CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
scnp

How can we classify "mood stabilizers" with different properties?

Tsuyoshi Kondo, M.D., Ph.D.

Department of Neuropsychiatry, Faculty of Medicine,
University of the Ryukyus, Okinawa, Japan

ABSTRACT

Mood stabilizers have been conventionally defined as drugs possessing efficacy in both acute and maintenance therapy for any polarity of bipolar disorder. Only lithium has been regarded as the gold standard mood stabilizer, fulfilling all of these conditions. Recently, evidence for the comprehensive mood-stabilizing effects of second-generation antipsychotics such as quetiapine and olanzapine has been found, although their safety in long-term use is still of great concern. Antiepileptic drugs do not appear to be ideal mood stabilizers because of selective effectiveness on a particular polarity -- for example, valproate and carbamazepine are predominantly antimanic, and lamotrigine is predominantly antidepressive. However, the mood-stabilizing effects of combinations of these drugs may be equivalent or even superior to that of lithium alone, especially in pathophysiologies less responsive to lithium, such as dysphoric mania, mixed features and rapid cycling.

Keywords: mood stabilizers, bipolar disorders, polarity, acute effect, relapse prevention

Received April 4, 2011 / Accepted May 6, 2011 / Published June 20, 2011

INTRODUCTION

Lithium (Li) is regarded as the standard mood stabilizer in the treatment of bipolar disorders. However, the term "mood stabilizer" has not yet been officially defined. Valproate (VPA), carbamazepine (CBZ) and lamotrigine (LTG) have been conventionally used to treat bipolar disorders, although the antiepileptic effects of these drugs are the primary pharmacological actions. Meanwhile, it has become increasingly evident that the second-generation antipsychotics, such as quetiapine (QTP), olanzapine (OLZ), aripiprazole (ARI), and risperidone (RIS), also have mood-stabilizing effects for bipolar disorders. The common underlying mechanisms of the mood-stabilizing effects of these diverse drugs having different pharmacological properties remain to be elucidated.

Therefore, the aforementioned drugs, which are for practical purposes effective in the treatment of bipolar disorders, have been conveniently labeled as a group as mood stabilizers mainly because of their clinical effects, despite the considerable differences among them in terms of their potency or spectrum of mood-stabilizing effects. In general, an optimal mood stabilizer should be selected for each individual since bipolar disorders encompass various pathophysiologies, including polarity (bipolar I/II, predominant polarity, mixed features and switching to the other polarity) and the duration/frequency of mood episodes (rapid cycling or prolonged course, and remission duration). However, no definite criteria exist for the rational selection of mood stabilizers based on markers of mood disorder psychopathology, and clinical trials of mood stabilizers are currently being conducted using various study designs.

In this article, we will define and classify mood stabilizers mainly based on their therapeutic characteristics, with the goal being the rational and optimal

Corresponding Author: Tsuyoshi Kondo, M.D., Ph.D., Department of Neuropsychiatry, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan
Fax: +81-98-895-1419 Tel.: +81-98-895-1157 Email: kondo@med.u-ryukyu.ac.jp

use of mood stabilizers in the treatment of bipolar disorders.

PRACTICAL DEFINITION OF MOOD STABILIZERS

Although no official definition of mood stabilizers has been established, Bauer and Mitchner [1] have suggested that an ideal mood stabilizer is a drug having bimodal effects that alleviates both manic and depressive symptoms and that also has acute efficacy and relapse prevention efficacy in the treatment of bipolar disorders (two-by-two definition). From a practical standpoint, mood stabilizers can also be defined as agents that 1) prevent patients from switching polarities, 2) reduce the duration of the manic or depressive episode, 3) prolong the duration of remission, and 4) prevent relapse or reduce the severity of the next episode [2].

Li, VPA and CBZ are indicated for the treatment of bipolar disorders, and are considered conventional mood stabilizers in Japan. In addition to these agents, the mood-stabilizing efficacy of newer antiepileptic drugs, including LTG and second-generation antipsychotics such as QTP and OLZ are internationally recognized. Although these relatively new mood stabilizer candidates have different effects (e.g., antimanic/antidepressive effects, efficacy in acute/ maintenance therapy), all of them have been approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMEA). However, if mood stabilizers are strictly defined as having efficacy in both acute and maintenance therapy for any polarity of bipolar disorder, only Li has been regarded as the gold standard mood stabilizer, fulfilling all of these conditions [1, 3].

Shared underlying mechanisms might exist between the pathophysiology of bipolar disorders and that of epilepsy due to their similarity in longitudinal course (e.g., the periodic occurrence of mood episodes and repetitive seizures in epilepsy). Bipolar disorders and epilepsy are also alike in that the threshold for future recurrence is diminished by repetitive and uncontrolled mood episodes or epileptic seizures such as kindling effects. The rationale for the clinical application of antiepileptic drugs to bipolar disorders has been at least partly based on this hypothesis. However, no antiepileptic drugs are sufficiently effective as monotherapy against acute bipolar depression [4]. Furthermore, VPA and CBZ are predominantly effective for the acute phase of mania and LTG for relapse prevention for depressive episodes [1, 5]. Although these antiepileptic drugs are generally effective for relapse prevention for bipolar disorders, these effects are selective for either polarity, as in the case of their acute effects in bipolar disorders [6, 7]. Accordingly, these antiepileptic agents appear to be incomplete or partial mood stabilizers compared to lithium.

