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Pharmacological management of bipolar disorder: Japanese expert consensus

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Abstract

Objectives: The aim of this study was to develop a consensus guideline by certified experts of the Japanese Society of Clinical Neuropsychopharmacology on the psychopharmacological treatment for bipolar disorders I and II (BP-I and BP-II), in order to fill the gap in the literature and provide more concrete guidance for challenging and controversial real-world situations.

Methods: Experts were asked to assess treatment options regarding 19 clinical situations of bipolar disorder with a nine-point Likert scale (one = "disagree" and nine = "agree"). According to the responses from 119 experts, the options were categorized into the first-, second-, and third-line treatments.

Results: For the treatment of BP-I, lithium monotherapy was categorized as a first-line treatment for manic episodes (mean ± standard deviation score, 7.0 ± 2.2), depressive episodes (7.1 ± 2.0), and the maintenance phase (7.8 ± 1.8). Combination therapy of lithium and an atypical antipsychotic was endorsed for manic episodes (7.7 ± 1.7), depressive episodes with (7.1 ± 2.0) and without mixed features (6.9 ± 2.2), and the maintenance phase (6.9 ± 2.1). Similarly, in BP-II, lithium monotherapy was

categorized as a first-line treatment for hypomanic episodes (7.3 ± 2.2), depressive episodes (7.0 ± 2.2), and the maintenance phase (7.3 ± 2.3), while combination therapy of lithium and an atypical antipsychotic was recommended for hypomanic episodes (6.9 ± 2.4).No antipsychotic monotherapy or antidepressant treatment was categorized as a first-line treatment for any type of episode.

Conclusions: These recommendations reflect the current evidence and represent the experts' consensus on using lithium for the treatment of bipolar disorder. Clinicians should consider the effectiveness and adverse effects of antipsychotic and antidepressant medications for the treatment of bipolar disorder.

KEYWORDS

bipolar disorder, expert consensus guideline, lithium, pharmacotherapy, treatment guideline

1 | INTRODUCTION

Treatment guidelines for bipolar disorder have been based on solid evidence to reflect the results of randomized controlled trials and meta-analyses.[1-7] However, these conventional treatment guidelines do not always address challenging situations in the real world because of probable discrepancies between research and clinical settings. Indeed, participants in clinical trials do not necessarily represent patients that physicians usually encounter in clinical practice; strict selection criteria limit generalizability.[8] Furthermore, treatment guidelines often fail to provide clear treatment recommendations on clinically important issues that are nevertheless difficult to examine and a high level of evidence is lacking, such as depressive episodes with mixed features.

A consensus guideline by experts in the field may fill this gap in the literature. The Japanese Society of Clinical Neuropsychopharmacology (JSCNP) is the largest academic society in the field of neuropsychopharmacology in Japan. The JSCNP has a board certification system in which psychiatrists are certified as experts in the field based on their academic activities and written examination scores regarding their professional expertise. A total of 277 psychiatrists have been certified as of November 2019. The Medical Education Panel of the society has recently developed an expert consensus guideline for depression. Thus, in this article, we aimed to create an expert consensus guideline regarding the treatment of bipolar disorders I and II (BP-I and BP-II), especially with regard to clinically challenging situations frequently encountered by psychiatrists in clinical practice. This was developed based on the practical recommendations by the board-certified experts of the JSCNP.

2 | MATERIAL AND METHODS

2.1 | Study design

This survey was conducted from March 7, 2019 to April 25, 2019. The Medical Education Panel of the JSCNP comprised of 13 experts, who created 19 questions regarding BP-I and BP-II that clinicians frequently encounter and find difficult to treat. For each question, treatment choices were suggested by the panel. The certified psychiatrists of the JSCNP were invited to participate in this survey by email. Those who agreed to participate were asked to evaluate the suggested treatment choices using a nine-point Likert scale (one = "disagree" and nine = "agree"). These clinical questions and treatment options are shown in Table S1. Experts were asked to choose a score of 9 for at least one choice, if they would use at least one treatment choice listed. They were also asked to choose a score of 1 for all choices if they would not use any of the treatment choices given. The survey took approximately 15-30 minutes to complete. The following participant information was also collected: age, sex, and work location.

