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Taiwan consensus on biological treatment of bipolar disorder during the acute, maintenance, and mixed phases: The 2022 update

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ABSTRACT

Background: Bipolar disorder is a mood dysregulation characterized by recurrent symptoms and episodes of mania, hypomania, depression, and mixed mood. The complexity of treating patients with bipolar disorder prompted the Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology (TSBPN) to publish the first Taiwan consensus on pharmacological treatment of bipolar disorders in 2012. This paper presents the updated consensus, with changes in diagnostic criteria (i.e., mixed features) and emerging pharmacological evidence published up to April 2022.

Methods: Our working group systemically reviewed the clinical research evidence and international guidelines and determined the levels of evidence for each pharmacological treatment on the basis of the most recent World Federation of Societies of Biological Psychiatry grading system. Four clinical-specific issues were proposed. The current TSBPN Bipolar Taskforce then discussed research evidence and clinical experience related to each treatment option in terms of efficacy and acceptability and then appraised final recommendation grades through anonymous voting.

Results: In the updated consensus, we include the pharmacological recommendations for bipolar disorder with mixed features considering its high prevalence, the severe clinical prognosis, and the absence of approved medications. Cariprazine, lurasidone, repetitive transcranial magnetic stimulation, and ketamine are incorporated as treatment options. In the maintenance phase, the application of long-acting injectable antipsychotics is emphasized, and the hazards of using antidepressants and conventional antipsychotics are proposed.

Conclusions: This updated Taiwan consensus on pharmacological treatment for bipolar disorder provides concise evidence-based and empirical recommendations for clinical psychiatric practice. It may facilitate treatment outcome improvement in patients with bipolar disorder.

1. Introduction

Bipolar disorder is characterized by chronic and complex mood dysregulation with recurrent symptoms and episodes of mania, hypomania, depression, and mixed mood. Bipolar disorder causes mood liability and cognitive and functional impairment and increases the risks of

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disability and premature mortality (McIntyre et al., 2020a). Even without recurrence, subsyndromal mood symptoms can cause considerable disabilities in patients and impair their psychosocial and socioeconomic functioning (Moot et al., 2022). The global prevalence of bipolar I and II disorder is 0.6–1.0% and 0.4–1.1%, respectively, while the prevalence of bipolar disorder in Taiwan is approximately 0.42% (Chen et al., 2019; Merikangas et al., 2011; Weissman et al., 1996). Understanding the complexity of pharmacological interventions for bipolar disorder, the Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology (TSBPN)—a country member of the World Federation of Societies of Biological Psychiatry (WFSBP) and International Society of Bipolar Disorder (ISBD)—developed the first version of a Taiwanese consensus on pharmacological treatment for bipolar disorder to facilitate international collaboration, research, and education in 2012 (Bai et al., 2013). Considering the continually emerging research evidence and novel drugs as well as changes in diagnostic criteria [from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV to DSM-5], this consensus is updated periodically in accordance with the opinions and recommendations of Taiwanese experts.

DSM-5 emphasizes the dimensional concept of mood dysregulation in bipolar disorder, particularly including the broad definition of mixed mood presentation. Here, mania with mixed features is characterized by a manic episode with at least three depressive symptoms, and bipolar depression with mixed features is characterized by a depressive episode with at least three hypomanic or manic symptoms. By contrast, in DSM-IV, the narrow categorical definition of a mixed episode, only indicating mania with mixed depression, was full syndromal mania and depression. Hitherto there is no specific medication approved by US or EU authorities for the broad and much more comprehensive dimensional DSM-5 mixed features in acute or maintenance treatment compared with DSM-IV-defined mixed episodes. However, the prevalence of mixed states in acute mania and bipolar depression is 20–70%, depending on diverging definitions of mixed states (Grunze et al., 2018). Patients with mixed states have more episodes in their lifetime, more irritability, and more psychiatric comorbidities; longer mood instability periods, higher rates of recurrence and lower rates of treatment response; and higher suicidality than those with pure symptoms (Grunze et al., 2018; McIntyre et al., 2019, 2020b). Given the high prevalence, severe clinical presentation, the worse prognosis of bipolar mixed states, and the unavailability of approved medication for them, the current updated consensus in Taiwan emphasizes these crucial issues and provides a relevant recommendation of pharmacological treatment for bipolar disorder with mixed features defined by DSM-5.

Similar to the previous consensus, this updated version is based on the template of the WFSBP guideline (Grunze et al., 2018, 2009, 2010, 2013) and other international guidelines, including the British Association for Psychopharmacology (Goodwin et al., 2016) and the Canadian Network for Mood and Anxiety Treatments (CANMAT) (Yatham et al., 2021, 2018). To emphasize the balance between efficacy and safety, Taiwanese experts' experience, and indications for pharmacological treatment options for bipolar disorder approved by the Taiwan Ministry of Health and Welfare (MOHW) were also considered to formulate the current concise, empirical, and practical reference for clinical practice. However, this consensus cannot be used as a reference for legal or insurance purposes.

This updated consensus includes the recommendations for pharmacological treatment options for manic episodes, depressive episodes, maintenance and mixed features, and four critical clinical issues related to bipolar disorder treatment. Each pharmacological treatment option is classified on the basis of five factors: the level of evidence (LoE), Taiwan recommendation grade (RG-T), MOHW's drug approval license, recommended dosage, and RG-T vote results (presented as percentages).

2. Methods

2.1. Literature review, guideline framework, and voting

The current working group, comprising six expert psychiatrists, initially reviewed the published clinical research evidence and guidelines and provided a comprehensive overview of the updated evidence relative to the previous Taiwan consensus in the kick-off meeting on October 30, 2020. Four clinical-specific issues were also proposed. We evaluated relevant studies and guidelines published inception to April 30, 2022. Next, we organized a TSBPN Bipolar Taskforce composed of 34 expert psychiatrists from university medical centers or psychiatric specialist medical centers, with an average of 26 years of clinical experience. It comprised 12 full professors, 7 associate professors, 6 assistant professors, and 5 lecturers. On October 1, 2021, this taskforce discussed and voted independently and anonymously for the RG-T of each treatment option based on the clinical evidence, acceptability, MOHW approval, and clinical experience (Table 1) in the consensus meeting. Re-voting was conducted between May 16 and 20, 2022, to confirm the RG-T of treatment options if the difference between two RG-T values was $\leq$ 10%. Finally, the consensus was presented and confirmed at the scientific symposium at the TSBPN annual meeting on June 11, 2022.