Meanwhile, the clinical application of several second-generation antipsychotic drugs (QTP, OLZ, ARI and RIS) to bipolar disorders has been intensively examined and justified based on the hypothesis that these antipsychotics may attenuate hyperfunction of the dopamine/noradrenaline system in mania and dysfunction of the serotonin/ noradrenaline/dopamine system in depression, which are the neurochemical model mechanisms of bipolar disorders. In fact, QTP, OLZ, ARI, RIS and paliperidone are known to have potent effects against acute mania as well as schizophrenia [6]. As for the treatment of acute bipolar depression, the efficacy of QTP monotherapy has been established [8], and OLZ exhibits similar efficacy when combined with fluoxetine (OLZ-fluoxetine combination: OFC) [9], both of which have been already approved by the FDA. In addition, it has been also confirmed that QTP [10, 11], OLZ [7, 11], ARI [5] and long-acting injection (LAI) of RIS [11] have unequivocal efficacy in relapse prevention for bipolar disorders. Among these antipsychotics, QTP and OLZ have shown promise recently as comprehensive mood stabilizers, and may be as or even more effective than Li.

Nevertheless, caution should be exercised when labeling mood stabilizers, since they tend to be used in long-term maintenance treatment following their use in the acute phase of bipolar disorders, so they will definitely have commercial value for pharmaceutical companies. On the other hand, all of us have to recognize the harsh truth that refractory bipolar disorders unresponsive to Li are not uncommon, especially in bipolar depression or recurrent depressive episodes of bipolar disorders. Therefore, a more wide-reaching search for possible candidates for mood stabilizers should be conducted that goes beyond the conventional pharmacological categories of antiepileptics, antipsychotics and antidepressants. For this purpose, some minimum requirements should be established for the characteristics of mood stabilizers when recruiting new candidates from a wider range of drug classes. When considering a looser definition of mood stabilizers, the following three characteristics should be kept in mind: mood

stabilizers should 1) have at least either antimanic or antidepressive properties, either when used alone or when used in combination with other agents; 2) be suitable for maintenance treatment for relapse prevention for recurrent bipolar pathophysiology; and 3) not induce mood switching to the other polarity.

Table 1. Therapeutic Spectra of Mood Stabilizers of Different Classes (Ref. [5-7, 11-14])

	Acute Efficacy		Maintenance Efficacy	
	Manic Episode	Depressive Episode	Manic Recurrence	Depressive Recurrence
Lithium	○	△	○	△
Valproate	○	△	△	△
Carbamazepine	○	×	△	×
Lamotrigine	×	△ (○: when added to another MS in more severe depression)	×	○
Olanzapine	○	△ (○: when combined with an SSRI)	○	△
Quetiapine	○	○	○	○
Aripiprazole	○	×	○	×
Risperidone Paliperidone	○	×	△ (LAI)	×

○: sufficiently effective; reliable evidence available
△: possibly effective; modest evidence available
×: no supportive evidence

MS: mood stabilizer
SSRI: selective serotonin reuptake inhibitor
LAI: long acting injection of risperidone

