PSYCHIATRIA ET NEUROLOGIA JAPONICA

Special Feature Article

Pharmacological Therapy for Patients with Treatment-resistant Bipolar Disorder

Mitsuhiro TADA, Kie TAKAHASHI, Shintaro NIO
Department of Psychiatry, Saiseikai Central Hospital
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Abstract

We reviewed "treatment-resistant" bipolar disorder especially treatment-resistant bipolar depression and rapid-cycling bipolar disorder. Encouraging results have been reported by randomized controlled trials on inositol, ketamine, lamotrigine, modafinil and pramipexole administration during resistant depressive phases. In particular, ketamine demonstrated significant improvement compared with the placebo. Rapid-cycling bipolar disorder refers to the presence of at least 4 mood episodes in the previous 12 months that meet the criteria for manic, hypomanic or major depressive episodes in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5). Rapid-cycling bipolar disorder has been reported to have a poorer outcome than non-rapid-cycling bipolar disorder. In addition, rapid cycling is associated with depression, substance abuse and suicide risk. Thus, clinicians need to pay closer attention when diagnosing and treating patients with rapid-cycling bipolar disorder. Quetiapine demonstrated significant improvement in double-blind placebo-controlled studies on rapid cycling. Hypothyroidism and antidepressants have been reported as risk factors for rapid-cycling bipolar disorder. Therefore, recent guidelines recommend that antidepressants be avoided and to administer quetiapine, especially during acute depressive episodes in rapid-cycling patients.

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Keywords: rapid cycling, bipolar disorder, treatment resistant, refractory, pharmacological therapy

Introduction.

Bipolar disorder consists of three phases: manic phase, depressive phase, and maintenance phase. There is some evidence for pharmacotherapy for treatment-resistant bipolar disorder conditions such as treatment-resistant bipolar depression (treatment-resistant depressive phase) and rapid cycling bipolar disorder (treatment-resistant maintenance phase). We present the current evidence on the treatment of these two conditions and discuss treatment strategies. As a non-biological treatment, adequate psychological education, which is the basis of treatment of bipolar disorder, is essential, but is not discussed here. Part of this review is based on my previous study 33), and mentions pharmacotherapy that is not indicated for use in Japan; thus, caution should be exercised in its actual use.

I. Diagnosis of bipolar disorder

Before discussing "treatment resistance" in daily clinical practice, it is necessary to reconsider the diagnosis. Two-thirds of patients with bipolar disorder have a depressive phase as their initial phase 8), and in bipolar II disorder, the proportion of depressive phase in all phases is 93% 20). Moreover, about half of patients with manic episodes lack awareness of their manic symptoms 14). This characteristic may be one of the reasons why bipolar disorder is underdiagnosed in the Diagnostic and Statistical Manual of Mental Disorders (DSM), which emphasizes the polarity of episodes across the board.

Research on bipolar disorder has progressed and some progress has been made in the clarification of its pathogenesis and diagnosis, but one of its harmful effects is overdiagnosis. As a result, depressed patients with anxiety and agitation, attention deficit/hyperactivity disorder, personality disorders, disruptive behaviors, impulse control, and behavioral disorders as well as child and adolescent patients with mood swings are diagnosed as bipolar disorder, and there is concern about the unnecessary administration of mood stabilizers and antipsychotics. If these non-bipolar patients are diagnosed with bipolar disorder and do not respond to bipolar disorder treatment, they may be judged to have treatment-resistant

bipolar disorder. The specific term "with mixed features" is used in the DSM-5th edition 2) is also concerned about overdiagnosis, and some symptoms (distractibility, irritability, and agitation) are excluded from the requirement because they can be seen in both manic and depressive states (Table 1). It is possible that depression with anxiety and agitation may be diagnosed as bipolar depression, and antidepressants may not be administered.