2.2. Level of Evidence (LoE) and Taiwan recommendation grade (RG-T)

Based on the new WFSBP grading system, the LoE for bipolar management was rated as A (strong), B (limited), C (low), or D (insufficient

Table 1
Taiwan recommendation grades.

RG-T	LoE and acceptability (based on Taiwanese expert consensus and Taiwan MOHW approval)
1 (Strong)	LoE of A with good acceptability; or LoE of A with moderate acceptability and recommended by Taiwanese experts; or LoE of B with good or moderate acceptability and recommended by Taiwanese experts
2 (Limited)	LoE of A with moderate acceptability; or LoE of B with good acceptability; or LoE of A with poor acceptability and recommended by Taiwanese experts; or LoE of B with moderate or poor acceptability and recommended by Taiwanese experts; or LoE of C with good, moderate, or poor acceptability and recommended by Taiwanese experts
3 (Weak)	LoE of A with poor acceptability; or LoE of B with moderate or poor acceptability; or LoE of C with good, moderate, or poor acceptability; or LoE of D with good, moderate, or poor acceptability and recommended by Taiwanese experts
4 (No recommendation possible)	Insufficient evidence (LoE of D) to give recommendations

RG-T is adapted from the recommendation grading system of the World Federation of Societies of Biological Psychiatry (WFSBP) and the recommendations of the current Taiwanese experts and their clinical experience. The acceptability is determined on the basis of the WFSBP criteria including the risk–benefit ratio (e.g., drug–drug interactions and adverse effects), cost–benefit ratio, applicability in the target population, ethical and legal aspects, service user preferences, and practicability.
LoE, Level of evidence; MOHW, Ministry of Health and Welfare; RG-T, Taiwan recommendation grade.

evidence) in accordance with the number of randomized controlled trials (RCTs), open studies, and case reports available to calculate the efficacy or effectiveness of the treatment options (Hasan et al., 2019). The LoE was considered to be C1 if at least one prospective open study (with a minimum of 10 evaluable patients per group) demonstrated efficacy; C2 if efficacy was noted only in case reports or case series with < 10 evaluable patients; and C3 if it was based on the opinion of experts in the field or the analysis of Taiwan National Health Insurance Research Database data with recommendations by Taiwanese experts.

For each bipolar disorder treatment option, the WFSBP-defined evidence-based recommendation grade was initially assessed on the basis of the combination of the LoE and acceptability (good, moderate, or poor) (Hasan et al., 2019). Then, the taskforce members were allowed to vote to adjust the recommendation on the basis of their clinical experience and MOHW approval to determine the RG-T value for each treatment option (Table 1). The recommendations could only be upgraded or downgraded by one grade.

3. Results

3.1. Acute manic phase

In patients previously treated with lithium or valproate alone (Ogawa et al., 2014), combination therapy with atypical antipsychotics was noted to increase the response by approximately 20% (Ketter, 2008). Moreover, combination therapy involving atypical antipsychotics and mood stabilizers was demonstrated to have superior efficacy to antipsychotic monotherapy (Ketter, 2008). The choice between monotherapy and combination therapy can be based on breakthrough episode occurrence, past therapeutic response to monotherapy, illness severity, clinical needs, medication safety and tolerability, or personal preference of the patient (Goodwin et al., 2016; Yatham et al., 2018) (Table 2). Few changes are made in the current consensus in the manic phase.

3.1.1. Monotherapy for manic phase

Classical mood stabilizers, namely lithium, valproate, and carbamazepine, are widely used as monotherapy for acute mania, with an LoE (A). Compared with carbamazepine, oxcarbazepine has a similar

Table 2
Manic phase therapy.

	Medication or treatment	LoE	2022 RG-T	Taiwan MOHW approval	Recommended daily dose for adults	RG-T vote results (%)
Monotherapy for acute manic phase						
1	Lithium	A	1	V	600–1200 mg (serum level, 0.8–1.3 mg/L)	**1: 94%**; 2: 6%
2	Valproate	A	1	V	1200–3000 mg (loading dose, 20–30 mg/kg body weight; serum level, 75–100 mg/L)	**1: 94%**; 2: 6%
3	Aripiprazole	A	1	V	15–30 mg	**1: 91%**; 2: 9%
4	Quetiapine	A	1	V	400–800 mg	**1: 88%**; 2: 12%
5	Risperidone	A	1	V	2–6 mg	**1: 94%**; 2: 6%
6	Cariprazine	A	1		3–6 mg	**1: 79%**; 2: 15%; 3: 6%
7	Olanzapine	A	2	V	10–20 mg	1: 44.1%; **2: 55.9%**
8	Ziprasidone	A	2	V	80–160 mg	1: 24%; **2: 76%**
9	Carbamazepine	A	2	V	600–1200 mg (serum level, 4–15 mg/L)	1: 18%; **2: 79%**; 3: 3%
10	Haloperidol	A	2		5–20 mg	1: 3%; **2: 91%**; 3: 6%
11	Paliperidone	B	2		3–12 mg (only 12 mg/day led to an LoE of B)	1: 21%; **2: 70%**; 3: 6%; 4: 3%
12	Amisulpride	B	2		400–1200 mg	1: 9%; **2: 88%**; 3: 3%
13	Chlorpromazine	B	3		300–1000 mg	2: 18%; **3: 82%**
14	Zotepine	C1	3		200–400 mg	**3: 100%**
15	Clozapine	C1	3		100–400 mg (reserved for treatment of refractory mania)	1: 3%; 2: 30%; **3: 67%**
16	Sulpiride	C3	3		400–800 mg	2: 9%; **3: 79%**; 4: 12%
17	Oxcarbazepine	C1	3		900–1800 mg	2: 3%; **3: 61%**; 4: 36%
18	Clothiapine	C3	3		40–160 mg	1: 3%; 2: 3%; **3: 48%**; 4: 24%; Exclusion: 21%
19	Flupenthixol	C3	3		3–18 mg	2: 6%; **3: 52%**; 4. 21%; Exclusion: 21%
20	Fluphenazine	C3				2: 3%; 3: 15%; 4. 15%; **Exclusion: 67%**
21	Loxapine	C3				3: 3%; 4. 18%; **Exclusion:79%**
22	Thioridazine	C3				3: 3%; 4. 15%; **Exclusion:82%**
23	Trifluoperazine	C3				3: 15%; 4. 12%; **Exclusion:73%**
Combination or adjunctive therapy for acute manic phase						
1	Lithium or valproate +Quetiapine	A	1	V		**1: 88%;** 2: 12%;
2	Lithium or valproate +Risperidone	A	1	V		**1: 94%**; 2: 6%
3	Lithium or valproate +Olanzapine	A	1	V		**1: 50%**; 2: 47.1%; 3: 2.9%
4	Lithium or valproate +Aripiprazole	B	1	V		**1: 53%**; 2: 47%
5	Lithium + valproate	C1	1			**1: 50%**; 2: 38.2%; 3: 8.8%
6	ECT + ongoing treatment	C1	3	V		1: 6%; 2: 41%; **3: 47%**; 4: 6%

