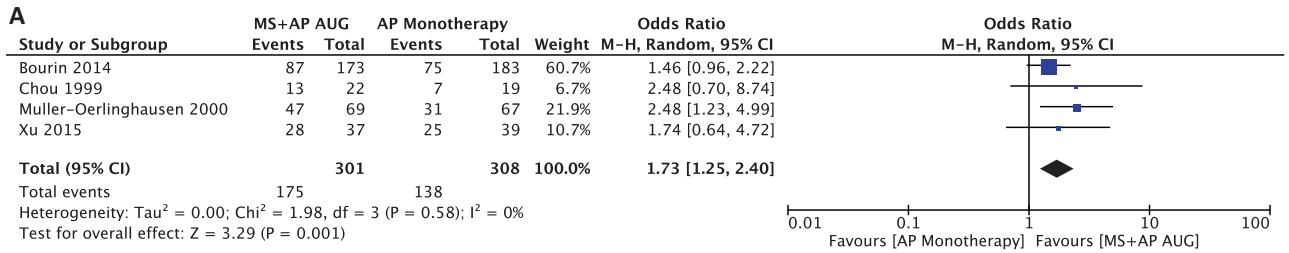
Interest Statement

A.T. received lecture fees from Sumitomo Dainippon Pharma, Eisai, Janssen Pharmaceutical, Meiji-Seika Pharma, Mitsubishi Tanabe Pharma, Otsuka, and Takeda Pharmaceutical. H.H. received speaker honoraria from Eisai, Eli Lilly, Janssen Pharmaceutical, Meiji-Seika Pharma, Otsuka, Pfizer, Sumitomo Dainippon Pharma, and Takeda Pharmaceutical. J.I. has received grant funding from the Ministry of Health, Labor, and Welfare of Japan; the Japan Society for the Promotion of Science; and speaker's honoraria from Sumitomo Dainippon Pharma, Otsuka, Meiji-Seika Pharma, Eli Lilly, MSD K.K., Janssen Pharmaceutical, Shionogi, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, Ono Pharmaceutical, Mochida Pharmaceutical, Viatris, Kyowa Pharmaceutical, Novartis, Sanofi K.K. Y.K. has received speaker honoraria from Otsuka, Meiji-Seika Pharma, and Takeda Pharmaceutical. Y.O. received grant funding from



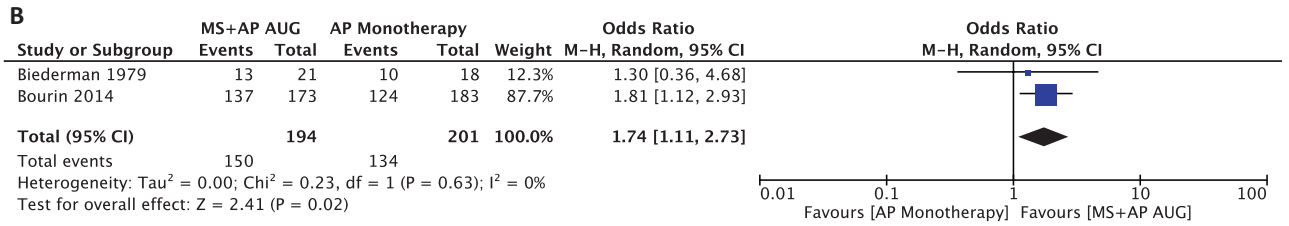
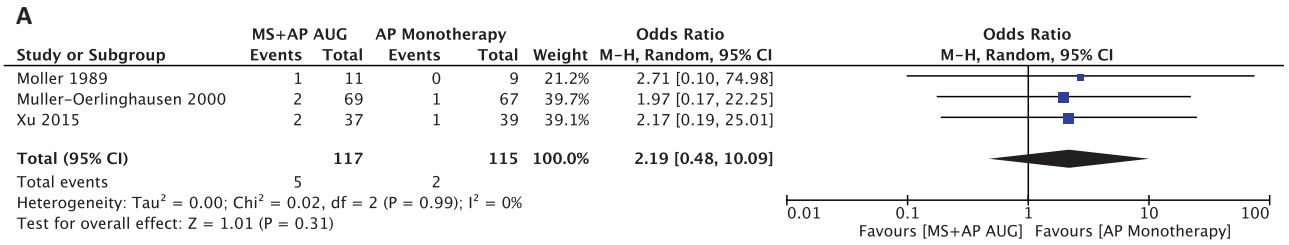


Figure 5. Response defined by each study (augmentation therapy [AUG] vs AP monotherapy).