2.2 | Analysis

The following values were calculated for each treatment option:the mean, standard deviation (SD), 95% confidence interval (CI), and the number of responses for1-3 (disagree), 4-6 (neutral), and 7-9 (agree). For each option, a Pearson's chi-squared test was performed to compare the frequencies of these responses (ie, disagree, neutral, and agree). When the responses were randomly distributed across the three types, as indicated by a *P*-value ≥.05 with Chi-squared test, it was considered that there was "no consensus" regarding the question. Treatment options with the lowest 95% CI value ≥6.5 were regarded as "first-line treatments"; those with the lowest 95% CI value ≥3.5 were considered as "second-line treatments"; and the others were considered as "third-line treatments." Choices rated 9 by more than 50% of the responders were defined as "treatments of choice." The first-line treatment is usually appropriate as the initial treatment for a given situation.[9] The treatment of choice, is a particularly strong first-line recommendation. The second-line treatment is a reasonable choice for patients who do not respond to or cannot tolerate the first-line treatment. The "no consensus" treatment is a controversial treatment strategy. The third-line treatment is usually inappropriate or used only when preferred alternatives are found to beineffective.[9]

TABLE 1 Consensus on pharmacological strategy for Manic episodes

	Manic episode in bipolar I	Hypomanic episode in bipolar II	Manic episode in elderly
Li + AAP	1st	1st	2nd
Li only	1st	1st	2nd
VAP + AAP	1st	2nd	2nd
VAP only	2nd	2nd	2nd
LTG + AAP	2nd	No consensus	No consensus
LTG only	3rd	3rd	3rd
CBZ only	No consensus	No consensus	3rd
OLZ only	2nd	2nd	2nd
ARP only	2nd	2nd	2nd
QTP only	No consensus	2nd	2nd
RIS only	No consensus	No consensus	2nd
ASP only	2nd	2nd	3rd
Li + VAP	2nd	2nd	No consensus
Li + LTG	2nd	No consensus	2nd
VAP + LTG	3rd	3rd	3rd
Li + TAP	No consensus	n.a.	n.a.
VAP + TAP	No consensus	n.a.	n.a.
LTG + TAP	3rd	n.a.	n.a.
TAP only	3rd	n.a.	n.a.
Li + AD	n.a.	3rd	3rd
VAP + AD	n.a.	3rd	3rd
LTG + AD	n.a.	3rd	3rd
AD only	n.a.	3rd	3rd
MS + TH	3rd	3rd	3rd

Abbreviations: AD, antidepressant; AAP, atypical antipsychotic; ARP, aripiprazole; ASP, asenapine; CBZ, carbamazepine; CI, confidence interval; Li, lithium; LTG, lamotrigine; MS, mood stabilizer; n.a. = not available; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; SD, standard deviation; TAP, typical antipsychotic; TH, thyroid hormone; VAP, valproic acid.

3 | RESULTS

3.1 | Characteristics of participants

Out of the 277 certified psychiatrists, 119 completed the questionnaire (response rate: 43.0%). Nineteen respondents (16.0%) were in their 30s, 40 (33.6%) were in their 40s, 35 (29.4%) were in their 50s, 24 (20.2%) were in their 60s, and one (0.8%) was 70 or older. The proportion of males was 91.6%. Forty-two respondents (35.3%) were affiliated with university hospitals, 39 (32.8%) with general hospitals, 14 (11.8%) with psychiatric hospitals, 10 (8.4%) with community clinics, and 14 (11.8%) with other institutions such as government offices.

3.2 | Pharmacological strategy for manic episodes

The consensus on the pharmacological strategy for manic episodes is shown in Table 1. Combination therapy of lithium and an atypical antipsychotic, and lithium monotherapy was categorized as first-line treatments for manic episodes in BP-I (mean ± SD score, 7.7 ± 1.7 and 7.0 ± 2.2, respectively) and hypomanic episodes in BP-II (6.9 ± 2.4 and 7.3 ± 2.2, respectively). While combination therapy of valproic acid and an atypical antipsychotic was also categorized as a first-line treatment for manic episodes in BP-I (7.2 ± 1.8), it was categorized as a second-line treatment for hypomanic episodes in BP-II (6.6 ± 2.3). The second-line choices included olanzapine monotherapy (6.8 ± 2.2) and aripiprazole monotherapy (6.3 ± 2.6) for BP-I, and valproic monotherapy (6.5 ± 2.2) and olanzapine monotherapy (6.4 ± 2.3) for BP-II.