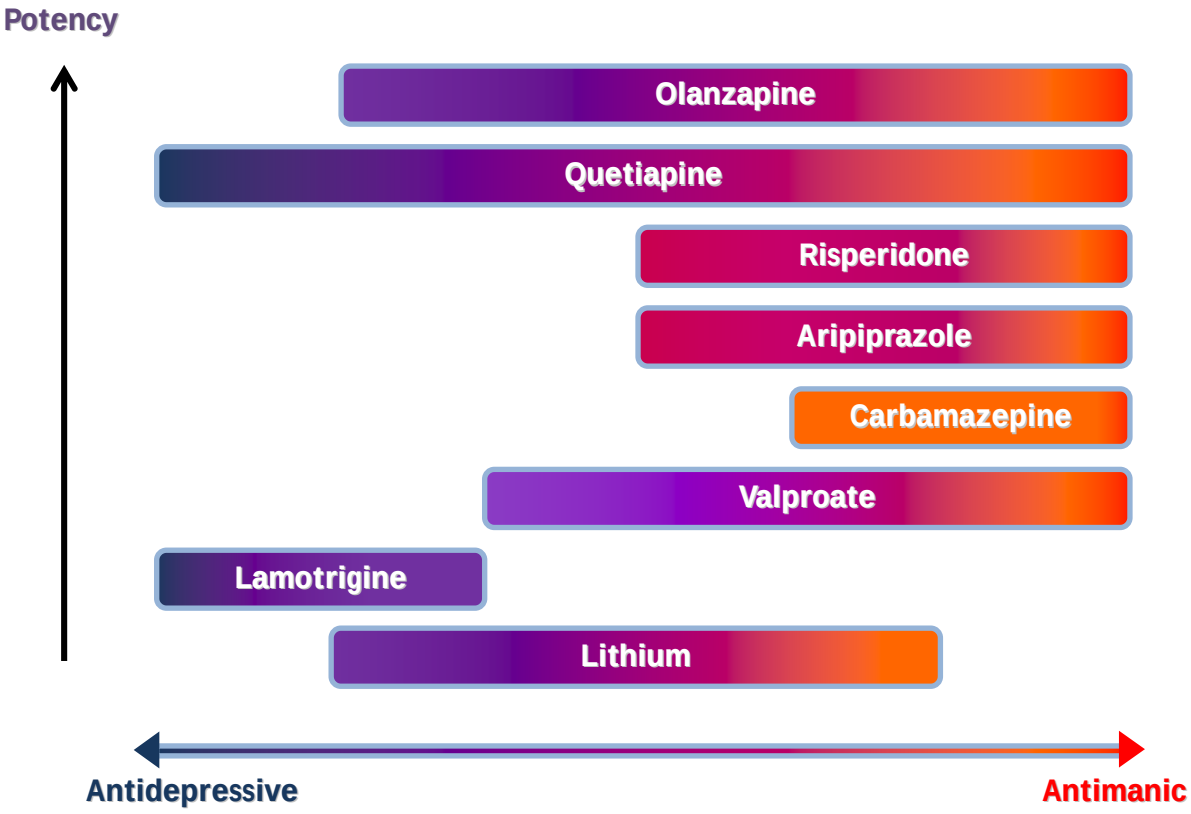

Fig. 1. Antimanic/Antidepressive Properties and Potency of Mood Stabilizers

TENTATIVE CLASSIFICATION OF MOOD STABILIZERS

The therapeutic spectrum of mood stabilizers of different classes is summarized in Table 1 and Fig.1, based on reliable systematic reviews published between 2006 and 2010 [5-7, 11-14]. In this chapter, mood stabilizers are classified into one of the following three subtypes based on their characteristic mood-stabilizing properties: 1) all-around mood stabilizers, 2) predominantly antimanic mood stabilizers; and 3) predominantly antidepressive mood stabilizers. This classification, while containing some informative value based on recent findings, is tentative, and may need to be revised based on information newly come to light.

All-Around Mood Stabilizers (Li, QTP, OLZ)

1. Li

Li has been regarded as a classic mood stabilizer, for which there is established evidence for acute and maintenance efficacy in both manic and depressive episodes of bipolar disorders [1, 3]. Li has been recommended as the first-line drug for the acute treatment of manic and depressive phases and relapse prevention for bipolar disorders by to American Psychiatry Association (APA, 2005) [15], the National Institute for Health and Clinical Excellence (NICE, 2006) [16], and the Canadian Network for Mood and Anxiety Treatments (CANMAT, 2009) [11]. In the acute treatment of bipolar disorders, Li alone exhibits modest and limited antidepressive or antimanic effects, but may not be sufficiently applicable to more severe psychopathology, in which combination therapy or replacement with other mood-stabilizing agents might be a better option [15, 16].

Meanwhile, some doubt has been cast on the acute antidepressive efficacy of Li by a meta-analytic review [6] that included recent randomized controlled studies [17], since these effects had been observed in small-sized observational studies with relatively short-term follow-up periods. As a result, the latest guideline by the World Federation of Societies of Biological Psychiatry (WFSBP, 2010) does not recommend Li monotherapy as the first-line treatment in acute bipolar depression [13]. In addition, it has been recently pointed out that Li has only limited and insufficient efficacy in relapse prevention for bipolar disorders, and that there is substantial concern over adverse effects during its long-term use, in a systematic review focusing on maintenance pharmacotherapy for bipolar disorders [7].

It should be noted that Li acts only as a mild and modest mood stabilizer; onset of efficacy is slow, and its true efficacy should be evaluated at optimal blood concentrations higher than 0.8 mEq/L, as recommended by the NICE guideline [16]. Although these pharmacological and pharmacokinetic characteristics of Li must be taken into consideration when conducting larger randomized controlled studies with Li, it is possible that at some point we may need to re-classify Li as a predominantly antimanic mood stabilizer rather than an all-around mood stabilizer.

2. QTP

Recently, QTP has seemingly taken over Li's position as the standard all-around mood stabilizer. It has been suggested that the efficacy of QTP monotherapy in acute mania is comparable to that of Li [18]. Also, the antimanic effect of Li or VPA is enhanced by the coadministration of QTP [19]. The NICE [16] and CANMAT [11] guidelines now recommend QTP as the first-line drug, especially for the more severe pathophysiology of acute mania, due to its rapid and potent antimanic effects.

Meanwhile, the efficacy of QTP monotherapy in acute bipolar depression has been consistently confirmed by such double-blind, placebo-controlled studies as BOLDER (BipOLar DEpRession) I/II [8, 20] and EMBOLDEN (Efficacy of Monotherapy SEROQUEL in BipOLar DEpressioN) I/II [17, 21]. The latter EMBOLDEN studies also examined the efficacy of QTP monotherapy in relapse prevention for bipolar disorders, and the results suggested that the preventive effect of QTP monotherapy is superior to that of placebo for both manic and depressive recurrence, and is superior to that of Li for depressive recurrence [11], and that the efficacy of Li or VPA for relapse prevention of any mood episode is clearly augmented by QTP coadministration [10, 22]. Accordingly, the NICE guideline recommended the addition of QTP in the acute phase treatment of moderate to severe bipolar depression [16], and the latest WFSBP guideline also recommends QTP monotherapy as the first-line treatment for acute bipolar depression [13]. Furthermore, the CANMAT guidelines suggest that QTP monotherapy is superior in all respects to the other available options for the acute and maintenance treatment of both manic and depressive episodes of bipolar disorders [11].

3. OLZ

The efficacy of OLZ in acute mania has been rated highly by the APA [15], NICE [16] and CANMAT [11], and its antimanic effects, which may be at least partly attributable to its own sedative/anxiolytic effects, with rapid onset of action, are superior to those of Li or VPA [23, 24]. Although it was also suggested that OLZ monotherapy would afford significant efficacy in acute bipolar depression compared to placebo, it did not improve the core depressive symptoms and exhibited lower efficacy than OLZ + fluoxetine (OFC) [9]. OLZ monotherapy was therefore not approved for bipolar depression. The FDA has approved OFC as a treatment option for acute bipolar depression, but the EMEA has not.

