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Review Article

Taiwan consensus of pharmacological treatment for bipolar disorder

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Abstract

Bipolar disorder is an important psychiatric disorder with different disease phases. The pharmacological treatment is complicated, and is updated frequently as new research evidence emerges. For the purpose of international collaboration, research, and education, the Taiwan consensus of pharmacological treatment for bipolar disorders was initiated by the Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology (TSBPN) – the Bipolar Chapter, which was established in August 2010 and approved as a member of International Society of Bipolar Disorder. TSBPN is the country member of the World Federation of Societies of Biological Psychiatry (WFSBP). The development of the Taiwan consensus for bipolar disorder was mainly based on the template of WFSBP Guidelines, with references to other international guidelines including the Canadian Network for Mood and Anxiety Treatments, and British Association for Psychopharmacology. We have also added Taiwanese experts' experience, Taiwan national health insurance data, and the indications for the pharmacological treatment of bipolar disorder given by the Taiwan Department of Health, to emphasize the balance between efficacy and safety, and to make this consensus a concise, empirical, and important reference for clinical psychiatric practice.

Keywords: bipolar disorder; consensus; pharmacotherapy; Taiwan

1. Introduction

Bipolar disorder is an important mental disorder with mood lability. The international prevalence is 1% for type I, and 1.1% for type II.[1] In Taiwan, the prevalence of bipolar disorder increased from 0.06% in 1996 to 0.4% in 2003, and according to the Taiwan National Health Insurance Research Database,[2–4] there are many patients who were not recognized and treated. Bipolar disorder has different phases, and the pharmacological treatment is complicated, and updated frequently with new research evidence. For the purpose of international collaboration, research, and education, the Taiwan consensus of pharmacological treatment for bipolar disorders was initiated by the Taiwanese Society of Biological Psychiatry and Neuropsychopharmacology (TSBPN) – the Bipolar Chapter,

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which was established in August 2010 and approved as a member of International Society of Bipolar Disorder (ISBD). TSBPN is the country member of the World Federation of Societies of Biological Psychiatry (WFSBP), therefore, the development of the Taiwan consensus for bipolar disorder was mainly based on the template of WFSBP Guidelines,[5,6] with references to other international guidelines, including the Canadian Network for Mood and Anxiety Treatments (CNMAT),[1] and British Association for Psychopharmacology (BAP).[7] We also added Taiwanese experts' experience, Taiwan national health insurance data, and the indications for the pharmacological treatment of bipolar disorder given by the Taiwan Department of Health (DOH) to emphasize the balance between efficacy and safety, and to make this consensus a concise, empirical, and important reference for clinical psychiatric practice. The consensus will be updated periodically based on new findings and clinical evidence, under the opinion and recommendation from Taiwan experts. The consensus will not be used as a reference for legal or insurance purposes.

The Taiwan consensus of pharmacological treatment for bipolar disorder includes three treatment phases: manic, depressive, and maintenance. Each pharmacological agent and treatment is listed in Table 1 with four columns: Category of evidence (CE), Taiwan recommendation grade (RG-T), DOH application, and recommended dosage.

2. CE: six categories from A−F

A. **Full evidence from controlled studies.** Based on two or more double-blind, parallel-group, randomized controlled trials (RCTs) showing superiority to placebo; and one or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control; or in a well-powered non-inferiority trial. In the case of existing negative studies, these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment.

B. **Limited positive evidence from controlled studies.** Based on one or more RCTs showing superiority to

Table 1
Manic phase therapy.

	Medication or treatment	Category of evidence	Taiwan recommendation grade	Approved by Taiwan Department of Health	Recommended daily dose for adults (variations may occur due to different approvals)
Monotherapy					
1	Lithium	A	1	V	600−1200 mg (serum level 0.8−1.3 mg/L)
2	Valproate	A	1	V	1200−3000 mg (loading dose 20−30 mg/kg body weight; serum level 75−100 mg/L)
3	Aripiprazole	A	1	V	15−30 mg
4	Olanzapine	A	1	V	10−20 mg
5	Quetiapine	A	1	V	400−800 mg
6	Risperidone	A	1	V	2−6 mg
7	Ziprasidone	A	1	V	80−160 mg
8	Carbamazepine	A	2	V	600−1200 mg (serum level 4−15 mg/L)
9	Haloperidol	A	2		5−20 mg
10	Paliperidone	B	2		3−12 mg; only 12 mg/d achieves B level
11	Amisulpride	B	2		400−1200 mg
12	Chlorpromazine	B	3		300−1000 mg
13	Zotepine	C1	3		200−400 mg
14	Clozapine	C1	3		100−400 mg (reserved for treatment of refractory mania)
15	Sulpiride	C3	3		400−800 mg
16	Oxcarbazepine	C1	4		900−1800 mg
17	Clothiapine (Etumine)	C3	4		40−160 mg
18	Fluphenazine (Modecate)	C3	4		5−40 mg
19	Flupenthixol (Fluanxol)	C3	4		3−18 mg
20	Loxapine (Rosup)	C3	4		20−100 mg
21	Thioridazine (Melleril)	C3	4		200−800 mg
22	Trifluoperazine (Stelazine)	C3	4		10−60 mg
23	ECT	C1	4		
Combination/augmentation or adjunctive/add-on therapy					
1	Lithium + valproate				
2	Lithium + aripiprazole/ Olanzapine/quetiapine/ risperidone/ziprasidone				
3	Valproate + aripiprazole/ Olanzapine/quetiapine/ risperidone/ziprasidone				

ECT = electroconvulsive therapy.

placebo; or randomized controlled comparison with a standard treatment without placebo control, with a sample size sufficient for a non-inferiority trial. In the case of existing negative studies, these must be outweighed by at least one more positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomized controlled comparison showing non-inferiority to an established comparator treatment.

