Pharmacological management of bipolar disorder: Japanese expert consensus

Hitoshi Sakurai1,2 | Masaki Kato3 | Norio Yasui-Furukori4 | Takefumi Suzuki5 | Hajime Baba6 | Koichiro Watanabe7 | Ken Inada8 | Ikuko Kishida9,10 | Yuka Sugawara Kikuchi11 | Toshiaki Kikuchi2 | Asuka Katsuki12 | Hiroyuki Uchida2

Medical Education Panel of the Japanese Society of Clinical Neuropsychopharmacology

1Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA
2Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan
3Department of Neuropsychiatry, Kansai Medical University, Osaka, Japan
4Department of Psychiatry, Dokkyo Medical University School of Medicine, Tochigi, Japan
5Department of Neuropsychiatry, University of Yamanashi Faculty of Medicine, Yamanashi, Japan
6Department of Psychiatry & Behavioral Science, Juntendo University Graduate School of Medicine, Tokyo, Japan
7Department of Neuropsychiatry, Kyorin University School of Medicine, Tokyo, Japan
8Department of Psychiatry, Tokyo Women’s Medical University School of Medicine, Tokyo, Japan
9Fujisawa Hospital, Kanagawa, Japan
10Department of Psychiatry, Yokohama City University School of Medicine, Kanagawa, Japan
11Department of Psychiatry, Akita University School of Medicine, Akita, Japan
12Department of Psychiatry, University of Occupational and Environmental Health, Fukuoka, Japan

Correspondence
Hiroyuki Uchida, Department of Neuropsychiatry, Keio University School of Medicine Psychopharmacology Lab, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan.
Email: hiroyuki.uchida.hu@gmail.com

Funding information
GlaxoSmithKline

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...
1 | INTRODUCTION

Treatment guidelines for bipolar disorder have been based on solid evidence to reflect the results of randomized controlled trials and meta-analyses. 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. 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 for 1-3 (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 (i.e., 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. 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 be ineffective.
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 1

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

| Choice               | 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           |
| O LZ 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; 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, the evidence supporting lithium for acute mania and depression in BP-I is weak. 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. 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. 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/IGSL 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. This range seems comparable to those suggested by other guidelines.

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. 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. 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; aripiprazole monotherapy for manic episodes and the maintenance phase in BP-I; aripiprazole for manic episodes and the maintenance phase in BP-I; aripiprazole for manic episodes and the maintenance phase in BP-I; aripiprazole for manic episodes and the maintenance phase in BP-I; aripiprazole for manic episodes and the maintenance phase in BP-I; aripiprazole for manic episodes and the maintenance phase in BP-I; aripiprazole for manic episodes and the maintenance phase in BP-I. The Korean expert consensus guideline also recommended...
antipsychotic monotherapy in several clinical situations. 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. 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.

The use of antidepressants was not strongly recommended for BP-I and BP-II, consistent with several treatment guidelines. 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. In a study conducted in 1994 using all available clinical trial data on selective serotonin re-uptake inhibitor (SSRIs) (ie, fluoxetine, fluvoxamine, 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%). 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. 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. 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. 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.

**ACKNOWLEDGMENTS**

This work was supported by the GlaxoSmithKline medical education project grant. The authors thank AsakiMatsuzaki for his support in the previous presentation.