The advantages of OLZ monotherapy over placebo in the maintenance treatment of bipolar disorders were confirmed by the double-blind, placebo controlled study [25]. However, its predominant relapse prevention effect appears to be reduction in manic recurrence [7]. Therefore, in the future, OLZ may be reclassified as a predominantly antimanic mood stabilizer, as is the case with Li, as described above. Despite the efficacy of OLZ at preventing manic episodes, using OLZ in the maintenance treatment of bipolar disorders is not necessarily a high priority because of the uncertain risk/benefit balance between the potential metabolic complications and the limited preventive efficacy in the long-term use of OLZ.

Predominantly Antimanic Mood Stabilizers (VPA, CBZ, ARI, RIS/Paliperidone)

1. VPA

Since the antimanic efficacy of VPA in the acute phase of bipolar mania has been well established [6, 26], most of guidelines have recommended VPA as a first-line option, alongside Li, for acute mania/mixed episodes [11, 15, 16]. VPA is more effective than Li in treating mixed episodes, and is better tolerated than Li in long-term use [27]. It is also noteworthy that optimal therapeutic concentrations of VPA for acute mania have been suggested in a previous report [28], in which greater efficacy than that of placebo was demonstrated starting from a concentration of 71.4 μg/ml, and superiority to the lowest concentration (55.0 μg/ml) was demonstrated starting from a concentration of 94.1 μg/ml.

Although VPA has been regarded as having insufficient efficacy for acute bipolar depression, a recent meta-analytic review, by contrast, supports the effectiveness of VPA in the acute phase of bipolar depression [29]. Accordingly, the NICE guidelines [16] recommend VPA as the first-line treatment for acute bipolar depression, alongside Li and QTP, while the CANMAT [11] and WFSBP [13] guidelines recommended VPA as the second-line option.

As far as maintenance therapy in bipolar disorders is concerned, although VPA has been recognized as primarily preventing manic recurrence, it has been suggested recently that VPA is somewhat effective against depressive recurrence compared to other mood stabilizers [7]. Especially in patients with a past history of good response to VPA for manic episodes and more severe depressive episodes, VPA is superior to Li in preventing depressive recurrence [30]. Summarizing these findings, VPA may be re-classified in the future as an all-around mood stabilizer, instead of its current classification as a predominantly antimanic mood stabilizer.

2. CBZ

Early studies by Okuma et al [31, 32] revealed the antimanic effects of CBZ in both the acute and maintenance treatment of bipolar mania, and these effects have recently been reconfirmed by randomized controlled studies of extended-release carbamazepine monotherapy in acute manic/mixed episodes [33, 34], although efficacy in relapse prevention for manic episodes was found to be lower than that of Li [35]. However, according to the guidelines of the APA [15], NICE [16] and CANMAT [11], CBZ has been regarded only as the second-line option for treatment of the acute phase of bipolar mania due to concerns about intolerance to CBZ and pharmacokinetic interactions with CBZ. Meanwhile, there have been very few studies which positively support the efficacy of CBZ in the acute and maintenance treatment of bipolar depression. CBZ is positioned as the second-line or lower treatment, and only as an additional option to previous medication, in all of the guidelines [11, 15, 16].

3. ARI

According to a meta-analytic review of reliable randomized controlled studies with placebo or active controls that examined the effects of ARI in acute bipolar mania, its antimanic properties were superior to those of placebo and comparable to those of Li and haloperidol [5].

On the other hand, a study investigating the acute efficacy of ARI in bipolar depression [36] demonstrated that, although ARI was superior to placebo during the first 6 weeks, at the end of the study (8 weeks), there was no difference in therapeutic efficacy, but more adverse effects and drop-outs

were seen with ARI than with placebo, suggesting that ARI affords no apparent efficacy in acute bipolar depression.
The efficacy of ARI for relapse prevention in maintenance treatment for bipolar disorders was limited to the prevention of manic recurrence; depressive recurrence was not prevented [37, 38]. These findings suggest that ARI can be categorized as a typical antimanic mood stabilizer.

4. RIS/Paliperidone

It has been well established that RIS, both as monotherapy and as adjunctive treatment, is more effective than placebo, and is comparable to haloperidol in reducing the manic symptoms of bipolar disorders [39]. An extended-release formulation of paliperidone, the active metabolite of RIS, also has been shown to be superior to placebo and noninferior to QTP in terms of efficacy in acute manic/mixed episodes [40]. Thus, the CANMAT guidelines [11] hold RIS in high regard, as the first-line treatment, and paliperidone as the second-line treatment, for acute mania due to their fast and potent antimanic effects. Moreover, the APA guidelines [15] already recommended RIS as one of the first-line pharmacological treatments for mixed episodes, whereas the NICE guidelines [16] suggest that RIS should be used for the more severe psychopathology of manic/mixed episodes.
By contrast, no guidelines have ever supported the efficacy of RIS or paliperidone in acute bipolar depression, suggesting that there is no established consensus on the antidepressive properties of RIS or paliperidone in the treatment of bipolar disorders [11, 13, 15, 16].
Although the long-term efficacy of oral RIS or paliperidone has not been investigated in detail, two recent studies demonstrated the efficacy of RIS-LAI as monotherapy [41] and as adjunctive therapy [42] in maintenance treatment for bipolar disorders, based on data showing a lower relapse rate and a longer time to relapse with the use of RIS-LAI. Accordingly, the CANMAT guidelines [11] have recently recommended RIS-LAI as one of the first-line maintenance pharmacotherapies for bipolar disorders. However, RIS-LAI is unlikely to exhibit prophylactic efficacy versus depressive recurrence due to its lack of acute efficacy in bipolar depression.