C. **Evidence from uncontrolled studies or case reports/ expert opinion**
   - C1 Uncontrolled studies based on one or more positive naturalistic open studies (with a minimum of 5 evaluable patients), or a comparison with a reference drug with a sample size insufficient for a non-inferiority trial, and no negative controlled studies existed.
   - C2 Case report based on one or more positive case reports and no negative controlled studies existed.
   - C3 Based on the opinion of experts in the field or clinical experience, or the analysis from Taiwan national health insurance data, and recommended by Taiwan experts.

D. **Inconsistent results.** Positive RCTs are outweighed by an approximately equal number of negative studies.

E. **Negative evidence.** The majority of RCTs or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or inferiority to comparator treatment.

F. **Lack of evidence.** Adequate studies proving efficacy or non-efficacy are lacking.

3. Taiwan recommendation grade (RG-T): from level 1 to 5, based on clinical efficacy, side effects, and DOH indication for bipolar disorders

RG-T 1: CE of A with good risk–benefit ratio; or CE of B or C, strongly recommended by Taiwan experts; and approved as indication for bipolar disorders by DOH.
RG-T 2: CE of A and moderate risk–benefit ratio; or CE of B or C, recommended by Taiwan experts.
RG-T 3: CE of B; or CE of C or D, recommended by Taiwan experts.
RG-T 4: CE of C; or CE of D, recommended by Taiwan experts.
RG-T 5: CE D.

4. Manic phase (Table 1)

Although < 10% of patients in acute mania receive monotherapy and some research evidence shows better efficacy of combination of atypical antipsychotics and mood stabilizers than monotherapy, the WFSBP guidelines still suggest that clinicians need to try to maximize the efficacy of monotherapy to avoid the side effects and risk of combination therapy, which is reserved for patients with severe symptoms, or as the subsequent treatment after failure of initial therapy.[5]

5. Monotherapy for the manic phase

1. The classical mood stabilizers, lithium, valproate, and carbamazepine all have CE of A and RG-T of 1. For dysphoric or mixed mania, valproate may have better efficacy than lithium.[8–10] Carbamazepine may have better efficacy than lithium for dysphoric and mixed-type mania.[11–13] The RG-T of carbamazepine is 2, because of its tolerability and drug–drug interactions. Genotyping HLA-B-1502 has been suggested to reduce the risk of Stevens–Johnson syndrome.[14–18] The genotyping is reimbursed by the Taiwan national health insurance. Oxcarbazepine has a similar chemical structure to carbamazepine, with better tolerance and fewer drug–drug interactions, but has a higher risk of hyponatremia.[19,20] Several small studies have shown inconclusive results for its efficacy for acute mania,[21] so the CE was lowered to C1, and RG-T to level 4.
2. The atypical antipsychotic drugs (second-generation), such as aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone, have a CE of A and RG-T of 1, and may have better efficacy for dysphoric/mixed/ psychotic manic episodes than lithium has. Olanzapine has more adverse effects such as weight gain and metabolic symptoms.[22,23] A head-to-head comparison showed that haloperidol can control manic symptoms more quickly than quetiapine.[24] Some other studies have suggested higher doses of quetiapine may have better responses,[25] but this was inconclusive.[26,27] Taking ziprasidone with high-calorie meals can increase its efficacy.[28]
3. Other atypical antipsychotic drugs. Paliperidone is the active metabolite of risperidone. The CE of the maximum dose of 12 mg/day is B, but the CE of lower doses (6 and 3 mg/day) is D.[29–31] Taking tolerance into consideration, the RG-T of paliperidone is 2. Although amisulpride is frequently used in clinical practice, only one randomized study, with combination of amisulpride and valproate, showed comparable efficacy of amisulpride and haloperidol,[32] with a CE of B and RG-T of 2. Higher doses of amisulpride may be required for acute mania, but they have a risk of hyperprolactinemia. Clozapine showed efficacy for refractory mania in several open trials with a CE of C1,[33–35] but it was limited to patients with a poor response to other antipsychotics. Clozapine has adverse effects of agranulocytosis, weight gain, and metabolic syndrome, therefore, its RG-T is 3. Several small studies showed the efficacy of zotepine for acute mania with a CE of C1,[36–38] but it had side effects of sedation and extrapyramidal symptoms (EPSs), thus, the RG-T is lowered to 3.
4. Conventional antipsychotic drugs (typical or first-generation antipsychotics). Although there is a concern with tolerance, they still have an important role for acute mania with excitement or violence. Conventional antipsychotics, especially at high dose, may exacerbate dysphoric or depressed mood.[39] Haloperidol has a CE of A, but because of EPS side effects and exacerbation of

depressed mood, the RG-T is 2. A randomized placebo-controlled study showed efficacy of chlorpromazine for acute mania,[40] and comparable efficacy with lithium. The CE is B, but the RG-T is 3 due to sedative and EPS effects. From the analysis of the Taiwan national health insurance database, other conventional antipsychotics are frequently prescribed, including sulpiride (Dogmatyl), clothiapine (Etumine), fluphenazine (Modecate), flupenthixol (Fluanxol), loxapine (Rosup), thioridazine (Melleril), and trifluoperazine (Stelazine). The CE is C3 and the RG-T is 4 because of the EPS side effects and possible exacerbation of depressed mood. Sulpiride has remained at the level of RG-T 3 due to its lower incidence of EPS adverse effects.

5. Electroconvulsive therapy (ECT) can be used for patients with poor response to other treatments, or under some special conditions, such as pregnancy. The results from chart review and case reports have shown comparable efficacy of ECT and lithium and some types of antipsychotics in acute mania.[41,42] The response rate is up to 80%.[43] The CE is C1 and RG-T is 4. The repetitive transcranial magnetic stimulation (rTMS) may be a substitute for ECT. However, a single blind study did not show comparable efficacy.[44]

6. Combination/augmentation or adjunctive/add-on treatment for the manic phase

1. The research evidence has shown that combination therapy with lithium and divalproex has 1.5-fold better efficacy than monotherapy with either drug. Combined lithium or divalproex with atypical antipsychotics also has better efficacy than monotherapy with lithium or divalproex.[8–10,45]
2. The research evidence has demonstrated no benefit for combined olanzapine and carbamazepine,[46] and a possible increase in the risk of dyslipidemia and weight gain. The combination is not recommended.