Recommended daily doses may have variations due to differences in approval.
RG-T, Taiwan recommendation grade; MOHW, Ministry of Health and Welfare; LoE, level of evidence.

chemical structure but is more tolerable and has fewer drug–drug interactions (Goodwin et al., 2016). No new RCTs on oxcarbazepine have been reported since the previous Taiwan consensus in 2012; nevertheless, a network meta-analysis noted that patients with acute mania respond similarly to oxcarbazepine and placebo (Kishi et al., 2022).

According to well-designed clinical trials and network meta-analyses, most atypical antipsychotic agents have favorable antimanic properties and acceptable tolerability (Kishi et al., 2022; Yildiz et al., 2015). Quetiapine, aripiprazole, and risperidone had an LoE(A) and RG-T 1. Compared with their grade in the 2012 Taiwan consensus, the RG-T of olanzapine and ziprasidone is downgraded from 1 to 2 in the current version despite them having an LoE(A). This is because the experts noted that olanzapine increases the risks of body weight gain and metabolic side effects (Niufan et al., 2008; Perlis et al., 2006). Nevertheless, the difference in the votes for downgrading the recommendation grades for olanzapine was marginal (44% and 56% of the experts voted for an RG-T 1 and 2, respectively). Regarding ziprasidone, the recommendation grade was downgraded because of its cardiovascular side effects, particularly QTc prolongation. The 2018 CANMAT and ISBD guideline also downgrade olanzapine and ziprasidone to second-line options due to similar concerns (Yatham et al., 2018). Cariprazine, with an RG-T 1, is added in the current consensus because several double-blinded RCTs have supported the efficacy of cariprazine in the acute treatment of manic or mixed episodes (Calabrese et al., 2015; Durgam et al., 2015; Sachs et al., 2015).

Asenapine is another atypical antipsychotic agent with high efficacy for acute mania treatment (Landbloom et al., 2016; McIntyre et al., 2009, 2010); however, asenapine is not added to the recommendation because it may not be available in Taiwan. An RCT on paliperidone monotherapy for manic episodes suggested that a high (12 mg/day), but not low (3 or 6 mg/day), dosage was more effective than placebo for alleviating manic symptoms (Berwaerts et al., 2012). Another RCT on paliperidone adopted a flexible dosage design (3–12 mg/day; median dosage=9 mg/day) and found that paliperidone was more effective than placebo and noninferior to quetiapine in acute mania treatment (Vieta et al., 2010). Therefore, in the current consensus, paliperidone (12 mg/day) had an LoE(B) and RG-T 2—somewhat different from in the 2018 CANMAT and ISBD guideline, where paliperidone is designated level 1 evidence (>6 mg/day) and considered a first-line treatment option (Yatham et al., 2018).

Regarding the conventional antipsychotic agents, haloperidol is the only drug with an LoE(A), but an RG-T 2 due to the related safety and tolerability concerns. The LoE is unchanged for other conventional antipsychotic agents; however, fluphenazine, loxapine, thioridazine, and trifluoperazine are removed from the current consensus because high-level evidence is lacking and unavailability used in Taiwan now. The RG-T of chlorpromazine, sulpiride, clothiapine, and flupenthixol is retained at 3.

3.1.2. Combination/augmentation or adjunctive/add-on therapy for manic phase

The combination of lithium and valproate is very common in clinical settings, but relevant evidence is noted as coming from only noncontrolled studies, with an LoE(C1) (Reischies et al., 2002a, 2002b). 50% of experts consider it to have an RG-T of 1 on the basis of their related clinical experience and difficulties in initiating new clinical trials.

Clinical trials on combination therapy for acute mania treatment have mostly employed an atypical antipsychotic agent and either lithium or valproate. Quetiapine, risperidone, or olanzapine in combination with lithium or valproate has an LoE(A) and RG-T 1 (Durgam et al., 2015). Notably, only 50% of the experts voted for an RG-T 1 for olanzapine–mood stabilizer combination therapy; the metabolic adversity, side effects, and tolerability of this combination remain serious concerns. This result is similar to that for olanzapine monotherapy in the manic phase. The recommendation reduction for olanzapine monotherapy is marginal: 44% and 56% of experts voted for an RG-T 1 and 2, respectively. The combination of aripiprazole with mood stabilizers had an LoE(B), evidenced by one RCT (Vieta et al., 2008c). Compared with other atypical antipsychotic agents used in combination therapy, aripiprazole may have a more favorable side effect profile, with an RG-T 1.

Electroconvulsive therapy(ECT) is considered for combination therapy after pharmacotherapy failure. An early comprehensive review on open studies and case reports indicated that ECT results in remission or considerable improvement in 80% of patients with mania (Mukherjee et al., 1994). However, the only double-blind RCT comparing ECT plus pharmacotherapy with pharmacotherapy alone was published in 1994; its results indicated that ECT combined with chlorpromazine was more efficacious (Sikdar et al., 1994). A recent meta-analysis on 12 RCTs found that, regardless of blinding status, ECT combined with pharmacotherapy is more efficacious in reducing manic symptoms than is pharmacotherapy alone, and the differences in efficacy occurred within three to five treatment sessions or after 1 week of treatment (Zhang et al., 2021). Despite a lack of sufficient evidence, ECT is recommended for patients with severe, delirious mania or severe mania during pregnancy and as a treatment option in patients with treatment-resistant mania (Goodwin et al., 2016; Grunze et al., 2009; Yatham et al., 2018). The experts acknowledged the unique role of ECT in the treatment for particularly severe mania because of its rapid effects and high efficacy; 47% and 41% of the experts voted for an RG-T 3 and 2, respectively.

3.2. Acute depressive phase

Most treatments for bipolar depression are unchanged compared with those in the 2012 consensus; however, the RG-T for valproate and lamotrigine is downgraded to 2 (Table 3).