No consensus was reached on the first-line treatment for manic episodes in elderly patients. Second-line treatment for manic episodes in elderly patients included aripiprazole monotherapy (6.4 ± 2.5), combination therapy of lithium and an atypical antipsychotic (6.4 ± 2.2), lithium monotherapy (6.4 ± 2.4), combination therapy of valproic acid and an atypical antipsychotic (6.2 ± 2.3), and valproic acid monotherapy (6.2 ± 2.5).

TABLE 2 Consensus on pharmacological strategy for depressive episodes

	Depressive episode in bipolar I	Depressive episode in bipolar II	Depressive episode in elderly	Depressive episode with mixed featuresin bipolar I	Depressive episode with mixed featuresin bipolar II
Li + AAP	1st	2nd	2nd	1st	2nd
Li only	1st	1st	2nd	2nd	2nd
VAP + AAP	No consensus	2nd	No consensus	2nd	2nd
VAP only	2nd	No consensus	2nd	2nd	No consensus
LTG + AAP	2nd	2nd	2nd	2nd	2nd
LTG only	2nd	2nd	2nd	No consensus	No consensus
CBZ only	3rd	3rd	3rd	2nd	2nd
OLZ only	2nd	2nd	2nd	2nd	2nd
ARP only	No consensus	2nd	No consensus	2nd	No consensus
QTP only	2nd	2nd	2nd	2nd	2nd
RIS only	No consensus	3rd	3rd	2nd	3rd
ASP only	3rd	3rd	3rd	3rd	3rd
Li + VAP	2nd	No consensus	2nd	2nd	2nd
Li + LTG	2nd	2nd	No consensus	2nd	2nd
VAP + LTG	No consensus	No consensus	3rd	No consensus	No consensus
Li + AD	No consensus	No consensus	3rd	3rd	3rd
VAP + AD	2nd	2nd	3rd	3rd	3rd
LTG + AD	2nd	2nd	3rd	3rd	3rd
AD only	3rd	3rd	3rd	3rd	3rd
MS + TH	3rd	3rd	3rd	3rd	3rd

Abbreviations: AD, antidepressant; AAP, atypical antipsychotic; ARP, aripiprazole; ASP, asenapine; CBZ, carbamazepine; CI, confidence interval; Li, lithium; LTG, lamotrigine; MS, mood stabilizer; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; SD, standard deviation; TH, thyroid hormone; VAP, valproic acid.

3.3 | Pharmacological strategy for depressive episodes

Lithium monotherapy was categorized as a first-line treatment for depressive episodes in both BP-I (7.1 ± 2.0) and BP-II (7.0 ± 2.2) (Table 2). While combination therapy of lithium and an atypical antipsychotic was categorized as a first-line treatment for depressive episodes in BP-I (6.9 ± 2.2), it was considered to be a second-line treatment in BP-II (6.7 ± 2.2). Other second-line choices included lamotrigine monotherapy (6.6 ± 2.3), combination therapy of lamotrigine and an atypical antipsychotic (6.6 ± 2.2), and quetiapine monotherapy (6.5 ± 2.3) for BP-I, and quetiapine monotherapy (6.6 ± 2.3), lamotrigine monotherapy (6.6 ± 2.5), and combination therapy of lamotrigine and an atypical antipsychotic (6.2 ± 2.4) for BP-II.

None of the choices were categorized as a first-line treatment for depressive episodes in elderly patients. Second-line treatment for depressive episodes in elderly patients included quetiapine monotherapy (6.3 ± 2.3), lithium monotherapy (6.2 ± 2.5), lamotrigine monotherapy (5.9 ± 2.6), combination therapy of lithium and an atypical antipsychotic (5.5 ± 2.5), and combination therapy of lamotrigine and an atypical antipsychotic (5.5 ± 2.3).

Antidepressant use was categorized as a third-line treatment for depressive episodes in BP-I (3.8 ± 2.2) and a second-line treatment in BP-II (4.4 ± 2.3) (Table S1 Q3 and Q9). When the respondents were asked to rate the use of adjunctive antidepressants concomitantly with an ongoing mood stabilizer for persistent depressive episodes, no specific antidepressant was categorized as a first-line treatment for both BP-I and BP-II (Table S1 Q4 and Q10). The second-line treatment included mirtazapine (5.4 ± 2.6) and escitalopram (5.3 ± 2.7) for BP-I, and escitalopram (5.7 ± 2.7), sertraline (5.5 ± 2.6), and mirtazapine (5.5 ± 2.6) for BP-II.