7. Depressive phase (Table 2)

7.1. Monotherapy for depressive phase

1. Only quetiapine has a CE of A. The research evidence confirms the efficacy of quetiapine monotherapy for depressive episodes,[47–51] with better efficacy than lithium monotherapy, paroxetine, and placebo for improvement of depressive symptoms and remission rate.[52,53] However, the tolerability and long-term safety need to be considered. The RG-T of quetiapine for the depressive phase is 1.
2. Lamotrigine has a CE of B,[54–56] but is not approved by the US Food and Drug Administration for the depressive phase. However, it is approved by the Taiwan DOH for the indication of bipolar depressive phase. The RG-T is 1 after taking into consideration prevention of depression relapse. Lamotrigine has side effects such as skin rash, Stevens–Johnson syndrome, and toxic epidermal necrolysis, therefore, the administration of lamotrigine should be started with low dose and slow titration, and requires close monitoring.
3. The CE of valproate for the depressive phase is B, but the level of RG-T is adjusted to 1 because it is widely

Table 2
Depressive phase therapy.

	Medication or treatment	Category of evidence	Taiwan recommendation grade	Approved by Taiwan Department of Health	Recommended daily dose for adults (variations may occur due to different approvals)
Monotherapy					
1	Quetiapine	A	1	V	300–600 mg
2	Lamotrigine	B	1	V	50–200 mg
3	Valproate	B	1	V	[C] = 70–90 mg/L
4	Lithium	D	2	V	[C] = 0.8–1.3 mg/L
5	Olanzapine	B	3		5–20 mg
6	Carbamazepine	D	5		[C] = 4–15 mg/L
Combination/augmentation or adjunctive/add-on therapy					
1	Valproate + lithium	B	2	V	
2	Lithium + lamotrigine	B	2	V	
3	Valproate + lamotrigine	C1	2	V	
4	Olanzapine + fluoxetine	B	3		
5	Quetiapine + SSRI	C1	3		
6	Lithium (or valproate) + fluoxetine/sertraline/paroxetine/bupropion	C3	3		
7	Modafinil + ongoing treatment	B	4		
8	Pramipexole + ongoing treatment	B	4		
9	Lithium (or valproate) + venlafaxine/L-thyroxine/topiramate	C1	4		
10	Lithium (or valproate) + sulpiride	C1	4		
Neurostimulation					
1	ECT + ongoing treatment	C1	4		
2	rTMS + ongoing treatment	C1	4		

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; SSRI = selective serotonin reuptake inhibitor.

prescribed, and approved by the Taiwan DOH. The side effects of weight gain, hair loss, teratogenicity[57,58] and polycystic ovarian syndrome [59−61] need to be considered.
4. The research evidence for use of lithium for depressive episodes is inconsistent, with a CE of D for a blood concentration of 0.8−1.3 mg/L.[52,62] There is still no Taiwan empirical data to take into account. Considering that lithium is widely prescribed in clinical practice in Taiwan, and approved by Taiwan DOH, the RG-T is adjusted to 2.
5. The CE of olanzapine is B, which is primarily based on two studies of olanzapine combined with fluoxetine.[63,64] However, the efficacy of olanzapine monotherapy is still inconclusive, and the side effects of weight gain and metabolic symptoms lower the RG-T to 3.
6. The research evidence for the use of carbamazepine for depressive episodes is inconclusive,[65] with a CE of D and RG-T of 5.

8. Combination/augmentation or adjunctive/add-on treatment for the depressive phase

1. Combination therapy with lithium and valproate/lamotrigine is the first-line approach in many treatment guidelines for better efficacy than monotherapy. The CE is B and RG-T is 2. Only open trials have been conducted for combination of valproate and lamotrigine; the CE is C1 and RG-T is 2. There is a concern that more side effects may occur with this combination therapy, especially in the central nervous system and skin.
2. Antidepressants are frequently prescribed for depressive episodes, but there has been a limited number of studies with small sample sizes or short study periods. The best evidence is for combination of olanzapine and fluoxetine,[63,64] with a CE of B and RG-T is 3 on account of weight gain and metabolic side effects. Some open trials have shown positive results for quetiapine combined with selective serotonin reuptake inhibitor, leading to a CE of C1 and RG-T of 3. Nonetheless, the evidence for combination of lithium (or valproate) with antidepressants (sertraline/paroxetine/bupropion) is inconsistent and CE is D in the WFSBP guidelines.[66,67] Due to the Taiwan national insurance database showing that antidepressants are widely prescribed for the depressive episodes in bipolar disorder, the CE has been adjusted to C3 and the RG-T to 3. Some other open trials have confirmed the efficacy of lithium (or valproate) combined with venlafaxine, L-thyroxine, or topiramate, which has led to a CE of C1. However, the RG-T has been adjusted to < 4 in consideration of the risk of switching to manic episodes.
3. Some studies have shown the efficacy of modafinil or pramipexole adjunctive/add-on therapy to ongoing treatments for bipolar depression,[68−71] leading to a CE of B, but the RG has been adjusted to 4 because of limited clinical use. Adverse skin reactions may be related to high doses of modafinil.[72,73]
4. Analysis of the Taiwan national health insurance database has shown that sulpiride is widely used for depressive episodes. One double-blind study showed that sulpiride has equivalent antidepressant activity to amitriptyline, with faster onset in the first week of the trial, and fewer side effects than amitriptyline.[74] The CE of sulpiride is C1 and the RG-T is 4 due to the side effects of EPSs, such as tardive dyskinesia.

9. Neurostimulation for the depressive phase

1. For patients with poor response to medication and high risk of suicide, ECT is still an important treatment of choice,[75] with a CE of C1 and RG-T of 4.
2. Research evidence has confirmed the efficacy of rTMS for refractory depression. In Taiwan, a small randomized, double-blind, sham-controlled trial has shown the efficacy of rTMS for refractory unipolar and bipolar depression,[76] but large studies are still limited. The CE of rTMS is C1 and RG-T is 4. The risk of switching to mania is a concern.