3.2.1. Monotherapy for bipolar depressive phase

Research evidence for lithium monotherapy in the depressive phase has been inconsistent, with an LoE(D). Considering that lithium is widely prescribed in clinical practice and approved by Taiwan MOHW, its RG-T remained at 2.

The LoE of valproate monotherapy in the depressive phase is B (Bond et al., 2010; Selle et al., 2014), but the RG-T was upgraded to 1 in the previous version because valproate is widely prescribed and approved by Taiwan's MOHW. The experts raised concerns regarding the metabolic influence and detrimental effects in pregnant women (Yatham et al., 2018), and voted for an RG-T 2 in the current consensus.

Although a meta-analysis indicated the efficacy of lamotrigine monotherapy in bipolar depression (Geddes et al., 2009), only one double-blind placebo-controlled study on lamotrigine monotherapy obtained a positive result (Calabrese et al., 1999). Concerns was raised for that the dose and titrating speed–dependent allergic reactions may affect the tolerability of lamotrigine in clinical practice (Huang et al., 2002; Wong et al., 1999); therefore, the LoE and RG-T of lamotrigine monotherapy is B and 2.

The RG-T of quetiapine monotherapy remains unchanged, at 1. Moreover, this treatment option is widely accepted as the first-line monotherapy for bipolar depression, with appropriate dosage being 300–600 mg/day (Datto et al., 2016; Maneeton et al., 2012; Sanford and Keating, 2012; Selle et al., 2014).

Monotherapy with lurasidone, a new atypical antipsychotic (Loebel et al., 2014a), has an LoE(A) and RG-T 1 for acute bipolar depression. Lurasidone has been widely used for first-line monotherapy and in combination therapy with lithium/valproate for bipolar depression treatment (Loebel et al., 2014a, 2014b; Suppes et al., 2016) at a dose of 40–120 mg, with favorable tolerability (Wang and Osser, 2020).

Cariprazine has an LoE(A) and RG-T 2; however, it has not yet been approved in Taiwan for bipolar depression treatment (Durgam et al., 2016).

Ketamine has been proven a newly fast-acting antidepressant and to be effective for treatment-resistant depression (McIntyre, 2021), widely

Table 3
Bipolar depressive phase therapy.

	Medication or treatment	LoE	2022 RG-T	Taiwan MOHW approval	Recommended daily dose for adults	RG-T vote results (%)
Monotherapy for bipolar depressive phase						
1	Lurasidone	A	1	V	20–120 mg	**1: 64%** vs.2: 33% vs. 3: 3%
2	Quetiapine	A	1	V	300–600 mg	**1: 97%** vs. 2: 3%
3	Cariprazine	A	2		1.5–3 mg	1: 42% vs. **2: 45%** vs.3: 12%
4	Lamotrigine	B	2	V	50–200 mg	1: 33% vs. **2: 67%**
5	Valproate	B	2	V	[C] = 70–90 mg/L	1: 21% vs.**2: 70%** vs. 3:
6	Olanzapine	B	2		5–20 mg	**2: 64%** vs. 3: 36%
7	Lithium	D	2	V	[C] = 0.8–1.3 mg/L	**2: 61%** vs.3: 36% vs. 4: 3%
8	Carbamazepine	D	4		[C] = 4–15 mg/L	3: 12% vs. **4: 88%**
Combination or adjunctive therapy for bipolar depressive phase						
1	Adjunctive Lurasidone	A	1	V		**1: 91%** vs. 2: 6% vs. 3: 3%
2	Pramipexole + ongoing treatment	B	3			2: 18% vs. **3: 48%** vs. 4: 33%
3	rTMS + ongoing treatment	C1	2			**2: 58%** vs. 3: 39% vs. 4: 3%
4	Ketamine + ongoing treatment	C1	3			1: 3% vs. 2: 12% vs. **3: 48%** vs. 4: 15% vs. No Consideration: 21%
5	Lithium or valproate +Venlafaxine/L-Thyroxine/Topiramate	C1	3			1: 3% vs. 2: 24% vs. **3: 48%** vs. 4: 24%
6	Lithium or valproate+ Sulpiride	C1	3			2: 6% vs. **3: 70%** vs. 4: 24%
7	ECT + ongoing treatment	C1	3			1: 3% vs. 2: 36% vs. **3: 61%**

Recommended daily doses may have variations due to differences in approval.
RG-T, Taiwan recommendation grade; MOHW, Ministry of Health and Welfare; LoE, level of evidence.

considered a risk factor for bipolar depression (Dudek et al., 2013). Several meta-analyses with nonpreplanned data summation have also confirmed the efficacy of ketamine in bipolar depression, with an LoE (C1) (Joseph et al., 2021; Romeo et al., 2015; Singh et al., 2021). Considering the lack of long-term safety data and its invasive protocols, ketamine is given an RG-T 3.

3.2.2. Combination/augmentation or adjunctive/add-on therapy for bipolar depression

Adjunctive lurasidone with mood stabilizers was demonstrated to be effective in treating bipolar depression (Loebel et al., 2014b). Moreover, in patients with a breakthrough acute depressive episode or poor response to antipsychotic monotherapy, lurasidone adjunctive therapy may be an alternative option (Yatham et al., 2018); with an LoE(A) and RG-T 1.

Pramipexole+lithium/valproate has limited evidence of clinical trials, with an LoE(B) and RG-T 3 (Fornaro et al., 2020; Tundo et al., 2019).

Venlafaxine/thyroxine+lithium/valproate was voted with an RG-T 3. The reported efficacies of antidepressant use in patients with bipolar depression have been inconsistent (Bahji et al., 2020; Hu et al., 2022); however, antidepressants monotherapy for bipolar depression should be avoided (Pacchiarotti et al., 2013; Vieta, 2014). Thyroxine treatment was reported effective against bipolar depression with concerns of possible hormonal side effects (Bauer and Whybrow, 2021).

Regarding the neurostimulation therapy of patients with bipolar depression, repetitive transcranial magnetic stimulation (rTMS) augmentation therapy has an RG-T 2 and ECT an RG-T 3. Although studies have reported inconsistent efficacy of rTMS for bipolar depression (Gold et al., 2019; Mutz et al., 2018), mood-switching is uncommon (Mutz et al., 2018). US Food and Drug Association (FDA) offers grants for breakthrough device designation to rTMS in treating bipolar depression (Camprodon, 2021); however, rTMS has not been formally approved by the US FDA for that. ECT can be used to treat emergent mood disorder or psychotic disorder with severe suicidal ideation (Schoeyen et al., 2015). In patients with intolerable medication side effects, ECT may be an alternative treatment option; however, no definite suggestions for unilateral or bilateral placement of the electrodes are available. The energy- or time-related cognitive impairment caused by ECT should be considered.