Predominantly Antidepressive Mood Stabilizers (LTG)

LTG is the only antidepressive mood stabilizer without any antimanic properties. Although early placebo-controlled, double-blind studies [43, 44] demonstrated the efficacy of LTG in the treatment of bipolar depression, subsequent meta-analysis that included additional randomized controlled studies failed to prove the efficacy of LTG monotherapy in acute bipolar depression [45]. Thus, the acute antidepressive effects of LTG have been underestimated or discounted for some time. However, Geddes et al [46] reexamined and reanalyzed individual patient data from five randomized trials, and demonstrated a better response to and higher remission rate with LTG treatment than with placebo. Furthermore, the superiority of LTG to placebo was marked in more severely depressed patients, a finding that was consistent with those of a previous study [44]. Accordingly, LTG is recommended as the first-line treatment for the acute phase of bipolar depression by both the APA [15] and the CANMAT [11] guidelines, and is also recommended as an additional treatment option for more severe psychopathologies, including rapid cycling, in the NICE guidelines [16].
In maintenance treatment for relapse prevention of bipolar disorders, LTG is not effective at preventing manic recurrence [47], but does not induce manic switching like antidepressants; the risk of manic switching in LTG treatment has been reported to be similar to that of placebo [12]. Meanwhile, a systematic review [7] suggested that LTG affords sufficient relapse prevention efficacy for depressive recurrence, while being well-tolerated, although its prophylactic efficacy versus manic recurrence is much lower than that of Li or QTP [7]. The APA [15] and NICE [16] guidelines classify LTG as a second-line maintenance therapy for bipolar disorders, but the recent CANMAT guidelines [11] highly recommended LTG as a first-line option, alongside Li, VPA, QTP and OLZ. Also, the coadministration of LTG with antimanic agents may be useful for broadening the mood-stabilizing spectrum, and may be especially effective for treating the refractory mood disorders that are common in depressive recurrence.

USE IN SPECIFIC PSYCHOPATHOLOGIES

The traditional gold standard, Li, is not necessarily a perfect mood stabilizer even though it has been widely used in all bipolar disorder psychopathologies. In particular, mixed polarity and the frequent

recurrence of mood episodes, such as dysphoric mania, mixed features and rapid cycling, have been considered less responsive to Li. Therefore, mood stabilizers need to be rationally and optimally selected for each of these refractory pathophysiologies. Below, we describe plausible scenarios for the use of different mood stabilizers in certain specific bipolar disorder psychopathologies, although there is still insufficient evidence in this field.

Bipolar II disorder

There is very little available evidence on mood-stabilizing treatments for bipolar II disorder, which is characterized by recurrent depressive episodes and less frequent hypomanic episodes. The efficacy of QTP monotherapy in bipolar II disorder was comprehensively investigated in the BOLDER I/II studies [8, 20]. Comprehensive analyses of these data revealed the rapid and consistent efficacy of QTP monotherapy for depressive episodes of bipolar II disorder [48]. Meanwhile, several smaller studies that Li, LTG and VPA exhibit efficacy in acute phase treatment for bipolar II depression [49, 50].

Since maintenance therapy for bipolar II disorder should focus mainly on preventing depressive recurrence, which is common, LTG, a predominantly antidepressive mood stabilizer, is highly recommended by the NICE guidelines as an option for poor responders in addition to the first-line mood stabilizers [16]. The recent CANMAT guidelines [11] recommend QTP as the first-line treatment for acute depressive episodes of bipolar II disorder, followed by Li, LTG or VPA as second-line treatments, whereas Li or LTG are recommended as the first-line treatments in maintenance therapy, and VPA is recommended as a second-line treatment. Furthermore, combinations of antidepressants and mood stabilizer have been extensively examined as an option for maintenance therapy in bipolar II disorder, since antidepressant-induced manic switching is less common in bipolar II disorder than in bipolar I disorder [51].

Mixed features

Mood stabilizers with rapid onset and consistent efficacy that also have bimodal efficacy for both manic and depressive psychopathologies are expected to be used in the treatment of mixed episodes and mixed depression. Li is known to be fairly effective for the classical psychopathology of euphoric mania or in patients with a family history of bipolar disorder, but less effective against mixed features of bipolar illness [52]. Thus, in reality, Li can be used as an additional option only in subjects exhibiting insufficient response to VPA or CBZ, since Li monotherapy is in general unlikely to be an excellent option for mixed features [53].

It has been suggested that VPA is superior to Li for treating mixed episodes and is also effective for mood episodes with dysphoric or psychotic features, which are unresponsive to Li [27]. However, it should be noted that VPA alone may not necessarily possess potent efficacy with rapid onset in mixed episodes. Therefore, second-generation antipsychotics possessing acute and potent antimanic features, such as QTP, OLZ, ARI and RIS, can be coadministered, especially when efficacy is urgently required for the emergent, unstable psychopathology of mixed features [54]. Regarding the treatment of acute mixed episodes, the APA guidelines also consider VPA superior to Li and CBZ as an alternative option in cases unresponsive to Li or VPA, and recommend the use of second-generation antipsychotics instead of first-generation antipsychotics [15].

