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.
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 I² 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 I² 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 absence of 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 (Debello 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 (I² = 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 (Table 2). 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 year of publication and 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).
| 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 |
| Delbello 2002 North America | DSM-IV, bipolar I, manic or mixed | 6 | lithium/valproate | placebo | 150 | 27.0 (5.0) | 40.0 (11.2) | MS |
| Garfinkel 1980 North America | Feighner, manic only | 3 | lithium | placebo | 15 | 30.7 | 14.5 (2.0) | MS |
| 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 |
| Loze 2013 Cross-continental | DSM-IV, bipolar I, manic or mixed | 12 | lithium/valproate | placebo | 189 | NA | 44.9 (13.0) | MS |
| NCT00183443 North America | DSM-IV, bipolar I, manic only | 12 | lithium/valproate | aripiprazole (0–30) mg | 26 | NA | 33.1 (9.3) | others |
| Sachs 2002 North America | DSM-IV, bipolar I, manic or mixed | 3 | lithium/valproate | placebo | 24 | NA | 39.5 (11.6) | others |
| Sachs 2004 North America | DSM-IV, bipolar I, manic or mixed | 3 | lithium/valproate | haloperidol 6.2mg | 53 | 27.3 (6.1) | (median) 44.0 | MS |
| Sachs 2012 North America | DSM-IV, bipolar I, manic or mixed | 3 | lithium/valproate | risperidone 3.8mg | 52 | 28 (5.5) | (median) 41.0 | MS |
| Sahrain 2018 Asia | DSM-IV, bipolar I, manic only | 8 | lithium | placebo | 51 | 28 (6.1) | (median) 42.1 | MS |
| Szegedi 2012 Cross-continental | DSM-IV, bipolar I, manic or mixed | 12 | lithium/valproate | placebo | 91 | 31.5 | 39.6 | MS |
| Tohen 2002 North America | DSM-IV, bipolar I, manic or mixed | 6 | lithium/valproate | placebo | 100 | 31.1 | 41.3 | MS |
| Tohen 2008 Cross-continental | DSM-IV, bipolar I, manic or mixed | 6 | lithium/valproate | placebo | 167 | 28.2 (5.8) | 39.0 (12.0) | MS |
Table 1A. Continued

| Study, year, area | DSM, Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, bipolar disorder, mania or mixed | Mood stabilizers, mean dose (range) | Antipsychotics, mean dose (range) | Prior treatment before randomization | Study duration (weeks) | Mood stabilizers, mean dose before randomization | Antipsychotics, mean dose before randomization | Population | Study year, area |
|------------------|-------------------------------------------------|----------------------------------|----------------------------------|-------------------------------|-------------------------|-----------------------------------------------|-----------------------------------------------|------------|------------------|
| Vieta 2008 Europe | lithium/valproate/Li: 1160mg/Va: 1225mg | lithium/valproate/Li: 985mg/Va: 1179mg | olanzapine 19.0 (15–30) mg | placebo 60 | 26.6 (5.6) | 23.0 (4.9) | 3.0 (0.7) | 26.6 (5.6) | 23.0 (4.9) |
| Xu 2015 Asia | valproate 1530mg | lithium/valproate/lithium/valproate/carbamazepine | olanzapine 423 (up to 800) mg | placebo 131 | 34.3 (6.1) | 31.7 (8.2) | 34.3 (6.1) | 31.7 (8.2) |
| Yatham 2003 Cross-continental | lithium/valproate | lithium/valproate | quetiapine 423 mg (up to 800) | placebo 105 | 33.3 | 30.9 | 33.3 | 30.9 |
| Yatham 2007 Cross-continental | lithium/valproate | lithium/valproate | placebo 105 | 31.6 | 30.1 |

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.

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. 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: -0.36, 0.28); however, only 1 old first-generation AP study was included in this comparison, and it was not possible to conclude on ineffectiveness (Figure 4).

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 1.74 (2 studies, 95% CI: 1.11 to 2.73), with no heterogeneity. 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).

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

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### Table 1B. Characteristics of included studies

| 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 |
| 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 |
| Chou 1999 North America | DSM-III-R, bipolar I, manic only | 3 | lithium | haloperidol 15.9mg | 22 | NA | 34.6 (11.5) | others |
| Garfinkel 1980 North America | Feighner, manic only | 3 | placebo | haloperidol 14.5mg | 19 | NA | 34.6 (11.5) | others |
| Moller 1989 Europe | ICD-9 and RDC, manic or schizomaniac syndrome | 3 | placebo | haloperidol 28.0mg | 7 | NA | 37.0 (5.3) | others |
| Moosavi 2014 Asia | DSM-IV, bipolar I, manic only7 | 3 | valproate (800–1200) mg | risperidone | 25 | NA | 24.0 (1.1) | others |
| Muller-Oerlinghausen 2000 Europe | ICD-10, manic only | 3 | placebo | haloperidol/perazine 8.2mg | 69 | 30.9 (8.1) | 39.0 (12.0) | AP |
| Xu 2015 Asia | DSM-IV, bipolar I, manic only4 | 4 | placebo | haloperidol/perazine 10.4mg | 67 | 30.9 (8.4) | 37.0 (11.0) | AP |

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
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.
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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 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, Leucht reported an increase in placebo response over the past decades. The same may be true for BD.

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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. 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. In the maintenance phase, AUG therapy is more effective than monotherapy (Kishi et al., 2021).
treatment is often initiated with AP. However, if there is no immediate improvement in the symptoms with AP mono-
therapy, 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. Acknowledgments: None.

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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
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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).
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