3.3. Maintenance phase

Maintenance or prophylactic treatment is administered to prevent recurring mood episodes. The continuation treatment period is defined as the first 6 months after an acute episode, whereas the maintenance phase is from months 6–12 after an acute episode enters remission. No international consensus on the indication of maintenance treatment has been reported yet. However, bipolar disorder is characterized by its chronicity and the ease of relapse. In addition, bipolar disorder may be linked to brain volume reduction in gray and white matter and exacerbation of cognitive impairment. Frequent relapse may also trigger shortening of the interepisode duration, a decrease in the interepisode functional recovery, and lessening of pharmacologic and psychotherapeutic effects (McIntyre et al., 2020a). Therefore, some guidelines suggest that almost all individuals with bipolar disorder should receive maintenance treatment (Malhi et al., 2020; Sakurai et al., 2020; Yatham et al., 2018). Successful long-term maintenance treatment can prevent subsequent episodes, alleviate residual and subsyndromal symptoms, and restore patients' functioning and quality of life. The current consensus, based on the WFSBP guideline and Netherland guideline (Grunze et al., 2013), suggests that the maintenance treatment should be administered under the consideration of three factors: the number of episodes, the severity of symptoms, and family history of bipolar disorder (Table 4).

3.3.1. Monotherapy for maintenance phase

Lithium is correlated with more side effects and twofold higher risk of discontinuation than valproate or lamotrigine; however, these three mood stabilizers have an RG-T 1. Most studies on carbamazepine have had methodological concerns, such as a lack of a placebo arm, an insufficient sample size or observation period, or a nonblinded study design (Grunze et al., 2021; Grunze et al., 2013), leading to an LoE(C1). However, the RG-T of carbamazepine is upgraded to 2 because of the drug's relatively few side effect for weight gain. Skin allergy may not be a concern during the maintenance phase, but drug–drug interactions may occur (Grunze et al., 2021).

Recent studies have suggested that the target lithium range in the maintenance phase should be 0.6–0.8 mmol/L (or mEq/L) in contrast to the target range of 0.6–1.2 mmol/L in the previous consensus. Lithium concentrations $>$ 0.8 mmol/L may increase the renal impairment risk (Goodwin et al., 2016; Hsu et al., 2021; Nolen and Weisler, 2013; Severus et al., 2008); by contrast, lithium concentrations $<$ 0.6 mmol/L

Table 4
Maintenance phase therapy.

	Medication or treatment	LoE	2022 RG-T	Taiwan MOHW approval	Recommended daily dose for adults	RG-T vote results (%)
Monotherapy for maintenance phase						
1	Lithium	A	1	V	600–1200 mg (serum level, **0.6–0.8 mmol/L**)	**1: 97%** vs. 2: 3%
2	Valproate	A	1	V	Serum level, 50–100 mg/L	**1: 50%** vs. 2: 44% vs.3: 6%
3	Lamotrigine	A	1	V	50–200 mg	**1: 58%** vs. 2: 27% vs.3: 15%
4	LAI Aripiprazole	A	1	V	300–400 mg/q4week	**1: 94%** vs. 2: 6%
5	Aripiprazole	A	1		15–30 mg	**1: 71%** vs. 2: 29%
6	Quetiapine	A	1		300–600 mg	**1: 61%** vs. 2: 36% vs. 3: 3%
7	Olanzapine	A	2	V	5–20 mg	1: 15% vs. **2: 85%**
8	LAI Risperidone	A	2	V	25–37.5 mg/Q2 of week, MOHW approval for nonrapid cycling patients	1: 39% vs. **2: 61%**
9	Carbamazepine	C1	2	V	600–1200 mg (serum level, 4–15 mg/L)	1: 6% vs. **2: 58%** vs. 3: 36%
10	Lurasidone	C1	2		20–120 mg	1: 21% vs. **2: 50%** vs. 3: 29%
Combination or adjunctive therapy for maintenance phase						
1	Lithium + valproate	B	1	V		**1: 88%** vs. 2: 9% vs. 3: 3%
2	Lithium + Carbamazepine	B	2	V		1: 24% vs. **2: 74%** vs. 3: 3%
3	Lithium + Lamotrigine	B	2	V		1: 15% vs. **2: 67%** vs. 3: 18%
4	Lithium or valproate or Lamotrigine + Aripiprazole	A	1	V	MOHW approval for combining lithium/valproate	**1: 82%** vs. 2: 18%
5	Lithium or valproate + LAI Risperidone	A	1	V	MOHW approval for rapid cycling patients	**1: 56%** vs. 2: 44%
6	Lithium or valproate +Quetiapine	A	1			**1: 94%** vs. 2: 6%
7	Lithium or valproate + Olanzapine	B	2	V		1: 12% vs. **2: 85%** vs. 3: 3%
8	Lithium or valproate + ziprasidone	B	2	V		1: 9% vs. **2: 76%** vs. 3: 15%
9	Lithium or valproate + Lurasidone	B	2			1: 12% vs. **2: 59%** vs. 3: 29%
10	Lithium or valproate + Risperidone	B	2			1: 21% vs. **2: 79%**
11	Olanzapine + Fluoxetine	B	3			1: 9% vs. 2: 42% vs. **3: 45%** vs. 4: 3%
12	Adjunctive Clozapine	C1	3			1: 3% vs. 2: 21% vs. **3: 67%** vs. 4: 9%
13	Adjunctive ECT	C1	4			2: 3% vs. 3: 45% vs. **4: 52%**
14	Adjunctive Topiramate	D	3			**3: 48%** vs. 4: 33% Further study needed: 18%
15	Lithium+ Oxcarbazepine	D	4			3: 30% vs. **4: 39%** Further study needed: 30%
16	Adjunctive Gabapentin	D	4			2: 3% vs. 3: 9% vs. **4: 52%** Further study needed: 36%

Recommended daily doses may have variations due to differences in approval.
RG-T, Taiwan recommendation grade; MOHW, Ministry of Health and Welfare; LoE, level of evidence; LAI, long-acting injectable.

may be associated increased risk of relapse (Nolen and Weisler, 2013).