Rapid cycling

Few data are available on rational treatments for rapid cycling with mood stabilizers. Earlier studies pointed out that any monotherapy for rapid cycling with Li, VPA or CBZ resulted in a poor outcome, suggesting the potential treatment-resistance of this pathophysiology [55, 56] However, the results of the recent BOLDER I study [20] suggest that QTP monotherapy may be effective for bipolar disorders with rapid cycling [57]. Comprehensive data analysis of BOLDER I and II [8, 20] also demonstrated the superiority of 300-600 mg/day of QTP to placebo in bipolar disorder patients with or without rapid cycling [58] Thus, QTP may be a first-line treatment option for rapid cycling psychopathology for which there is now supportive evidence.

Conventional guidelines recommend the single or combined use of classical mood stabilizers like Li or VPA (APA) [15], or the combination of Li and VPA (NICE) [16] as the first-line option for rapid cycling, followed by LTG as the second-line. Although it had once been expected that LTG might be effective for rapid cycling based on the results of earlier studies [44, 59, 60], the current thinking on LTG holds that it has no practical usefulness for rapid cycling [61]. However, our latest study has demonstrated that LTG augmentation may be sufficiently effective for the treatment of any treatment-resistant mood disorders, especially those with unremitted depression of shorter duration and more recurrent

depressive episodes [62]. Therefore, the potential efficacy of LTG for refractory pathophysiology associated with frequent recurrence of mood episodes, including rapid cycling, needs to be reexamined.

ANOTHER PERSPECTIVE

Since a long-term pharmacological strategy (2-5 years) incorporating mood stabilizers is usually needed for maintenance therapy of bipolar disorders [16], the selection and use of mood stabilizers should be at least partly determined from the standpoints of their long-term tolerability and safety. Therefore, the possible risks of teratogenicity with Li or VPA [63, 64] and impaired cognitive development in the offspring of mothers exposed to VPA [65], the risks and benefits of Li use in elderly subjects, who may possess latent renal dysfunction and apparent physical complications and may be under treatment with potentially interacting drugs, and tardive extrapyramidal adverse effects/metabolic problems in long-term use of second-generation antipsychotics are critical factors to consider when selecting mood stabilizers for long-term maintenance therapy.

Meanwhile, the efficacy of combining mood stabilizers with different mood-stabilizing spectra (i.e., antimanic mood stabilizer plus antidepressive mood stabilizer) should be investigated in the future, as well. Although a concrete definition of "mood stabilizer" has not yet been established, mood stabilizers are generally regarded as essential for treating bipolar disorders. It is increasingly expected that the molecular biology behind the mechanisms of the various mood-stabilizing actions will be clarified, leading to innovative new drug discovery efforts, while the collection of new and better information and knowledge on currently available mood stabilizers should be continued in order to achieve a more rational and optimal procedure for selecting mood stabilizers in the treatment of bipolar disorders.

REFERENCES

[1] Bauer MS, Mitchner I. What is a "mood stabilizer"? An evidence-based response. Am. J. Psychiatry 2004; 161: 3-18.

[2] Kondo T. Treatment of bipolar disorders. In: The Japanese Society of Clinical Neuropsychopharmacology (ed) Text for Clinical Neuropsychopharmacology (2nd edition). Seiwa Shoten, Tokyo, 2008, pp. 331-339. (In Japanese)

[3] Goodwin GM, Malhi GS. What is a mood stabilizer? Psychol Med 2006; 37: 609-614.

[4] Pacchiarotti I, Mazzarini L, Colom F, Sanchez-Moreno J, Giardi P, Kotzalidis GD, Vieta E. Treatment-resistant bipolar depression: towards a new definition. Acta Psychiatr Scand 2009; 120: 429-440.

[5] Fountoulakis KN, Vieta E. Efficacy and safety of aripiprazole in the treatment of bipolar disorder: a systematic review. Ann Gen Psychiatry 2009; 8: 16.

[6] Geddes JR, Briess D. Bipolar disorder. Clin Evid 2007; 08: 1014.

[7] 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.

[8] Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR; BOLDER II Study Group. 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: 600-609.

[9] Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW, Evans AR, Beymer K, Dube S, Tollefson GD, Breier A. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003; 60: 1079-1088.

[10] Altamura AC, Mundo E, Dell' Osso B、Tacchini G, Buoli M, Calabrese JR. Quetiapine and classical mood stabilizers in the long-term treatment of bipolar disorder: a 4-year followup naturalistic study. J Affect Disord 2008; 110: 135-141.

[11] Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, MacQueen G, Mclntyre RS, Sharma V, Ravindran A, Young LT, Young AH, Alda M, Milev R, Vieta E, Calabrese JR, Berk M, Ha K, Kapczinski F. 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: 225-255.

[12] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Moller HJ, Kasper S. 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.

[13] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, Kasper S. 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.

[14] Malhi GS, Adams D, Berk M. Medicating mood with maintenance in mind: bipolar depression pharmacotherapy. Bipolar Disord 2009; 11 (Suppl. 21): 55-76.

[15] Hirschfeld RMA. Guideline watch (November 2005): practice guideline for the treatment of patients with bipolar disorder, 2nd Edition. Focus 2007; 5: 34-39, 2007.

[16] National Institute for Health and Clinical Excellence. Bipolar Disorder: The management of bipolar disorder in adults, children and adolescents, in primary and secondary care: Clinical Guidelines 38. London: NHS, 2006.

[17] Young AH, McElroy SL, Bauer M, Philips N, Chang W, Olausson B, Paulsson B, Brecher M; EMBOLDEN I (Trial 001) Investigators. 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: 150-162.

[18] Bowden CL, Grunze H, Mullen J, Brecher M, Paulsson B, Jones M, Vågerö M, Svensson K. A randomized double-blind, placebo-controlled efficacy and safety study of quetiapine or lithium as monotherapy for mania in bipolar disorder. J Clin Psychiatry 2005; 66: 111-121.