Regarding depressive episodes with mixed features, only combination therapy of lithium and an atypical antipsychotic was categorized as a first-line treatment for BP-I (7.1 ± 2.0) (Table 2). Second-line treatments were lithium monotherapy (6.7 ± 2.2), combination therapy of valproic acid and an atypical antipsychotic (6.5 ± 2.1), olanzapine monotherapy (6.3 ± 2.3), and combination therapy of lithium and valproic acid (6.3 ± 2.2). None of the choices were categorized as a first-line treatment for depressive episodes with mixed features in BP-II. The following choices were categorized as second-line treatments: lithium monotherapy (6.7 ± 2.3), combination therapy of lithium and an atypical antipsychotic (6.6 ± 2.3), quetiapine monotherapy (6.2 ± 2.4), combination therapy of valproic acid and an atypical antipsychotic (6.1 ± 2.3), and olanzapine monotherapy (6.1 ± 2.3).

3.4 | Maintenance treatment for bipolar disorder

Lithium monotherapy was considered a treatment of choice for the maintenance phase in BP-I (7.8 ± 1.8) and a first-line treatment in BP-II (7.3 ± 2.3) (Table 3). Combination therapy of lithium and an atypical antipsychotic was categorized as a first-line treatment for the maintenance phase in BP-I (6.9 ± 2.1) and a second-line treatment in BP-II (6.7 ± 2.2). These were followed by second-line choices, including combination therapy of lithium and lamotrigine (6.4 ± 2.5), combination therapy of lithium and valproic acid (6.4 ± 2.4), and lamotrigine monotherapy (6.2 ± 2.3) for BP-I, and lamotrigine monotherapy (6.4 ± 2.5), quetiapine monotherapy (6.2 ± 2.3), and combination therapy of lamotrigine and an atypical antipsychotic (6.1 ± 2.3) for BP-II.

Regarding the maintenance phase in rapid cycling bipolar disorder, none of the choices were categorized as a first-line treatment. The second-line treatment included combination therapy of lithium and an atypical antipsychotic (6.8 ± 2.3), lithium monotherapy (6.6 ± 2.4), combination therapy of lithium and valproic acid (6.5 ± 2.4), combination therapy of valproic acid and an atypical antipsychotic (6.5 ± 2.2), and valproic acid monotherapy (6.1 ± 2.5).

Blood tests were recommended to be performed every 4-6 months as the second-line option for patients who were treated with the same dose of lithium for over a year and showed no apparent

TABLE 3 Consensus on pharmacological strategy for maintenance treatment

	Bipolar I	Bipolar II	Rapid cycling
Li + AAP	1st	2nd	2nd
Li only	Treatment of choice	1st	2nd
VAP + AAP	No consensus	2nd	2nd
VAP only	2nd	No consensus	2nd
LTG + AAP	2nd	2nd	2nd
LTG only	2nd	2nd	No consensus
CBZ only	3rd	2nd	2nd
OLZ only	2nd	2nd	2nd
ARP only	No consensus	2nd	No consensus
QTP only	2nd	2nd	2nd
RIS only	3rd	3rd	2nd
ASP only	3rd	3rd	3rd
Li + VAP	2nd	2nd	2nd
Li + LTG	2nd	2nd	2nd
VAP + LTG	No consensus	No consensus	No consensus
Li + AD	2nd	No consensus	3rd
VAP + AD	3rd	3rd	3rd
LTG + AD	3rd	3rd	3rd
AD only	3rd.	3rd	3rd
MS + TH	3rd	3rd	3rd

Abbreviations: AD, antidepressant; AAP, atypical antipsychotic; ARP, aripiprazole; ASP, asenapine; CBZ, carbamazepine; CI, confidence interval; Li, lithium; LTG, lamotrigine; MS, mood stabilizer; OLZ, olanzapine; QTP, quetiapine; RIS, risperidone; SD, standard deviation; TH, thyroid hormone; VAP, valproic acid.

side effects (6.5 ± 2.4), which was followed by every 2-3 months (6.3 ± 2.7) (Table S1 Q16). Specific blood tests that the respondents considered as high priority were renal function (8.3 ± 1.3), thyroid function (8.1 ± 1.5), and electrolytes (7.4 ± 1.8) (Table S1 Q17).