10. Maintenance phase (Table 3)

Maintenance and prophylactic treatment aim to prevent recurrence of new mood episodes. The time period for continuation treatment is defined as the first 6 months after an acute episode, and the maintenance phase of treatment is for months 6−12 after remission of an acute episode. There is no international consensus for the indication for maintenance treatment. The indication for maintenance treatment is more liberally defined in North America and is recommended for all patients after the first episode and ever thereafter. Most European guidelines recommend that maintenance treatment is indicated only after the second episode recurred and with an interval of < 3 years between the two episodes. The WFSBP guidelines, following the Netherland guidelines,[77] suggest that maintenance treatment needs to be administered under the consideration of three factors: frequency of episodes, severity of symptoms, and first-degree relatives with psychiatric disorders. Maintenance treatment is recommended for: (1) patients with first episode, severe symptoms, and psychiatric family history; (2) those with a second episode, with a psychiatric family history or severe symptoms; and (3) those with a third episode.

11. How long to continue maintenance/prophylactic treatment

There is no international consensus for how long to continue maintenance/prophylactic treatment,[78] because the natural course of bipolar recurrence is around 16−18 months. If the prophylactic treatment only persists for 6−12 months, it is difficult to judge whether to stop the treatment, unless the treatment would have lasted for 2−3 years (Goodwin FK and Jamison KR: Manic-Depressive Illness, 2nd Ed: *Bipolar Disorders and Recurrent Depression.* 2007; p799-801). The duration of maintenance treatment is still based on individual consideration.

12. Monotherapy for maintenance phase

1. All the three mood stabilizers, lithium, valproic acid, and lamotrigine, have a CE of A and RG-T of 1. However,

Table 3
Maintenance phase therapy.

	Medication or treatment	Category of evidence	Taiwan recommendation grade	Approved by Taiwan Department of Health	Recommended daily dose for adults (variations may occur due to different approvals)
Monotherapy					
1	Lithium	A	1	V	600–1200 mg (serum level 0.6–1.2 mg/L)
2	Valproic acid	A	1	V	Serum level 50–100 mg/L
3	Lamotrigine	A	1	V	50–200 mg
4	Olanzapine	A	2	V	5–20 mg
5	Quetiapine	A	2		300–600 mg
6	Risperidone LAI	A	2		25–37.5 mg/q2wk
7	Aripiprazole	A	2		15–30 mg
8	Carbamazepine	B	1	V	600–1200 mg (serum level 4–15 mg/L)
Combination/augmentation or adjunctive/add-on therapy					
1	Lithium or valproic acid + quetiapine	A	1	V	
2	Lithium + divalproex	B	1	V	
3	Lithium + carbamazepine	B	1	V	
4	Lithium or valproic acid + risperidone LAI	A	2	V	
5	Lithium or valproic acid + ziprasidone	A	2	V	
6	Lithium or valproic acid or lamotrigine + aripiprazole	A	2	V	
7	Lithium + olanzapine	B	2		
8	Lithium + risperidone	B	2		
9	Lithium + lamotrigine	B	2		
10	Olanzapine + fluoxetine	B	3		
11	Adjunctive clozapine	C1	3		
12	Adjunctive topiramate	D	4		
13	Adjunctive oxcarbazepine	D	4		
14	Adjunctive gabapentin	D	4		
15	Adjunctive ECT	F	4		

ECT = electroconvulsive therapy; LAI = long-acting injection.

lithium has more side effects and a twofold risk of discontinuation compared to the other two mood stablizers. Another mood stabilizer, carbamazepine, has a CE of B and the RG-T is elevated to 1 due to fewer side effects of weight gain, and the issue of skin allergy is less of a concern during the maintenance phase.

2. Four atypical antipsychotics, olanzapine, quetiapine, long-acting risperidone injection (RLAI), and aripiprazole, all have a CE of A, but RG-T is 2 because of the side effects of weight gain, less efficacy in preventing depressive episodes, and no Taiwan DOH indication for monotherapy (quetiapine or RLAI).

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

1. Combination therapy with lithium/valproic acid and quetiapine may have better efficacy than monotherapy, with a CE of A and RG-T of 1, but may also have more side effects of weight gain and metabolic syndrome.
2. Combination therapy with lithium, divalproex, and carbamazepine is commonly seen in clinical psychiatric practice, with a CE of B and RG-T of 1.
3. Research evidence confirms that combination therapy with lithium/divalproex, lithium, or valproic acid and RLAI,[79] ziprasidone,[80] or aripiprazole,[81,82] has a CE of A, but with less efficacy for preventing depressive episodes, the RG-T is 2.
4. Combinations of lithium with olanzapine, risperidone or lamotrigine all have a CE of B and RG-T of 2, although there is concern about the adverse effects of weight gain and metabolic syndrome.
5. Open trials have shown that clozapine monotherapy or combined with other agents can improve symptoms and prevent rehospitalization[83–86]; the CE is C1 and RG-T is 3. The side effects of weight gain and metabolic syndrome are of concern.
6. Adjunctive treatment with topiramate, oxcarbazepine, and gabapentin has yielded inconsistent results; the CE is D and RG-T is 4. Topiramate may reduce body weight.
7. Adjunctive ECT is not supported by the results of any randomized or open trial; the CE is F and RG-T is 4. It is only recommended for patients with a poor response to other treatments.