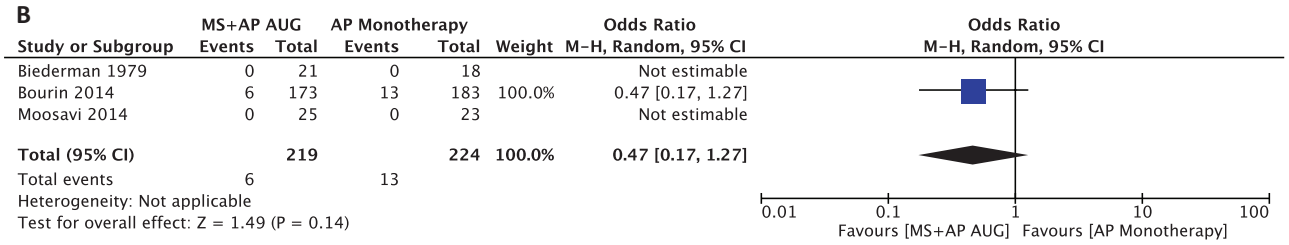


Figure 6. Dropout from the study due to side effects (augmentation therapy [AUG] vs AP monotherapy).

the Japan Society for the Promotion of Science KAKENHI (grant no. 19K10661). K.W. has received manuscript fees or lecture fees from Eisai, Eli Lilly, Janssen Pharmaceutical, Kyowa Pharmaceutical, Lundbeck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, MSD, Otsuka Pharmaceutical, Pfizer, Shionogi, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Viatris, and Yoshitomi and received research/grant support from Daiichi Sankyo, Eisai, Mitsubishi Tanabe Pharma, Meiji Seika Pharma, MSD, Otsuka Pharmaceutical, Pfizer, and Sumitomo Dainippon Pharma. He is also a consultant for the Bollinger Ingelheim, Eisai, Eli Lilly, Kyowa Pharmaceutical, Lundbeck, Luye Life Sciences Group, Mitsubishi Tanabe Pharma, Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, and Viatris. T.K. received grants and personal fees from Japan Agency for Medical Research and Development (AMED), grants and personal fees from Ministry of Education, Culture, Sports, Science and Technology (MEXT)/Japan Society for the Promotion of Science (JSPS), during the conduct of the study; personal fees from Kyowa Hakko Kirin Co., Ltd., personal fees from Eli Lilly Japan K.K., grants and personal fees from Otsuka Pharmaceutical Co., Ltd., personal fees from GlaxoSmithKline K.K., personal fees from Taisho Pharma Co., Ltd., grants and personal fees from Dainippon Sumitomo Pharma Co., Ltd., personal fees from Meiji Seika Pharma Co., Ltd., personal fees from Pfizer Japan Inc., personal fees from Mochida Pharmaceutical Co., Ltd., grants and personal fees from Shionogi & Co., Ltd., personal fees from Janssen Pharmaceutical K.K., personal fees from Janssen Asia Pacific, personal fees from Yoshitomiyakuhin, personal fees from Astellas Pharma Inc., personal fees from Nippon Boehringer Ingelheim Co. Ltd., personal fees from MSD K.K., personal fees from Kyowa Pharmaceutical Industry Co., Ltd., grants and personal fees from Takeda Pharmaceutical Co., Ltd., personal fees from Taisho Pharmaceutical Co., Ltd., personal fees from Taisho Toyama Pharmaceutical Co., Ltd., grants and personal fees from Eisai Co., Ltd., grants and personal fees from Mitsubishi Tanabe Pharma Corporation, grants from Teijin Pharma, personal fees from Viatris, personal fees from Mylan N.V., outside the submitted work. K.M. has received speaker honoraria from Sumitomo Dainippon Pharma, Eisai, Janssen Pharmaceutical, MSD, Meiji-Seika Pharma, Viatris, Lundbeck, Mochida, Kyowa, Otsuka, and Takeda Pharmaceutical and received a research