Various factors were suggested to be taken into consideration before discontinuing a mood stabilizer: duration of clinical stabilization (7.6 ± 2.1), patient's understanding of relapse prevention (7.6 ± 1.8), wish to have children (7.6 ± 1.7), presence/degree of side effects (7.6 ± 1.7),severity of previous manic symptoms (7.5 ± 2.1), residual manic symptoms (7.5 ± 2.1), patient's understanding of early signs of relapse (7.5 ± 1.8), understanding of illness (7.5 ± 1.8), severity of previous depressive symptom (7.3 ± 2.0), and current social adaptation (7.2 ± 1.8) (Table S1 Q19).

Regarding the duration of concomitant use of benzodiazepine anxiolytics, the only first-line option was "pro re nata (PRN)" (7.3 ± 2.2) (Table S1 Q18). The only second-line option was "within 1 month" (6.3 ± 2.5).

4 | DISCUSSION

Bipolar disorder is characterized by mood swings; treatment has been determined by the patient's mood phase (ie, depressive, manic, and maintenance phase). Furthermore, interpreting the results of maintenance treatment is complicated since the studies that assess this usually adopt an enrichment design[10]; information is critically lacking on strategies to use in patients who inadequately respond to standard treatments. Long-term studies are necessary for this frequent chronic condition, but are challenging to perform in the real-world. Due to the many possible treatment options, it is difficult to conduct rigorous clinical trials to shed light on their relative effectiveness. Understanding this is of high clinical relevance, and using the knowledge of the experts in the field can fill this gap.

In this study, practical treatment options for bipolar disorder were evaluated by the Japanese experts in psychopharmacology. Lithium monotherapy and combination therapy were highly endorsed for several situations, including manic, depressive, and maintenance phases, and mixed features, in BP-I and BP-II. Antipsychotic monotherapy or antidepressant treatment was not recommended as first-line treatment in any type of episode. In addition, benzodiazepines were recommended to be prescribed as briefly as possible. These recommendations reflect the current evidence and demonstrate the experts' consensus on the use of lithium for the treatment of bipolar disorder.

For the treatment of BP-I, lithium monotherapy was categorized as a first-line treatment for manic episodes, depressive episodes, and the maintenance phase, and combination therapy of lithium and an atypical antipsychotic for manic episodes, depressive episodes with and without mixed features, and the maintenance phase. While lithium is considered to be the most effective in preventing relapse and hospitalizations during the maintenance treatment of BP-I,[11,12] the evidence supporting lithium for acute mania and depression in BP-I is weak.[1,5,6] However, in the recently published Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guideline, lithium monotherapy and combination therapy were listed as first-line treatments for acute mania and depression in BP-I. This recommendation is based on the notion that medications used for bipolar disorder should be multifunctional as they not only treat acute mania or depressive symptoms, but also prevent relapse.[7] In addition, monotherapy with a mood stabilizer and combination therapy with lithium or valproate, were categorized as the first-line strategies for acute mania, acute bipolar disorder, and relapse prevention in the Korean expert consensus guideline.[13,14] The experts who participated in the present study also endorsed lithium for the treatment of BP-I in almost all situations, possibly in the light of its efficacy during different phases of this illness. According to a systematic review and recommendations from the ISBD/IGSLI Task Force, an optimal lithium serum level for the maintenance treatment is suggested to be 0.60-0.80 mmol/L while dose should be adjusted depending on treatment response, tolerance, and age of each patient.[15] This range seems comparable to those suggested by other guidelines.[16]

Similarly, lithium monotherapy was categorized as a first-line treatment for hypomanic episodes, depressive episodes, and the maintenance phase in BP-II, while combination therapy of lithium and an atypical antipsychotic was endorsed for hypomanic episodes in BP-II. These findings are generally consistent with the Korean expert consensus guideline, except for the strategy for hypomania where only mood stabilizer and atypical antipsychotic monotherapies were recommended.[13,14] However, due to inadequate evidence, conventional treatment guidelines other than the CANMAT and ISBD guideline did not include specific treatment recommendations for BP-II. In addition, the CANMAT and ISBD guidelines did not include specific treatment recommendations for hypomania, since the reported studies had significant weaknesses, including small sample sizes and mixed samples. This is also the case for the acute treatment of depressive episodes with mixed features, acute treatment of manic and depressive episodes in the elderly, and the maintenance treatment for rapid cycling bipolar disorder. Notably, there were no first-line treatment options for geriatric bipolar disorder in the present study, which may reflect physicians' struggle to manage this challenging condition with psychopharmacological treatment. Further investigations are clearly needed to fill this gap in the literature.