14. Role of antidepressants in the maintenance phase

The role of antidepressants in maintenance phase treatment is still debatable, although > 50% of patients have residual depressive symptoms.[83] The research evidence about the risk of switching to mania with antidepressants is inconsistent. Only limited evidence supports that antidepressants can prolong the remission period of depression. Most studies have suggested that antidepressants can be only used in combination with mood stabilizers; otherwise, the risk of switch to

mania is increased.[84,85] In addition, the combination of antidepressants with mood stablizers is only suggested for patients with type II bipolar disorder because a higher risk of switching to mania has been reported with type I bipolar disorder.[86] The drug-induced mania switch occurs particularly in those receiving a tricyclic antidepressant or a serotonin and norepinephrine reuptake inhibitor.[84,87]

15. Pharmacotherapy combined with psychosocial intervention improves treatment efficacy

Nonpharmacological, psychosocial intervention is important to the success of pharmacotherapy. Psychoeducation can improve patients' insight, facilitate their understanding of the impact of bipolar disorder, and improve self-monitoring, self-regulation, and adherence to medication.[7] Other treatment modalities including group psychotherapy, cognitive behavioral therapy, interpersonal and social rhythm therapy, and family-focused therapy also reduce the relapse rate and improve medication adherence.[5−7,88]

16. Treatment of bipolar disorder in women

Pregnancy is a risk period for relapse of bipolar disorders, which occurs in up to 45−52%, or even 70% of cases. For all women of child-bearing age, the plan of pregnancy should be discussed, focusing on the risk of drug use during pregnancy, contraceptive methods, possible interaction of medication and contraceptives, supporting system, genetic inheritance, relapse risk during pregnancy, labor, postpartum, and breast feeding. For patients who are preparing for pregnancy, titrating to discontinuation of medication may take 3−6 months. Medication with the potential for teratogenicity should be avoided. Taking folic acid 5 mg/day is suggested to reduce the risk of teratogenicity. During pregnancy, collaborative care from psychiatrists and gynecologists is important for close monitoring of both the fetus and the mother. Enough sleep and rest are important for preventing relapse of bipolar disorder.

17. Issues related to medication during pregnancy[89−92]

1. Valproate has increased risk of polycystic ovary syndrome.
2. Risperidone has the side effect of hyperprolactinemia.
3. Carbamazepine, topiramate and oxcarbazepine can decrease the efficacy of oral contraceptives.
4. Oral contraceptives decrease the serum level of lamotrigine to 50%.
5. Lithium can cause Ebstein's cardiovascular anomaly; valproate has a risk of spina bifida; carbamazepine/oxcarbazepine have the risk of neural tube defects; lamotrigine is a relatively safer mood stabilizer to cause teratogenicity.
6. The first-generation antipsychotic drugs generally have less risk of teratogenicity. There are only limited data on the second-generation antipsychotic drugs, but there is no evidence of increased risk of teratogenicity.
7. ECT is relatively safer than polypharmacy for patients with severe depressive symptoms during pregnancy; rTMS may be a choice for treatment in bipolar depression, but it requires more studies.

18. Summary of the results

1. Clinical types: bipolar I: 47%; bipolar II: 35%; and mixed or NOS: 18%
2. They agreed to give long-term maintenance therapy for the first episode of bipolar disorder in patients who had a history of suicide, significant family history of affective disorders, or comorbid psychotic symptoms.
3. Almost all the experts have seen bipolar cases switched from depression; most of which were related to antidepressant use. Sixty percent of the experts reported that they have seen monomania, even it occurred rare.
4. The rate of bipolar cases with adherence to follow-up schedule (50% returning to the clinic) and regularly taking medication was around 79%, while the other 21% was not compliant.
5. For the acute manic phase, 75% of the experts would like to use combination therapy with mood stabilizers (valproic acid or lithium) and atypical antipsychotics (quetiapine, risperidone, or olanzapine). Another 25% of the experts were inclined to use monotherapy with the first choice of DVP, followed by lithium, and then atypical antipsychotics in the sequence of quetiapine, risperidone and finally olanzapine. In the cases with acute hypomania, 87% preferred to use monotherapy (90% mood stabilizers and 10% atypical antipsychotics). The suggested dose was reduced to a half to a third of the dose used in the acute manic phase. Once the hypomanic symptoms disappeared, only 11% of the experts suggested decreasing the dose, and 89% maintained the original dose (50% suggested to maintain for 1−3 months; 27% for 3−6 months; and 12% for 6−12 months).
6. With regard to treatment of bipolar depression, 80% of the experts would like to administer combination treatment and 20% monotherapy. For combination treatment, the distribution was as follows: mood stabilizers + antidepressants (38%); mood stabilizers + atypical antipsychotics (25%); atypical antipsychotics + antidepressants (16%); and antidepressants + atypical antipsychotics + mood stabilizers (6.2%). For monotherapy, the first choice was lamotrigine, followed by mood stabilizers (valproic acid, lithium or quetiapine). Experts also suggested that the first choice for combination treatment was (1) lamotrigine + lithium or quetiapine; or (2) valproic acid + escitalopram. Professor Sachs from Harvard Medical School reported that there was no different treatment effect between mood stabilizers + antidepressants and mood stabilizers + placebo, indicating no beneficial effect of antidepressants for bipolar depression.[66] However, in this questionnaire survey, we found that 70−80% of the experts still used antidepressants in addition to mood stabilizers or atypical antipsychotics to treat bipolar depression. This observation was similar to the recent report at the Annual Meeting of the ISBD in Istanbul, Turkey in March 2012. During combination treatment, the experts preferred to

reduce the dose or discontinue antidepressants after symptoms of depression diminished or improved. It was suggested that combination treatment be maintained for 1−3 months (30%), 3−6 months (36%), or > 6 months (only 20%).

7. For the maintenance phase of patients with remitted bipolar disorder, 75% of the experts would maintain combination treatment while the remaining 25% would use monotherapy. With respect to monotherapy, valproic acid was the first choice, followed by lithium and then quetiapine. If mood stabilizers were not chosen, quetiapine would be the first priority, followed by lamotrigine and then risperidone. For combination therapy, the priority use was valproic acid + quetiapine, lithium or risperidone. The next choice was valproic acid + olanzapine, or lithium + quetiapine, selective serotonin reuptake inhibitor or olanzapine. If the bipolar condition became stable and remitted, 35% of the experts maintained treatment for 3−6 months and 38% for 6−12 months. For patients who were refractory to pharmacological treatment, 25% of the experts suggested combined polypharmacy + cognitive behavioral therapy, followed by 28% with polypharmacy, and 14% with polypharmacy + ECT. Only 6% needed long-term hospitalization.