**CONFLICT OF INTEREST**

Dr Sakurai reports grants from Japanese Society of Clinical Neuropsychopharmacology, grants from Uehara Memorial Foundation, personal fees from Dainippon-Sumitomo Pharma, personal fees from Otsuka Pharmaceutical, personal fees from Meiji-Seika Pharma, personal fees from Eli Lilly, personal fees from Tanabe Mitsubishi Pharma, personal fees from Yoshitomi Yakuhin, outside the submitted work. Dr Kato has received grant funding from Japan Society for the Promotion of Science, SENSHIN Medical Research Foundation and Japan Research Foundation for Clinical Pharmacology, and speaker’s honoraria from Dainippon-Sumitomo Pharma, Otsuka, Meiji-Seika Pharma, Eli Lilly, MSD KK, GlaxoSmithKline, Pfizer, Janssen Pharmaceutical, Shionogi, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical and Ono Pharmaceutical. Dr Norio Yasui-Furukori has been a speaker for Dainippon-Sumitomo Pharmaceutical, Mochida Pharmaceutical, Otsuka Pharmaceutical and MSD for other studies within the past three years. The funders had no role in the study design, data collection and analysis, the decision to publish, or the preparation of the manuscript. Dr Suzuki has received manuscript or speaker’s fees from Astellas, Dainippon Sumitomo Pharma, Eisai, Eli Lilly, Elsevier Japan, Janssen Pharmaceuticals, Kyowa Yakuhin, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, MSD, Novartis, Otsuka Pharmaceutical, Shionogi, Tsumura, Wiley Japan, and Yoshitomi Yakuhin, and research grants from Eisai, Mochida Pharmaceutical, Meiji Seika Pharma and Shionogi. Dr Baba reports grants from Novartis, personal fees from MSD, personal fees from Otsuka, personal fees from Dainippon Sumitomo, personal fees from Meiji Seika, personal fees from Eli Lilly, personal fees from Yoshitomi, personal fees from Janssen, personal fees from Kyowa, personal fees from Mitsubishi Tanabe, personal fees from Ono, personal
fears from Pfizer, personal fees from Takeda, outside the submitted work. Dr Watanabe has received manuscript fees or speaker’s honoraria from Daiichi Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Kyowa Pharmaceutical, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, MSD, Otsuka Pharmaceutical, Pfizer, Shionogi, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, Yoshide, and has received research/grant support from Astellas Pharma, Daiichi Sankyo, Eisai, MSD, Mitsubishi Tanabe Pharma, Meiji Seika Pharma, Otsuka Pharmaceutical, Pfizer, Shionogi, Sumitomo Dainippon Pharma, and is a consultant of Eisai, Eli Lilly, Kyowa Pharmaceutical, Otsuka Pharmaceutical, Pfizer, Sumitomo Dainippon Pharma, Taisho Toyama Pharmaceutical, and Takeda Pharmaceutical. Dr Inada reports personal fees from Dainippon Sumitomo Pharma, personal fees from Eisai, personal fees from Eli Lilly Japan, personal fees from Janssen pharmaceutical, personal fees from Meiji-Seika Pharmaceutical, personal fees from Mochida, grants and personal fees from MSD, personal fees from Novartis, personal fees from Otsuka Pharmaceutical, personal fees from Shionogi, personal fees from Tanabe-Mitsubishi Pharma, personal fees from Yoshitomi Yakuhin, outside the submitted work. Dr Kishida and Dr Yuka Sugawara Kikuchi have nothing to disclose. Dr Toshiaki Kikuchi reports personal fees from Otsuka Pharmaceutical, personal fees from Dainippon-Sumitomo, personal fees from Eli Lilly, personal fees from Mochida, personal fees from Meiji-Seika, personal fees from Yoshitomi-Yakuhin, personal fees from Takeda, personal fees from MSD, personal fees from Pfizer, outside the submitted work. Dr Katsuki reports personal fees from Dainippon Sumitomo Pharma. Dr Uchida has received grants from Eisai, Otsuka Pharmaceutical, Dainippon-Sumitomo Pharma, and Meiji-Seika Pharmaceutical; speaker’s honoraria from Otsuka Pharmaceutical, Eli Lilly, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, and MSD; and advisory panel payments from Dainippon-Sumitomo Pharma within the past three years.

**ETHICAL APPROVAL**

None.

**DATA AVAILABILITY STATEMENT**

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

**ORCID**

Hitoshi Sakurai [https://orcid.org/0000-0002-5399-7946](https://orcid.org/0000-0002-5399-7946)

Masaki Kato [https://orcid.org/0000-0001-6727-7272](https://orcid.org/0000-0001-6727-7272)

Hiroyuki Uchida [https://orcid.org/0000-0002-0628-7036](https://orcid.org/0000-0002-0628-7036)

**REFERENCES**

1. Fountoulakis KN, Yatham L, Grunze H, et al. The International College of Neuropsychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 2: review, grading of the evidence, and a precise algorithm. *Int J Neuropsychopharmacol*. 2017;20(2):121-179. [https://doi.org/10.1093/ijnp/pyw100](https://doi.org/10.1093/ijnp/pyw100)

2. Goodwin GM, Haddad PM, Ferrier IN, et al. Evidence-based guidelines for treating bipolar disorder: Revised third edition recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2016;30(6):495-553. [https://doi.org/10.1177/0269881116636545](https://doi.org/10.1177/0269881116636545)

3. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: acute and long-term treatment of mixed states in bipolar disorder. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry*. 2018;19(1):2-58. [https://doi.org/10.1080/15622975.2017.1384850](https://doi.org/10.1080/15622975.2017.1384850)

4. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry*. 2013;14(3):154-219. [https://doi.org/10.3109/15622975.2013.770551](https://doi.org/10.3109/15622975.2013.770551)

5. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2010 on the treatment of acute bipolar depression. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry*. 2010;11(2):81-109. [https://doi.org/10.3109/15622975.2010.9709355588](https://doi.org/10.3109/15622975.2010.9709355588)