[19] Sussman N, Mullen J, Paulsson B, Vågerö M. Rates of remission/euthymia with quetiapine in combination with lithium/divalproex for the treatment of acute mania. J Affect Disord 2007; 100 (Suppl. 1): S55-S63.

[20] Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Culter AJ, McCoy R, Wilson E, Mullen J. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005; 162: 1351-1360.

[21] McElroy SL, Weisler RH, Chang W, Olausson B, Paulsson B, Brecher M, Agambaram V, Merideth C, Nordenhem A, Young AH; EMBOLDEN II (Trial D1447C00134) Investigators. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry 2010; 71: 163-174.

[22] Vieta E, Suppes T, Eggens I, Persson I, Paulsson B, Brecher M. Efficacy and safety of quetiapine in combination with lithium or divalproex for maintenance of bipolar I disorder. J Affect Disord 2008; 109: 251-263.

[23] Niufau G, Tohen M, Qiuqing A, Fude Y, Pope E, McElroy H, Ming L, Gaohua W, Xinbao Z, Huichun L, Liang S. Olanzapine versus lithium in the acute treatment of bipolar mania: a double-blind, randomized, controlled trial. J Affect Disord 2008; 105: 101-108.

[24] Tohen M, Ketter TA, Zarate CA, Suppes T, Frye M, Altshuler L, Zajecka J, Schuh LM, Risser RC, Brown E, Baker RW. Olanzapine versus divalproex sodium for the treatment of acute mania and maintenance of remission: a 47-week study. Am J Psychiatry 2003; 160: 1263-1271.

[25] Tohen M, Calabrese JR, Sachs GS, Banov MD, Detke HC, Risser R, Baker RW, Chou JC, Bowden CL. Randomized, placebo-controlled trial of olanzapine as maintenance therapy in patients with bipolar I disorder responding to acute treatment with olanzapine. Am J Psychiatry 2006; 163: 247-256.

[26] Smith LA, Cornelius V, Warnock A, Tacchi MJ, Taylor D. Pharmacological intervention for acute bipolar mania: a systematic review of randomized placebo-controlled trials. Bipolar Disord 2007; 9: 551-560.

[27] Bowden CL. The effectiveness of divalproate in all forms of mania and the broader spectrum: many questions, few answers. J Affect Disord 2004; 79 (Suppl.1): S9-S14.

[28] Allen MH, Hirschfeld RM, Wozniak PJ, Baker JD, Bowden CL. Linear relationship of valproate serum concentration to response and optimal serum levels for acute mania. Am J Psychiatry 2006; 163: 272-275.

[29] Smith LA. Cornelius VR, Azorin JM, Perugi G, Vieta E, Young AH, Bowden CL. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J Affect Disord 2010; 122: 1-9.

[30] Gyulai L, Bowden CL, McElroy SL, Calabrese JR, Petty F, Swann AC, Chou JC, Wassef A, Risch CS, Hirschfeld RM, Nemeroff CB, Keck PE Jr, Evans DL, Wozniak PJ. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 2003; 28: 1374-1382.

[31] Okuma T, Inanaga K, Otsuki S, Sarai K, Takahashi R, Hazama H, Mori A, Watanabe M. Comparison of the antimanic efficacy of carbamazepine and chlorpromazine: a double-blind controlled study. Psychopharmacology 1979; 66: 211-217.

[32] Okuma T, Inanaga K, Otsuki S, Sarai K, Takahashi R, Hazama H, Mori A, Watanabe S. A preliminary double-blind study on the efficacy of carbamazepine in prophylaxis of manic-depressive illness. Psychopharmacology 1981; 73: 95-96.

[33] Weisler RH, Kalali AH, Ketter TA, SPD417 Study Group. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. J Clin Psychiatry 2004; 65: 478-484.

[34] Weisler RH, Keck PE Jr, Swann AC, Culter AJ, Ketter TA, Kalali AH; SPD417 Study Group. 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: 323-330.

[35] Hartong EG, Moleman P, Hoogduin CA, Broekman TG, Nolen WA; LitCar Group. Prophylactic effect of lithium versus carbamazepine in treatment-naïve bipolar patients. J Clin Psychiatry 2003; 64: 144-151.

[36] Thase ME, Jonas A, Khan A, Bowden CL, Wu X, McQuade RD, Carson WH, Marcus RN, Owen R. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J Clin Psychopharmacol 2008; 28: 13-20.

[37] Keck PE Jr, Calabrese JR, McQuade RD, Carson WH, Carlson BX, Rollin LM, Marcus RN, Sanchez R; Aripiprazole Study Group. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry 2006; 67: 626-637.

[38] Keck PE Jr, Calabrese JR, Mclntyre RS, McQuade RD, Carson WH, Eudicone JM, Carlson BX, Marcus RN, Sanchez R; Aripiprazole Study Group. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007; 68: 1480-1491.

[39] Rendell JM, Gijsman HJ, Bauer MS, Goodwin GM, Geddes GR. Risperidone alone or in combination for acute mania. Cochrane Database Syst Rev 2006; 25: CD004043.

[40] Vieta E, Nuamah IF, Lim P, Yuen EC, Palumbo JM, Hough DW, Berwaerts J. A randomized, placebo- and active-controlled study of paliperidone extended release for the treatment of acute manic and mixed episodes of bipolar I disorders. Bipolar Disord 2010; 12: 230-243.