In contrast, antipsychotic monotherapy was not categorized as a first-line treatment for any type of episode in BP-I and BP-II, which is inconsistent with several treatment guidelines.[1,4,7] For example, the CANMAT and ISBD guidelines endorse antipsychotic monotherapies as the first-line treatment for several situations:quetiapine for manic episodes, depressive episodes, and the maintenance phase in BP-I and BP-II, except for manic episodes in BP-II;asenapine monotherapy for manic episodes and the maintenance phase in BP-I; aripiprazole for manic episodes and the maintenance phase in BP-I;cariprazine for manic episodes in BP-I;lurasidone for depressive episodes in BP-I;paliperidone for manic episodes in BP-I;risperidone for manic episodes in BP-I.[7] The Korean expert consensus guideline also recommended

antipsychotic monotherapy in several clinical situations.[13,14] This discrepancy may be because the Japanese experts consider the susceptibility of patients to potential adverse effects of antipsychotics problematic, including weight gain, prolactin elevation, akathisia, sedation, QTc prolongation, and anticholinergic side-effects.[17,18] The prevalence and severity of lithium-induced adverse effects are generally associated with its serum concentration; however, it is difficult to predict the side effects of antipsychotics beforehand.[19]

The use of antidepressants was not strongly recommended for BP-I and BP-II, consistent with several treatment guidelines.[1,2,5,7] This is due to the potential risk of antidepressant-induced switching to mania and rapid-cycling. In a within-individual comparison study in 3240 patients with bipolar disorder using the Swedish national registry, antidepressant monotherapy was associated with a three-fold increased risk of mania 3 months after the start of antidepressant treatment.[20] In a study conducted in 1994 using all available clinical trial data on selective serotonin re-uptake inhibitor (SSRIs) (ie, fluoxetine, fluvoxamlne, paroxetine, and sertraline) compared to tricyclic antidepressants (TCAs) or placebo demonstrated that treatment-emergent manic switch was more frequently observed in bipolar patients treated with TCAs (14 patients out of 125, 11.2%) than with SSRIs (9 patients out of 242, 3.7%) or placebo (2 patients out of 48, 4.2%).[21] In a sub-analysis of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, a higher frequency of mood episodes was reported in rapid cyclers who continued to take antidepressants in addition to a mood stabilizer, than those who discontinued.[22] In terms of antidepressants to be used, mirtazapine and escitalopram were ranked high as second-line treatments for BP-I, and escitalopram and sertraline for BP-II. In another expert consensus guideline, the first-line choices of antidepressants included bupropion and SSRIs for bipolar depression.[23] However, only short-term venlafaxine monotherapy and long-term fluoxetine monotherapy have been reported to be superior to lithium in BP-II without significantly increasing in hypomanic symptoms.[24,25] The evidence as well as experts' consensus still indicates that the use of antidepressants remains controversial for bipolar disorder.

There are several limitations to be noted in this study. First, although highly practical, an expert consensus guideline is considered to provide less evidence than randomized controlled trials and meta-analyses. Second, psychosocial interventions were not evaluated in this survey since they were beyond our scope in the present study, although their relevance should be highly acknowledged in patients with bipolar disorder. Third, there may not be enough information to choose the appropriate treatment options in some questions. Heterogeneity of the patients should be acknowledged when the recommendations in this guideline are translated into clinical practice. Fourth, the generalizability of our findings may be limited, as all of the experts who participated in this study were Japanese. Moreover, some of the medications listed in the questionnaire are not available outside of Japan. Fifth, although we obtained responses from over 100 specialists, the response rate was relatively low. Finally, our distinction into three categories [ie, 1-3 (disagree), 4-6 (neutral), and 7-9 (agree)] and methods of analyses are somewhat arbitrary.

In conclusion, the Japanese experts highly recommend lithium monotherapy and combination therapy for both bipolar disorders I and II, regardless of illness phases or episodes. The use of antidepressants remains controversial. Although antipsychotic drugs are considered to be reasonable choices in case of treatment failure or intolerable side effects, clinicians are advised to carefully monitor potentially serious side effects, particularly during long-term maintenance treatment for bipolar disorder.

PREVIOUS PRESENTATIONS

115th Academic Meeting of Japanese Society of Psychiatry and Neurology, Niigata, June 21, 2019.

Medical Education Seminar of Japanese Society of Clinical Neuropsychopharmacology, Tokyo, July 21, 2019.

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CONFLICT OF INTEREST

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ETHICAL APPROVAL

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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