6. Grunze H, Vieta E, Goodwin GM, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2009 on the treatment of acute mania. *World J Biol Psychiatry Off J World Fed Soc Biol Psychiatry*. 2009;10(2):85-116. [https://doi.org/10.1080/15622975.2009.97090823202](https://doi.org/10.1080/15622975.2009.97090823202)

7. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord*. 2018;20(2):97-170. [https://doi.org/10.1111/bdi.12609](https://doi.org/10.1111/bdi.12609)

8. Zimmerman M, Chełmiński I, Posternak MA. Exclusion criteria used in antidepressant efficacy trials: consistency across studies and representativeness of samples included. *J Nerv Ment Dis*. 2004;192(2):87-94. [https://doi.org/10.1097/01.nmd.000010279.23893.82](https://doi.org/10.1097/01.nmd.000010279.23893.82)

9. Allen MH, Currier GW, Hughes DH, Docherty JP, Carpenter D, Ross R. Treatment of behavioral emergencies: a summary of the expert consensus guidelines. *J Psychiatr Pract*. 2003;9(1):16-38.

10. Cipriani A, Barbui C, Rendell J, Geddes JR. Clinical and regulatory implications of active run-in phases in long-term studies for bipolar disorder. *Int J Clin Pract*. 2004;58(5):318-322. [https://doi.org/10.1046/j.1470-0170.2004.03141.x](https://doi.org/10.1046/j.1470-0170.2004.03141.x)

11. Joas E, Karanti A, Song J, Goodwin GM, Lichtenstein P, Landén M. Pharmacological treatment and risk of psychiatric hospital admission in bipolar disorder. *Br J Psychiatry J Ment Sci*. 2017;210(3):197-202. [https://doi.org/10.1192/bjp.bp.116.187989](https://doi.org/10.1192/bjp.bp.116.187989)

12. Severus E, Taylor MJ, Sauer C, et al. Lithium for prevention of mood episodes in bipolar disorders: systematic review and meta-analysis. *Int J Bipolar Disord*. 2014;2:15. [https://doi.org/10.1186/s40345-014-0015-8](https://doi.org/10.1186/s40345-014-0015-8)

13. Woo YS, Bahk W-M, Lee JG, et al. Korean Medication Algorithm Project for Bipolar Disorder 2018 (KMAP-BP 2018): Fourth Revision. *Clin Psychopharmacol Neuosci Off Sci J Korean Coll Neuropsychopharmacol*. 2018;16(4):434-448. [https://doi.org/10.9758/cpn.2018.16.4.434](https://doi.org/10.9758/cpn.2018.16.4.434)

14. Jeong J-H, Bahk W-M, Woo YS, et al. Korean Medication Algorithm for Bipolar Disorder 2018: comparisons with other treatment guidelines. *Clin Psychopharmacol Neuosci Off Sci J*
15. Nolen WA, Licht RW, Young AH, et al. What is the optimal serum level for lithium in the maintenance treatment of bipolar disorder? A systematic review and recommendations from the ISBD/IGSLI Task Force on treatment with lithium. *Bipolar Disord.* 2019;21(5):394-409. https://doi.org/10.1111/bdi.12805

16. Hiemke C, Bergemann N, Clement H, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry.* 2018;51(1–02):9-62. https://doi.org/10.1055/s-0043-116492

17. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet Lond Engl.* 2019;394(10202):939-951. https://doi.org/10.1016/S0140-6736(19)31135-3

18. Gao K, Ganocy SJ, Gajwani P, Muzina DJ, Kemp DE, Calabrese JR. A review of sensitivity and tolerability of antipsychotics in patients with bipolar disorder or schizophrenia: focus on somnolence. *J Clin Psychiatry.* 2008;69(2):302-309. https://doi.org/10.4088/jcp.v69n0217

19. Grandjean EM, Aubry J-M. Lithium: updated human knowledge using an evidence-based approach. Part II: clinical pharmacology and therapeutic monitoring. *CNS Drugs.* 2009;23(4):331-349. https://doi.org/10.2165/00023210-200923040-00005

20. Viktorin A, Lichtenstein P, Thase ME, et al. The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. *Am J Psychiatry.* 2014;171(10):1067-1073. https://doi.org/10.1176/appi.ajp.2014.13111501

21. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. *Br J Psychiatry J Ment Sci.* 1994;164(4):549-550. https://doi.org/10.1192/bjp.164.4.549

SUPPORTING INFORMATION

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

How to cite this article: Sakurai H, Kato M, Yasui-Furukori N, et al. Pharmacological management of bipolar disorder: Japanese expert consensus. *Bipolar Disord.* 2020;22:822-830. https://doi.org/10.1111/bdi.12959