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Maintenance phase: Ching-Jui Chang, Shang-Ying Tsai, Chau-Shoun Lee, Tiao-Lai Huang, Ming-Hong Hsieh, Ya Mei Bai, Cheng-Sheng Chen, Shao-Tsu Chen, Chia-Chen Chan, Mei-Chun Hsiao, Shang-Wen Chang, Ying-Jay Liou, Yen-Kuang Yang, Tsuo-Hung Lan.

Appendix

The questionnaire regarding the pharmacological treatment of bipolar disorders in clinical practice was collected from 38 psychiatrists, who are the experts in the field of bipolar disorders. They were from medical centers and large mental hospitals, aged > 40 years, and had 10 years clinical experience. The bipolar patients came from outpatient clinics and inpatient units.

References

1. Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord* 2009;**11**:225−55.
2. Bih SH, Chien IC, Chou YJ, Lin CH, Lee CH, Chou P. The treated prevalence and incidence of bipolar disorder among national health insurance enrollees in Taiwan, 1996−2003. *Soc Psychiatry Psychiatr Epidemiol* 2008;**43**:860−5.
3. Huang KL, Su TP, Chen TJ, Chou YH, Bai YM. Comorbidity of cardiovascular diseases with mood and anxiety disorder: a population based 4-year study. *Psychiatry Clin Neurosci* 2009;**63**:401−9.
4. Chien IC, Chou YJ, Lin CH, Bih SH, Chou P. Prevalence of psychiatric disorders among National Health Insurance enrollees in Taiwan. *Psychiatr Serv* 2004;**55**:691−7.
5. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, 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* 2009;**10**:85−116.
6. Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, 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* 2010;**11**:81−109.
7. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: revised second edition − recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2009;**23**:346−88.
8. Smith LA, Cornelius V, Warnock A, Bell A, Young AH. Effectiveness of mood stabilizers and antipsychotics in the maintenance phase of bipolar disorder: a systematic review of randomized controlled trials. *Bipolar Disord* 2007;**9**:394−412.
9. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Pharmacological interventions for acute bipolar mania: a systematic review of randomized placebo-controlled trials. *Bipolar Disord* 2007;**9**:551−60.
10. Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Acute bipolar mania: a systematic review and meta-analysis of co-therapy vs. monotherapy. *Acta Psychiatr Scand* 2007;**115**:12−20.
11. Ceron-Litvoc D, Soares BG, Geddes J, Litvoc J, de Lima MS. Comparison of carbamazepine and lithium in treatment of bipolar disorder: a systematic review of randomized controlled trials. *Hum Psychopharmacol* 2009;**24**:19−28.
12. Owen RT. Extended-release carbamazepine for acute bipolar mania: a review. *Drugs Today (Barc)* 2006;**42**:283−9.
13. Weisler RH, Keck Jr PE, Swann AC, Cutler AJ, Ketter TA, Kalali AH. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2005;**66**:323−30.
14. Zhang Y, Wang J, Zhao LM, Peng W, Shen GQ, Xue L, et al. Strong association between HLA-B*1502 and carbamazepine-induced Stevens−Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. *Eur J Clin Pharmacol* 2011;**67**:885−7.
15. Hu FY, Wu XT, An DM, Yan B, Stefan H, Zhou D. Pilot association study of oxcarbazepine-induced mild cutaneous adverse reactions with HLA-B*1502 allele in Chinese Han population. *Seizure* 2011;**20**:160−2.
16. An DM, Wu XT, Hu FY, Yan B, Stefan H, Zhou D. Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population. *Epilepsy Res* 2010;**92**:226−30.
17. Ferrell Jr PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens−Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics* 2008;**9**:1543−6.
18. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Stevens−Johnson syndrome. *Nature* 2004;**428**:486.
19. Lin CH, Lu CH, Wang FJ, Tsai MH, Chang WN, Tsai NW, et al. Risk factors of oxcarbazepine-induced hyponatremia in patients with epilepsy. *Clin Neuropharmacol* 2010;**33**:293−6.
20. Dong X, Leppik IE, White J, Rarick J. Hyponatremia from oxcarbazepine and carbamazepine. *Neurology* 2005;**65**:1976−8.
21. Kakkar AK, Rehan HS, Unni KE, Gupta NK, Chopra D, Kataria D. Comparative efficacy and safety of oxcarbazepine versus divalproex sodium in the treatment of acute mania: a pilot study. *Eur Psychiatry* 2009;**24**:178−82.
22. Niufan G, Tohen M, Qiuqing A, Fude Y, Pope E, McElroy H, et al. Olanzapine versus lithium in the acute treatment of bipolar mania: a