II. Treatment Strategies for Bipolar Depression

In 2004, Gijsman et al. conducted a systematic review and meta-analysis of the efficacy and safety of antidepressants in the acute treatment of bipolar depression 15). They found that antidepressants were more effective than placebo in the acute treatment of bipolar depression in terms of response rate (relative risk [RR] = 1.86, 95% confidence interval [CI] = 1.49-2.30), remission rate (RR = 1.41, 95% CI = 1.41, 95% CI = 1.49-2.30), and mania rate (RR = 1.41, 95% CI = 1.49-2.30). The response rate (RR=1.86, 95% CI = 1.49-2.30) and remission rate (RR = 1.41, 95% CI = 1.11-1.80) were significantly higher with antidepressants than with placebo. Mania occurred in 3.8% of patients on antidepressants and 4.7% on placebo, with no significant difference. Thus, the evidence of about 15 years ago was that antidepressants were effective in the acute treatment of bipolar depression and that mania did not occur; therefore, antidepressants should be used more and more.

However, a systematic review and meta-analysis by Sidor et al. in 2011 overturned their conclusions 31). Since Gijsman's article in 2004, six RCTs (N = 1,034) have been conducted, which are included in the present review. There were no significant differences in response, remission, mania, or tolerability between antidepressants and placebo; thus, it was concluded that antidepressants are not effective in the acute treatment of bipolar depression and that mania does not occur. This is the current consensus.

A report by Sachs et al. in 2007 was particularly influential in changing the conclusions of this meta-analysis 28). In a large U.S. clinical trial, 366 patients with bipolar disorder in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) were treated with mood stabilizers plus antidepressants as adjunctive therapy compared with placebo for 26 weeks. The primary outcome was the rate of durable recovery (mood stabilization over 8 weeks), and the secondary outcome. The results showed no significant difference in durable

recovery (P = 0.40) or manic switch (P = 0.84) between the groups (Table 2).

The following is a list of international treatment guidelines for bipolar depression (Table 3). Quetiapine is commonly recommended as the first-line treatment in all recent guidelines, followed by lurasidone in several guidelines. In addition, some guidelines include the use of mood stabilizers and antidepressants in their recommendations. A 2018 guideline jointly developed by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) 37) recommends the following: bupropion and selective serotonin reuptake inhibitors, and olanzapine and fluoxetine as second-line treatment for the depressive phase of bipolar I disorder, as well as sertraline and venlafaxine for bipolar II disorder. In bipolar II disorder, sertraline and venlafaxine alone are listed as second choices only in patients without mixed symptoms. In addition, sertraline and venlafaxine are listed as second-line drugs in bipolar II disorder only in patients who do not show mixed symptoms. The concurrent use of olanzapine and fluoxetine was listed as a first-line treatment in the 2010 World Federation of Societies of Biological Psychiatry guidelines 18), but was removed as first-line treatment in the 2013 revision 19). On the other hand, the British Association for Psychopharmacology (BAP) guideline 17) of 2016 and The International College of Neuro-Psychopharmacology (CINP) guideline 12) of 2017 suggest that the use of the drug should be considered as a first-line treatment. The Japanese Society for the Study of Depression's treatment guideline for bipolar disorder 27), which was published in 2017, states that the risk of manic or rapid cycling should always be considered when using antidepressants for bipolar depression, and that antidepressants alone are not recommended. Antidepressants are not recommended for rapid cycling, even in combination with mood stabilizers, and antidepressants should be used with caution in bipolar II disorder.

III. Treatment-resistant bipolar depression

According to a review published by Tondo et al. in 2014, there are different definitions of treatment-resistant bipolar depression; however, a point of agreement is that at least one or two reasonable treatments have failed to produce satisfactory results 34). RCTs of pharmacotherapy for treatment-resistant bipolar depression have included pramipexole, lamotrigine, inositol, modafinil, and ketamine.