Three oral antipsychotics (aripiprazole, quetiapine, and olanzapine) and two long-acting injectable (LAI) atypical antipsychotics (LAI aripiprazole and LAI risperidone) all have an LoE(A). However, oral quetiapine and aripiprazole have not been approved by Taiwan's MOHW for maintenance monotherapy. Nevertheless, considering being widely used and acceptable safety, oral quetiapine and aripiprazole are given an RG-T 1. Oral olanzapine and LAI risperidone are given an RG-T 2 for the side effects of weight gain, elevated prolactin, and low efficacy in preventing depressive episodes. Although LAI aripiprazole may prevent mainly the recurrence of manic episodes, the RG-T was 1 regarding their LoE(A), benefit of drug adherence, acceptable safety of weight change, and approval by Taiwan MOHW.

A 2-year open-label study including patients who responded to lurasidone monotherapy in the acute depressive phase reported that lurasidone monotherapy led to a lower relapse rate than did standard maintenance treatment (Pikalov et al., 2017). Given its confirmed antidepressant efficacy in acute bipolar depressive episodes and its minimal effects on weight and metabolic parameters, as observed in the aforementioned study (e.g., mean weight change, +0.8 kg), lurasidone is given an upgraded RG-T 2, with its LoE(C1) (Higuchi et al., 2021; Pikalov et al., 2017).

3.3.2. Combination/augmentation or adjunctive/add-on therapy for maintenance phase

Lithium+valproate, which is commonly used clinically, has an LoE (B) and RG-T 1. An RCT study confirmed that lithium+lamotrigine provides a longer time to relapse/recurrence than lithium+placebo (van der Loos et al., 2011), with LoE(B) and RG-T 2.

Aripiprazole+lithium/valproate led to longer time to any mood relapse than placebo+ lithium/valproate (Marcus et al., 2011; Woo et al., 2011). Furthermore, in a double-blind RCT study, additional marginal prophylactic effects against manic/mixed relapse were noted in treatment with aripiprazole+lamotrigine compared with lamotrigine monotherapy (HR=0.55, $p = 0.058$) (Carlson et al., 2012). Overall, the LoE is A and the RG-T is 1.

In terms of preventing any mood, depressive, or manic episodes, quetiapine+lithium/valproate has higher efficacy than lithium or valproate alone; however, it is more likely to cause weight gain and metabolic syndrome. The LoE and RG-T for quetiapine+lithium/valproate to be A and 1 (Suppes et al., 2009; Vieta et al., 2008b).

Although LAI risperidone can cause weight gain and elevate prolactin levels, an RCT investigating patients with rapid-cycling bipolar disorder confirmed that LAI risperidone+ lithium/valproate leads to a longer time to relapse of any mood episode than placebo injection+lithium/valproate (Fagiolini et al., 2010; Macfadden et al., 2009). Considering MOHW approval of LAI risperidone for rapid cycling bipolar patients, the RG-T was upgraded to 1.

Olanzapine+lithium/valproate outperformed placebo+lithium/valproate in preventing relapse, but at the expense of a greater body weight increase (Tohen et al., 2004), with an LoE(B) and RG-T 2. For patients who responded to it in their acute bipolar depressive phase, the olanzapine–fluoxetine combination (OFC) could maintain and further stabilize both depressive and manic symptoms than lamotrigine alone, with an LoE(B) and RG-T 3 (Brown et al., 2009).

The combination of ziprasidone (Bowden et al., 2010) or oral risperidone (Valdes et al., 2019; Yatham et al., 2016) with lithium/valproate demonstrated efficacy against any mood or manic relapse

but not against depressive episodes, with its LoE(B) and RG-T 2.

An RCT reported that lurasidone+lithium/valproate led to a marginally longer time to recurrence of any mood episode (HR=0.71, $p = 0.078$) than placebo+lithium/valproate. Further preplanned subgroup analysis demonstrated that adjunctive lurasidone led to a significantly low recurrence for any mood episode in patients with an index episode of depression (HR=0.57, $p = 0.039$) and with any index episode except rapid cycling (HR=0.69, $p = 0.046$) (Calabrese et al., 2017). Another 2-year open-label continuation study demonstrated that adjunctive lurasidone has probability of relapse similar to that reported by other RCTs on adjunctive atypical antipsychotics (Pikalov et al., 2017). The LoE is B and the RG-T is 2.

Case reports, open randomized studies, and registry studies have reported that adding clozapine to ongoing treatments can alleviate symptoms and prevent rehospitalization and any mood relapse (Hummel et al., 2002; Nielsen et al., 2012; Puri et al., 1995; Suppes et al., 1999) in patients with treatment-refractory or incompletely responding bipolar disorder. Adjunctive clozapine may reduce total medication use (Suppes et al., 1999). However, metabolic syndrome, weight gain risks and hematologic safety issue are concerns. The LoE and RG-T are considered to be C1 and 3, respectively.

No RCT supporting the prophylactic effects of adjunctive topiramate has been reported; however, some naturalistic studies have confirmed the additional mood-stabilizing effects of adjunctive topiramate on both polarity symptoms in the maintenance phase (Marcotte, 1998; Vieta et al., 2002). Topiramate has acceptable side effects and several potential benefits such as decreased body weight gain (Roy Chengappa et al., 2006) and comorbid obsessive symptom alleviation (Sahraian et al., 2014), with an LoE(D) and RG-T 3.

Adjunctive gabapentin or oxcarbazepine has inconsistent results or insufficient evidence to advice or against the use of the intervention. A small placebo-controlled trial reported adjunctive gabapentin may decrease the clinical disease severity but did not have statistical benefit for preventing any episode relapses (Vieta et al., 2006). In a small RCT, the maintenance effects of lithium+oxcarbazepine and lithium+placebo had no differences in terms of mood relapse, but lithium+oxcarbazepine tended to prevent depressive episodes (Vieta et al., 2008a).

Accumulating evidence (Loo et al., 2011; Madero et al., 2022; Petrides et al., 2011; Santos Pina et al., 2016) from naturalistic studies, case reports and retrospective reviews has confirmed that adjunctive ECT may reduce the number of future mood episodes or hospitalization days, with LoE(C1). However, differentiating continuation ECT from maintenance ECT in the literature is challenging. ECT sessions in stable and euthymic patients may not be reasonable (Grunze et al., 2013). Considering the related rationality, anesthesia risk, and ECT-induced cognitive side effects, the experts downgrade ECT's RG-T to 4 and suggest that maintenance ECT should be administered only to patients with poor responsiveness to or nontolerance of other treatments. The ECT protocols and frequencies used among the reviewed studies were nonuniform.