double-blind, randomized, controlled trial. *J Affect Disord* 2008;**105**:101−8.
23. Perlis RH, Baker RW, Zarate Jr CA, Brown EB, Schuh LM, Jamal HH, et al. Olanzapine versus risperidone in the treatment of manic or mixed states in bipolar I disorder: a randomized, double-blind trial. *J Clin Psychiatry* 2006;**67**:1747−53.
24. Citrome L. Drug safety evaluation of ziprasidone. *Expert Opin Drug Safety* 2011;**10**:437−48.
25. DelBello MP, Kowatch RA, Adler CM, Stanford KE, Welge JA, Barzman DH, et al. A double-blind randomized pilot study comparing quetiapine and divalproex for adolescent mania. *J Am Acad Child Adolesc Psychiatry* 2006;**45**:305−13.
26. Pajonk FG, Schwertner AK, Seelig MA. Rapid dose titration of quetiapine for the treatment of acute schizophrenia and acute mania: a case series. *J Psychopharmacol* 2006;**20**:119−24.
27. Khazaal Y, Tapparel S, Chatton A, Rothen S, Preisig M, Zullino D. Quetiapine dosage in bipolar disorder episodes and mixed states. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;**31**:727−30.
28. Gandelman K, Alderman JA, Glue P, Lombardo I, LaBadie RR, Versavel M, et al. The impact of calories and fat content of meals on oral ziprasidone absorption: a randomized, open-label, crossover trial. *J Clin Psychopharmacol* 2009;**70**:58−62.
29. Berwaerts J, Lane R, Nuamah IF, Lim P, Remmerie B, Hough DW. Paliperidone extended-release as adjunctive therapy to lithium or valproate in the treatment of acute mania: a randomized, placebo-controlled study. *J Affect Disord* 2011;**129**:252−60.
30. Berwaerts J, Xu H, Nuamah I, Lim P, Hough D. Evaluation of the efficacy and safety of paliperidone extended-release in the treatment of acute mania: a randomized, double-blind, dose-response study. *J Affect Disord* 2010;**136**:e51−60.
31. Vieta E, Nuamah IF, Lim P, Yuen EC, Palumbo JM, Hough DW, et al. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorder. *Bipolar Disord* 2010;**12**:230−43.
32. Thomas P, Vieta E. Amisulpride plus valproate vs haloperidol plus valproate in the treatment of acute mania of bipolar I patients: a multicenter, open-label, randomized, comparative trial. *Neuropsychiatr Dis Treat* 2008;**4**:675−86.
33. Masi G, Mucci M, Millepiedi S. Clozapine in adolescent inpatients with acute mania. *J Child Adolesc Psychopharmacol* 2002;**12**:93−9.
34. Green AI, Tohen M, Patel JK, Banov M, DuRand C, Berman I, et al. Clozapine in the treatment of refractory psychotic mania. *Am J Psychiatry* 2000;**157**:982−6.
35. Calabrese JR, Kimmel SE, Woyshville MJ, Rapport DJ, Faust CJ, Thompson PA, et al. Clozapine for treatment-refractory mania. *Am J Psychiatry* 1996;**153**:759−64.
36. Chan HY, Jou SH, Juang YY, Chang CJ, Chen JJ, Chen CH, et al. A single-blind, comparative study of zotepine versus haloperidol in combination with a mood stabilizer for patients with moderate-to-severe mania. *Psychiatry Clin Neurosci* 2010;**64**:162−9.
37. Amann B, Sterr A, Mergl R, Dittmann S, Seemüller F, Dobmeier M, et al. Zotepine loading in acute and severely manic patients: a pilot study. *Bipolar Disord* 2005;**7**:471−6.
38. Harada T, Otsuki S. Antimanic effect of zotepine. *Clin Ther* 1986;**8**:406−14.
39. Cipriani A, Rendell JM, Geddes JR. Haloperidol alone or in combination for acute mania. *Cochrane Database Syst Rev* 2006;**3**:CD004362.
40. Klein DF. Importance of psychiatric diagnosis in prediction of clinical drug effects. *Arch Gen Psychiatry* 1967;**16**:118−26.
41. Volpe FM, Tavares A. Manic patients receiving ECT in a Brazilian sample. *J Affect Disord* 2004;**79**:201−8.
42. Sikdar S, Kulhara P, Avasthi A, Singh H. Combined chlorpromazine and electroconvulsive therapy in mania. *Br J Psychiatry* 1994;**164**:806−10.
43. Mukherjee S, Sackeim HA, Schnur DB. Electroconvulsive therapy of acute manic episodes: a review of 50 years' experience. *Am J Psychiatry* 1994;**151**:169−76.
44. Kaptsan A, Yaroslavsky Y, Applebaum J, Belmaker RH, Grisaru N. Right prefrontal TMS versus sham treatment of mania: a controlled study. *Bipolar Disord* 2003;**5**:36−9.
45. Scherk H, Pajonk FG, Leucht S. Second-generation antipsychotic agents in the treatment of acute mania: a systematic review and meta-analysis of randomized controlled trials. *Arch Gen Psychiatry* 2007;**64**:442−55.
46. Tohen M, Bowden CL, Smulevich AB, Bergstrom R, Quinlan T, Osuntokun O, et al. Olanzapine plus carbamazepine v. carbamazepine alone in treating manic episodes. *Br J Psychiatry* 2008;**192**:135−43.
47. Calabrese JR, Keck Jr PE, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 2005;**162**:1351−60.
48. Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). *J Clin Psychopharmacol* 2006;**26**:600−9.
49. Suppes T, Hirschfeld RM, Vieta E, Raines S, Paulsson B. Quetiapine for the treatment of bipolar II depression: analysis of data from two randomized, double-blind, placebo-controlled studies. *World J Biol Psychiatry* 2008;**9**:198−211.
50. Suppes T, Datto C, Minkwitz M, Nordenhem A, Walker C, Darko D. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. *J Affect Disord* 2010;**121**:106−15.
51. Weisler RH, Calabrese JR, Thase ME, Arvekvist R, Stening G, Paulsson B, et al. Efficacy of quetiapine monotherapy for the treatment of depressive episodes in bipolar I disorder: a post hoc analysis of combined results from 2 double-blind, randomized, placebo-controlled studies. *J Clin Psychiatry* 2008;**69**:769−82.
52. Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, et al. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). *J Clin Psychiatry* 2010;**71**:150−62.
53. McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). *J Clin Psychiatry* 2010;**71**:163−74.
54. Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 1999;**60**:79−88.
55. Calabrese JR, Huffman RF, White RL, Olausson B, Paulsson B, Brecher M, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord* 2008;**10**:323−33.
56. Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. *Br J Psychiatry* 2009;**194**:4−9.
57. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. *Lancet Neurol* 2011;**10**:609−17.
58. Shallcross R, Bromley RL, Irwin B, Bonnett LJ, Morrow J, Baker GA. Child development following in utero exposure: levetiracetam vs sodium valproate. *Neurology* 2011;**76**:383−9.
59. McIntyre RS, Mancini DA, McCann S, Srinivasan J, Kennedy SH. Valproate, bipolar disorder and polycystic ovarian syndrome. *Bipolar Disord* 2003;**5**:28−35.
60. Joffe H, Taylor AE, Hall JE. Polycystic ovarian syndrome − relationship to epilepsy and antiepileptic drug therapy. *J Clin Endocrinol Metab* 2001;**86**:2946−9.
61. Genton P, Bauer J, Duncan S, Taylor AE, Balen AH, Eberle A, et al. On the association between valproate and polycystic ovary syndrome. *Epilepsia* 2001;**42**:295−304.
62. Zornberg GL, Pope Jr HG. Treatment of depression in bipolar disorder: new directions for research. *J Clin Psychopharmacol* 1993;**13**:397−408.
63. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003;**60**:1079−88.