[41] Quiroz JA, Yatham LN, Palumbo JM, Karcher K, Kushner K, Kushner S, Kusumaker V. Risperidone long-acting injectable monotherapy in the maintenance treatment of bipolar I disorder. Biol Psychiatry 2010; 70: 1001-1012.

[42] Macfadden W, Alphs L, Haskins JT, Turner N, Turkoz I, Bossie C, Kujawa M, Mahmoud R. A randomized, double-blind, placebo-controlled study of maintenance treatment with adjunctive risperidone long-acting therapy in patients with bipolar I disorder who relapse frequently. Bipolar Disord 2009; 11: 827-839.

[43] 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.

[44] Frye MA, Ketter TA, Kimbell TA, Dunn RT, Speer AM, Osuch EA, Luckenbaugh DA, Cora-Ocatelli G, Leverich GS, Post RM. A placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders. J Clin Psychopharmacol 2000; 20: 607-614.

[45] Calabrese JR, Huffman RF, White RL, Edwards S, Thompson TR, Ascher JA, Monaghan ET, Leadbetter RA. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disord 2008; 10: 323-333.

[46] Geddes JR, Calabrese JR, Goodwin GM. Lamotrigine for treatment of bipolar

depression: independent meta-analysis and meta-regression of individual patient data from five randomized trials. Br J Psychiatry 2009; 194: 4-9.

[47] Goodwin GM, Bowden CL, Calabrese JR, Grunze H, Kasper S, White R, Greene P, Leadbetter R. A pooled analysis of 2 placebo-controlled 19-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J Clin Psychiatry 2004, 65: 432-441.

[48] 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.

[49] Suppes T, Marangell LB, Bernstein IH, Kelly DI, Fischer EG, Zboyan HA, Snow DE, Martinez M, Al Jurdi R, Shivakumar G, Sureddi S, Gonzalez R. A single blind comparison of lithium and lamotrigine for the treatment of bipolar II depression. J Affect Disiord 2008; 111: 334-343.

[50] Wang PW, Nowakowska C, Chandler RA, Hill SJ, Nam JY, Culver JL, KellerKL, Ketter TA. Divalproex extended-release in acute bipolar II depression. J Affect Disord 2010; 124: 170-173.

[51] Bond DJ, Noronha MM, Kauer-Sant'Anna M, Lam RW, Yatham LN. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry 2008; 69: 1589-1601.

[52] American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002; 159 (Suppl.4): 1-50.

[53] Krüger S, Young LT, Bräunig P. Pharmacotherapy of bipolar mixed states. Bipolar Disord 2005; 7: 205-215.

[54] Kondo T. Pharmacotherapy of mixed episodes in bipolar disorder. Jap J Clin Psychopharmacol 2007; 10: 2195-2201. (In Japanese)

[55] Calabrese JR, Shelton MD, Rapport DJ, Kimmel SE. Bipolar disorders and the effectiveness of novel anticonvulsants. J Clin Psychiatry 2002; 63 (Suppl. 3): 5-9.

[56] Denicoff KD, Smith-Jackson EE, Disney ER, Ali SO, Leverich GS, Post RM. Comparative prophylactic efficacy in lithium, carbamazepine, and the combination in bipolar disorder. J Clin Psychiatry 1997; 58: 470-478.

[57] Vieta E, Calabrese JR, Goikolea JM, Raines S, Macfadden W; BOLDER study Group. Quetiapine monotherapy in the treatment of patients with bipolar I or II depression and a rapid-cycling disease course: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2007; 9: 413-425.

[58] Thase ME. Quetiapine monotherapy for bipolar depression. Neuropsychiatr Dis Treat 2008; 4: 11-21.

[59] Calabrese JR, Suppes T, Bowden CL, Sachs GS, Swann AC, McElroy SL, Kusumakar V, Ascher JA, Earl NL, Greene PL, Monaghan ET. A double-blind, placebo-controlled, prophylaxis study of lamotrigine in rapid cycling bipolar disorder. J Clin Psychiatry 2000; 61: 841-850.

[60] Obrocea GV, Dunn RM, Frye MA, Ketter TA, Luckenbaugh DA, Leverich GS, Speer AM, Osuch EA, Jajodia K, Post RM. Clinical predictors of response to lamotrigine and gabapentin monotherapy in refractory affective disorders. Biol Psychiatry 2002; 51: 253-260.

[61] Nassir Ghaemi S, Shirzadi AA, Filkowski M. Publication bias and the pharmaceutical industry: the case of lamotrigine in bipolar disorder. Medscape J Med 2008; 10: 211.

[62] Kagawa S, Nemoto K, Suzuki T, Nagai G, Nakamura A, Mihara K, Kondo T. Lamotrigine augmentation for the treatment-resistant mood disorders. Clinical Neuropsychopharmacology and Therapeutics 2010; 1: 35-42.

[63] Harden CL, Meador KJ, Pennell PB, Hauser WA, Gronseth GS, French JA, JA, Wiebe S, Thurman D, Koppel BS, Kaplan PW, Robinson JN, Hopp J, Ting TY, Gidal B, Hovinga CA, Wilner AN, Vazquez B, Holmes L, Krumholz A, Finnell R, Hirtz D, Le Guen C; American Academy of Neurology; American Epilepsy Society. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009; 73: 133-141.

[64] Schou M., Goldfield MD, Weinstein MR, Villeneuve A. Lithium and pregnancy. I. Report from the Register of Lithium Babies. Br Med J 1973; 2: 135-136.

[65] Meador KJ, Baker JA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009; 360: 1579-1605.