1. Pramipexole

In 2004, Goldberg et al. reported on an RCT of pramipexole or placebo administered to patients with refractory bipolar depression to determine outcome after 6 weeks. The results showed that 8 of 12 patients in the pramipexole group (mean highest dose given during the study period was 1.7 mg) and 2 of 10 patients in the placebo group had at least 50% improvement in Hamilton Depression Scale scores, while one patient in the pramipexole group developed hypomania during the study period. In 2016, Fawcett et al. published a guideline for the use of pramipexole in refractory mood disorders, which states that pramipexole dosage should be adjusted between 1.0 and 5.0 mg, and of 18 patients with refractory bipolar depression, nine had remission and five had response 11).

2. Lamotrigine, inositol

In 2006, Nierenberg et al. reported the results of augmentation therapy with lamotrigine, inositol, and risperidone added to current treatment for up to 16 weeks in 66 patients with refractory bipolar depression who participated in STEP-BD 26). The primary outcome was defined as the rate of recovery (no significant symptoms for 8 weeks). The recovery rate was 23.8% for lamotrigine, 17.4% for inositol, and 4.6% for risperidone, but the difference between groups was not significant. On the other hand, in the secondary analysis, the lamotrigine group showed significant improvement in Clinical Global Impression Severity Scores and Global Assessment of Functioning Scores compared with the other two groups 26).

3. Modafinil

In 2007, Frye et al. assigned 85 bipolar depressed patients who had not responded to mood stabilizers to modafinil or placebo groups and evaluated the results after 6 weeks. The response rate and remission rate were significantly higher in the modafinil group (44% and 39%, respectively), than the placebo group (23% and 18%, respectively) 13).

4. Ketamine

In 2010, Diazgranados et al. reported a double-blind study of 18 patients with bipolar depression who scored 20 or more on the Montgomery-Åsberg Depression Rating Scale (MADRS) despite taking adequate doses of lithium or valproate for more than 4 weeks with regular monitoring of blood levels. Furthermore, we reported a double-blind study of 18 patients with depression who scored 20 or higher on the MADRS despite taking lithium or valproate for more than 4 weeks 9). After a 2-week washout period in which

all medications except lithium and valproate were discontinued, nine patients were assigned to receive ketamine (0.5 mg/kg IV) or placebo. The ketamine group showed a significant improvement in depressive symptoms from 40 minutes to 3 days. In 2012, Zarate et al. conducted a similar study in independent subjects and replicated the antidepressant effect of the ketamine group; moreover, they reported an improvement in suicidal ideation 39). The American Psychiatric Association Task Force has suggested that ketamine may be a promising treatment option for intractable mood disorders, but due to its pharmacological effects, a thorough pre-administration evaluation should be conducted 29). Specifically, diagnosis should be made by considering factors such as the presence or absence of a history of substance abuse. Moreover, the severity of illness should be assessed prior to administration to determine treatment efficacy; appropriate antidepressant treatment should be confirmed; potential risks of ketamine use should be assessed; physical examination should be performed according to guidelines; physical and psychiatric records should be reviewed including family history; and informed consent should be obtained.

IV. Rapid cycling bipolar disorder

Bipolar disorder with rapid cycling is defined in the DSM-5 as the presence of four or more mood episodes of depression, mania, or hypomania in the past 12 months 2). Each episode is identified by a partial or complete remission of at least 2 months or by a transition to the opposite phase (such as from a depressive phase to manic phase), and applies to both bipolar I and II disorders.

The concept of rapid alternation was first reported by Dunner et al. 10) in 1974. Earlier, in his book Manic-Depressive Insanity, Kraepelin referred to disease progression and cycle length 23). In general, the duration of each phase in the rapid-onset form is several weeks to several months, but in rare cases, days to weeks (ultrarapid-onset) or mood swings within a day (ultracircadian) have been reported 24). A systematic review of prevalence by Carvalho et al. reported that 5.0% to 33.3% of bipolar patients were identified as rapid cycling at one year, and 25.8% to 43.0% over a lifetime 6). Furthermore, Schneck et al. reported that of the 1,742 patients with bipolar I/II disorder who participated in STEP-BD, 32% met DSM-IV criteria 1) for identification of rapid cycling at the time of study entry, suggesting that rapid cycling bipolar disorder may occur 30). Rapid cycling bipolar disorder is

thought to respond worse to pharmacotherapy than non-rapid cycling bipolar disorder 4)25). In addition, it is associated with depressive symptoms 7), substance abuse, and suicide-related events 6). The relatively poor outcome of rapid cycling bipolar disorder requires careful diagnosis and treatment.