3.3.3. Suggested maintenance or prophylactic treatment duration

No international consensus has been reached regarding the most appropriate treatment period for maintenance or prophylactic treatment. Bipolar disorder tends to recur in around 16–18 months (Swann, 2005), but the duration in most maintenance/prophylactic studies was only 6–12 months; to determine the time point at which the treatment should be discontinued, studies spanning 2–3 years are required (Frederick K. Goodwin, 2007). The maintenance treatment period is mainly based on individual considerations, such as patient preferences, safety issues, and specific circumstances (e.g., pregnancy). Psychoeducation and psychological interventions to ensure patient compliance are key to preserving patient functioning and preventing bipolar disorder sequelae.

3.3.4. Role of antidepressants in maintenance phase

Although approximately half of patients with bipolar disorder in the maintenance phase have residual depressive symptoms, antidepressant treatment in this phase may have questionable efficacy in prolonging the remission period of depression. Reports on the risk of manic-switching with antidepressants have been inconsistent (Arvilommi et al., 2010; Grunze et al., 2018). Generally tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitor may increase the risk of drug-induced manic-switching (Ghaemi et al., 2008; Post et al., 2006). The combination of antidepressant and mood stabilizer may prevent the potential hazards of manic-switching than using an antidepressant alone (Ghaemi et al., 2008; Sachs and Thase, 2000). Additionally, in patients with acute bipolar depression, antidepressants have been noted to induce de novo mixed states or exacerbate current mixed features, although these findings were reported by observational studies and case reports (Dilsaver and Swann, 1995; El-Mallakh et al., 2008; Grunze et al., 2018).

3.3.5. Use of typical antipsychotics in maintenance phase

Typical antipsychotics may have effective outcomes in treating acute mania but incur high risks of extrapyramidal side effects, tardive dyskinesia, and neuroleptic malignant syndrome (Carbon et al., 2017; Gao et al., 2008; Tural and Onder, 2010). These side effects may contribute to high risks of nonadherence to treatment in the maintenance phase. Long-term use of typical antipsychotics can be neurotoxic and cause the loss of gray matter volume in patients with schizophrenia (Chen and Nasrallah, 2019). After remission of a manic episode, continual adjunctive perphenazine cannot effectively prevent manic relapses but increase discontinuation/dropout rates, depressive relapse risk and intolerable side effect incidence (Zarate and Tohen, 2004). Similarly, the prophylactic effects of flupenthixol decanoate have been inconsistent, but this treatment might be associated with a significant increase of depressive episodes and duration of depressive symptoms (Grunze et al., 2013).

3.3.6. Role of LAI antipsychotics in maintenance phase

LAI antipsychotics, such as LAI risperidone and LAI aripiprazole have been approved by Taiwan's MOHW for maintenance treatment. Poor adherence/nonadherence to medication is common in bipolar disorder; it is strongly associated with increased risks of relapse, suicidality, and impaired functioning (Chakrabarti, 2016; Jawad et al., 2018; Karadağ et al., 2019; Montes et al., 2013; Perlis et al., 2010). LAI antipsychotics provide consistent medication concentrations to ensure a relatively low risk of nonadherence (Pacchiarotti et al., 2019). 94% of experts agree that LAI antipsychotics should be listed as monotherapy alternatives in the maintenance phase.

3.4. Bipolar mixed features: Acute and maintenance phases

Many definitions of bipolar mixed states and related terms (e.g., dysphoric mania) have been mentioned over the centuries; however, the unavailability of a generally accepted definition in the literature has impeded the collection of evidence on the various therapeutic responses. Treating mixed features may not be equal to combing the treatment of pure mania and pure depression. Extremely few studies containing nonpreplanned post-hoc analyses of RCTs or naturalistic studies have provided evidence of the efficacy of pharmacological interventions in patients with mixed features (Grunze et al., 2018). This treatment consensus used the concept of DSM-5 mixed features. A proxy DSM-5 definition (meeting pure mood episodes with ≧3 opposite pole symptoms by scales (McIntyre et al., 2019; Tohen et al., 2014b) or meeting DSM-IV criteria of the mixed episode (Baker et al., 2003; Houston et al., 2009; Sachs et al., 2006) was operationalized in those post-hoc studies. Worth noting some of these studies were too statistically underpowered to differentiate the efficacies of these interventions from placebo. These limitations and uncertainty mean that additional comprehensive

investigations on the treatment of bipolar mixed features are warranted. There is no LoE and RG-T information reported in the current recommendations for acute and maintenance therapies in patients with bipolar mixed features, concerning the absence of sufficient evidence. The relevant recommendations should be considered with caution and may be revised as further evidence accumulates.

3.4.1. Acute manic mixed features

For its efficacy and acceptability, the experts suggest considering aripiprazole alone (Sachs et al., 2006), cariprazine alone (McIntyre et al., 2019), olanzapine (+lithium/valproate) (Baker et al., 2004; Baker et al., 2003; Houston et al., 2009; Tohen et al., 2014b), quetiapine+lithium/valproate (Suppes et al., 2013; Zarate et al., 2000), and valproate alone (Swann et al., 1997) for treating acute manic mixed features.

For their efficacy against symptoms, aripiprazole, olanzapine (+lithium/valproate), and quetiapine+lithium/valproate can alleviate manic and depressive symptoms; however, valproate alone may improve only manic symptoms because outcomes for depressive symptoms have not been reported thus far (Swann et al., 1997). Cariprazine can improve manic symptoms but only significantly alleviate depressive symptoms in patients with a baseline MADRS score$\geq$ 10 (McIntyre et al., 2019). Similarly, olanzapine(+lithium/valproate) may improve depressive symptoms in patients with baseline moderate-to-severe depressive symptoms (i.e., 21-item HDRS score$\geq$20) (Baker et al., 2004, 2003).

3.4.2. Acute depressive mixed features

For acute depressive mixed features, the evidence related to pharmacological interventions is much more limited than that for acute manic mixed features. Bipolar mixed depression has received less attention than mixed mania for a long time. For instance, definitions for acute depressive mixed episodes corresponding to the DSM-IV criteria are unavailable.

Recently, the debate has risen about whether DSM-5-defined bipolar depression with mixed features could fully capture the mixed population, given the still low prevalence of DSM-5-defined mixed features (Shim et al., 2019). Several studies have reported that having 3 or fewer manic symptoms ("less strict") may be sufficient to define a mixed population (Goldberg et al., 2009; McIntyre et al., 2015; McIntyre et al., 2020b; Miller et al., 2016). Therefore, two recent studies defined the presence of mixed features as a baseline YMRS score $\geq$ 4 (McIntyre et al., 2015; McIntyre et al., 2020b).