64. Brown EB, McElroy SL, Keck Jr PE, Deldar A, Adams DH, Tohen M, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry* 2006;**67**:1025−33.
65. Zhang ZJ, Kang WH, Tan QR, Li Q, Gao CG, Zhang FG, et al. Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. *J Psychiatr Res* 2007;**41**:360−9.
66. Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 2007;**356**:1711−22.
67. Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry* 2007;**164**:1348−55.
68. Calabrese JR, Ketter TA, Youakim JM, Tiller JM, Yang R, Frye MA. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry* 2010;**71**:1363−70.
69. Gupta S, Vincent JL, Frank B. Pramipexole: augmentation in the treatment of depressive symptoms. *CNS Spectrums* 2006;**11**:172−5.
70. Zarate Jr CA, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, et al. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. *Biol Psychiatry* 2004;**56**:54−60.
71. Sporn J, Ghaemi SN, Sambur MR, Rankin MA, Recht J, Sachs GS, et al. Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. *Ann Clin Psychiatry* 2000;**12**:137−40.
72. Frye MA, Grunze H, Suppes T, McElroy SL, Keck Jr PE, Walden J, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 2007;**164**:1242−9.
73. Nasr S, Wendt B, Steiner K. Absence of mood switch with and tolerance to modafinil: a replication study from a large private practice. *J Affect Disord* 2006;**95**:111−4.
74. Bocchetta A, Bernardi F, Burrai C, Pedditzi M, Del Zompo M. A double-blind study of L-sulpiride versus amitriptyline in lithium-maintained bipolar depressives. *Acta Psychiatr Scand* 1993;**88**:434−9.
75. Kessler U, Vaaler AE, Schoyen H, Oedegaard KJ, Bergsholm P, Andreassen OA, et al. The study protocol of the Norwegian randomized controlled trial of electroconvulsive therapy in treatment resistant depression in bipolar disorder. *BMC Psychiatry* 2010;**10**:16.
76. Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *J Clin Psychiatry* 2005;**66**:930−7.
77. Grunze H, Kasper S, Goodwin G, Bowden C, Moller HJ. The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders, part III: maintenance treatment. *World J Biol Psychiatry* 2004;**5**:120−35.
78. Swann AC. Long-term treatment in bipolar disorde. *J Clin Psychiatry* 2005;**66**(Suppl 1):7−12.
79. Fagiolini A, Casamassima F, Mostacciuolo W, Forgione R, Goracci A, Goldstein BI. Risperidone long-acting injection as monotherapy and adjunctive therapy in the maintenance treatment of bipolar I disorder. *Expert Opin Pharmacother* 2010;**11**:1727−40.
80. Bowden CL, Vieta E, Ice KS, Schwartz JH, Wang PP, Versavel M. Ziprasidone plus a mood stabilizer in subjects with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind trial. *J Clin Psychiatry* 2010;**71**:130−7.
81. Woo YS, Bahk WM, Chung MY, Kim DH, Yoon BH, Lee JH, et al. Aripiprazole plus divalproex for recently manic or mixed patients with bipolar I disorder: a 6-month, randomized, placebo-controlled, double-blind maintenance trial. *Hum Psychopharmacol* 2011;**26**:543−53.
82. Marcus R, Khan A, Rollin L, Morris B, Timko K, Carson W, et al. Efficacy of aripiprazole adjunctive to lithium or valproate in the long-term treatment of patients with bipolar I disorder with an inadequate response to lithium or valproate monotherapy: a multicenter, double-blind, randomized study. *Bipolar Disord* 2011;**13**:133−44.
83. Arvilommi P, Suominen K, Mantere O, Leppamaki S, Valtonen HM, Isometsa E. Maintenance treatment received by patients with bipolar I and II disorders−a naturalistic prospective study. *J Affect Disord* 2010;**121**:116−26.
84. Ghaemi SN, Wingo AP, Filkowski MA, Baldessarini RJ. Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. *Acta Psychiatr Scand* 2008;**118**:347−56.
85. Sachs GS, Thase ME. Bipolar disorder therapeutics: maintenance treatment. *Biol Psychiatry* 2000;**48**:573−81.
86. Amsterdam JD, Shults J. Does tachyphylaxis occur after repeated antidepressant exposure in patients with Bipolar II major depressive episode? *J Affect Disord* 2009;**115**:234−40.
87. Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 2006;**189**:124−31.
88. Goodwin GM, Anderson I, Arango C, Bowden CL, Henry C, Mitchell PB, et al. ECNP consensus meeting. Bipolar depression. Nice, March 2007. *Eur Neuropsychopharmacol* 2008;**18**:535−49.
89. Freeman MP, Smith KW, Freeman SA, McElroy SL, Kmetz GE, Wright R, et al. The impact of reproductive events on the course of bipolar disorder in women. *J Clin Psychiatry* 2002;**63**:284−7.
90. Viguera AC, Whitfield T, Baldessarini RJ, Craig J, Lindhout D, Sabers A, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry* 2007;**164**:1817−24.
91. Newport DJ, Stowe ZN, Viguera AC, Calamaras MR, Juric S, Knight B, et al. Lamotrigine in bipolar disorder: efficacy during pregnancy. *Bipolar Disord* 2008;**10**:432−6.
92. Yatham LN, Kennedy SH, O'Donovan C, Schaffer A, Beaulieu S, Alda M, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. *Bipolar Disord* 2005;**7**(Suppl 3):5−69.