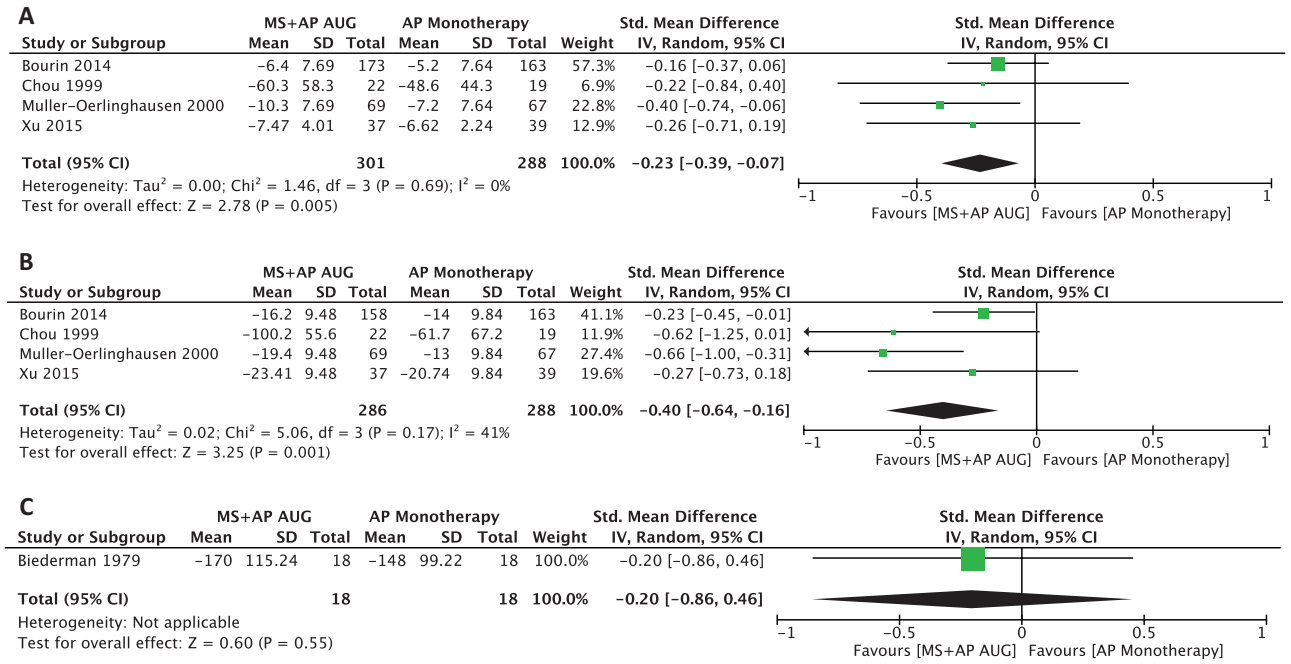


Figure 7. Improvement of manic symptoms on a continuous scale (augmentation therapy [AUG] vs AP monotherapy).

grant from Otsuka, Esai, and Tsumura. K.M. has received speaker honoraria from Sumitomo Dainippon Pharma, Eisai, Janssen Pharmaceutical, MSD, Meiji-Seika Pharma, Viatris, Lundbeck, Mochida, Kyowa, Otsuka, and Takeda Pharmaceutical and received a research grant from Otsuka, Esai, and Tsumura. M.K. has received grant funding from the Ministry of Health, Labor and Welfare of Japan; the Japan Society for the Promotion of Science; SENSHIN Medical Research Foundation and Japan Research Foundation for Clinical Pharmacology; and speaker's honoraria from Sumitomo Dainippon Pharma, Otsuka, Meiji-Seika Pharma, Eli Lilly, MSD K.K., GlaxoSmithKline, Pfizer, Janssen Pharmaceutical, Shionogi, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, Lundbeck, and Ono Pharmaceutical. All other authors declare that they have no competing interests.

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