The experts suggest considering cariprazine(McIntyre et al., 2020b), lurasidone (McIntyre et al., 2015), olanzapine (Tohen et al., 2014a), and adjunctive ziprasidone (Patkar et al., 2012) for treating acute depressive mixed features.

For the efficacy, cariprazine, lurasidone, and adjunctive ziprasidone can improve depressive symptoms but not manic symptoms. Olanzapine can improve depressive and manic symptoms. The discrepancy in the antimanic efficacies of cariprazine and ziprasidone here with the recommendation in treating acute mania may result from a low baseline severity of manic symptoms for mixed symptoms in the reviewed studies (i.e., the floor effect) (Yatham et al., 2021).

3.4.3. Maintenance treatment after an acute mixed episode/feature

There was no study for maintenance treatment after an acute mixed feature defined by DSM-5 or proxy criteria. The following expert recommendations are based on studies for mixed episodes defined by DSM-IV:

The experts suggest considering quetiapine+lithium/valproate (Suppes et al., 2009; Vieta et al., 2008b; Vieta et al., 2012), quetiapine monotherapy or lithium monotherapy (Weisler et al., 2011), and aripipirazole+lamotrigine (Carlson et al., 2012) for maintenance treatment after an acute mixed episode/feature.

Regarding prophylactic efficacy against bipolar symptoms after an acute mixed episode/feature, the experts note that quetiapine+lithium/valproate or quetiapine monotherapy prevents any/manic/depressive relapses; that lithium alone can prevent any/manic relapses; and that aripiprazole+lamotrigine can prevent depressive episodes.

4. The updated TSBPN guideline and actual prescription practice across Asia for bipolar disorder

This updated guideline referred to not only research evidence but also the expert opinion of 34 psychiatrists with an average of 26 years of clinical experience. Indeed, data on real-world prescription patterns for bipolar disorder across Asian countries partially support the treatment recommended in the updated TSBPN guideline. For example, lithium, valproate, olanzapine, quetiapine, and aripiprazole were the most commonly prescribed psychotropics for outpatients or patients upon discharge (Grover et al., 2021; Lin et al., 2022; Reddy et al., 2019; Shinozaki et al., 2022). As the present guideline recommends, the prescription patterns support their broad effectiveness on manic, depressive and even mixed symptoms, and their roles in acute and maintenance treatment. This updated guideline didn't prioritize monotherapy over combination therapy for the acute treatment of mania since the latter may be more frequently used in clinical practice (Reddy et al., 2019). Typical antipsychotics are seldom used nowadays and were removed from this updated guideline. Indeed, a multicentric study recently observed approximately 3% of bipolar patients received typical antipsychotics several months after achieving clinical remission (Grover et al., 2021; Lin et al., 2022). About 30–40% of bipolar patients were prescribed antidepressants, even in their manic or mixed episodes or in clinically symptomatic remission (i.e., having a duration of remission of more than 6 months) (Grover et al., 2021; Reddy et al., 2019; Tokumitsu et al., 2020; Yoon et al., 2018). Of note, a Korean report demonstrated the prescription rate of antidepressants for bipolar disorder was sustained and gradually increased in recent years (Yoon et al., 2018). Although a combination strategy of antidepressants with mood stabilizers and/or atypical antipsychotics was mentioned in various guidelines, more rigorous evidence is warranted to elaborate on the actual effectiveness of antidepressants in combination treatment and the risk of switch to manic polarity in the acute and maintenance phase of bipolar depression (Shinozaki et al., 2022; Yoon et al., 2018). On the other hand, the considerably lower prescription of evidence-based lamotrigine and lurasidone for bipolar depression in the acute and maintenance phase could be seen as a deviation from the recommendation of the treatment guidelines. For example, the prescription rates of lamotrigine were 1.7% in India and 4% in Taiwan, but a high rate of 20% in Japan (Grover et al., 2021; Lin et al., 2022; Shinozaki et al., 2022). The high prescription rate of 60–70% of atypical antipsychotics in real-world clinical practice reflects the increasingly important role of atypical antipsychotics in treating bipolar in this updated guideline (Grover et al., 2021; Lin et al., 2022; Shinozaki et al., 2022).

5. Summary of the results

In the acute manic phase, lithium, valproate, aripiprazole, quetiapine, risperidone, and cariprazine are recommended as the first-line monotherapy. Taiwanese experts also suggest a combination regimen of mood stabilizers plus quetiapine, risperidone, or olanzapine, followed by that of a mood stabilizer plus aripiprazole and then by that of lithium plus valproate.

In the acute depressive phase, the experts recommend lurasidone monotherapy, followed by adjunctive lurasidone and quetiapine monotherapy. Other monotherapies such as mood stabilizers (lithium, valproate, or lamotrigine) and atypical antipsychotics (cariprazine and olanzapine) can be considered. Ketamine or rTMS combined with ongoing treatment can be considered for patients who cannot tolerate their ongoing regimen and those for whom this regimen has limited efficacy.

In the maintenance phase, mood stabilizer monotherapy (lithium, valproate, or lamotrigine) and atypical antipsychotic monotherapy (quetiapine, oral and LAI aripiprazole) is most recommended. Mood stabilizers combined with aripiprazole, quetiapine, or LAI risperidone and lithium+valproate are designated effective combination regimens.

Considering the high episode recurrence and high subthreshold symptom or mood instability prevalence, treatment should be maintained for as long as possible in the maintenance phase. In patients with history of mixed episodes, prophylactic treatments including certain antidepressants or typical antipsychotics should applied cautiously; their use should be avoided in the maintenance phase because of the risk of provoking a mixed state or opposite-polarity episodes (El-Mallakh et al., 2008; Grunze et al., 2018; Wu and Okusaga, 2015). 80% of the experts do not recommend the use of typical antipsychotics in the maintenance phase. Moreover, 94% of the experts agree to list LAI atypical antipsychotics as monotherapy alternatives in the maintenance phase.

For acute and maintenance treatment of mixed features/episodes, the experts suggest the following regimens:

1. For acute manic mixed features: aripiprazole, cariprazine, olanzapine (+lithium/valproate), quetiapine+lithium/valproate, and valproate monotherapy.
2. For acute depressive mixed features: cariprazine, lurasidone, olanzapine, and adjunctive ziprasidone.
3. For maintenance regimen after an acute mixed episode/ feature: quetiapine+lithium/valproate, quetiapine monotherapy, lithium monotherapy, and aripiprazole+lamotrigine.

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