V. Risk Factors for Rapid Cycling Bipolar Disorder

Next, risk factors for rapid cycling bipolar disorder will be introduced. The main known risk factors are hypothyroidism and antidepressant use. In a prospective study of 30 patients with rapid cycling bipolar disorder, 18 patients were found to have hypothyroidism (Grade I: 7, Grade II: 8, Grade III: 3). Regarding antidepressants, Wehr et al. reported that five female patients with bipolar disorder underwent rapid cycling due to the use of tricyclic antidepressants 36). In a prospective study of 109 patients with rapid cycling bipolar disorder by Koukopoulos et al. 22), antidepressant use correlated with rapid cycling. Furthermore, in a prospective study by Schneck et al. in STEP-BD, antidepressant use was associated with an increase in mood episodes over the following year in patients diagnosed with rapid cycling bipolar disorder at the time of entry into the study 30). On the other hand, reports that antidepressants did not correlate with rapid cycling bipolar disorder include Yildiz et al.'s study of 223 patients with bipolar I/II disorder 38) and Coryell et al.'s long-term prognostic study of 345 patients with bipolar I/II disorder who were followed up for an average of 13.7 years of whom 89 were identified as rapid cyclers 7). Thus, at present, rapid cycling has a syndromic character, and it can be inferred that there are mixed effects of psychoactive substances, hypothyroidism, and personality predisposition in the course of treatment for bipolar disorder. In addition, there are few studies designed only for rapid alternation. Most of the evidence comes from subgroup analyses of rapid alternation and non-rapid alternation in bipolar disorder studies. This may be the reason for the insufficient accumulation of high-quality evidence for treatment.

VI. Treatment Guidelines for Rapid Cycling Bipolar Disorder

The treatment guideline published by CINP in 2017 states that clinical features, including rapid cycling, should be identified before initiating treatment, and describes the recommended level of each pharmacotherapy 12) (Table 4, Table 5). Some of the representative studies discussed in this guideline are as follows. Quetiapine in the depressive

phase was reported by Vieta et al. in 2007. In this study, 108 patients with bipolar I/II disorder in the rapid cycling phase of depression were randomized to placebo, quetiapine 300 mg, or 600 mg groups, and the outcome at 8 weeks was evaluated. In a placebo-controlled RCT of quetiapine extended-release treatment in 2010, the quetiapine extended-release group showed a significant improvement in MADRS scores compared with the placebo group 35). In the maintenance phase of rapid cycling bipolar disorder, most physicians believe that valproate is more effective than lithium for long-term management; however, a 2005 report by Calabrese et al. reported that in a 2005 RCT of 60 patients with rapid cycling bipolar disorder with a 20-month follow-up, there was no significant difference between valproate and lithium in the rate of recurrent mood episodes and the time to recurrence, and this common belief was not supported 5). Kemp et al. (2009) compared the relapse rate of mood episodes in 149 rapidly alternating patients with a history of substance dependence in the lithium monotherapy group and the lithium plus valproate group, and again found no significant difference 21).

The BAP guidelines published in 2016 suggest that hypothyroidism and the use of psychoactive substances should be confirmed when rapid alternation is identified, and discontinuation of antidepressants should be considered when antidepressant involvement in phase alternation is suspected 17). For maintenance therapy, previous studies suggest that there is no difference in therapeutic efficacy among medications, and multidrug therapy is often unavoidable. We recommend that the efficacy of medications be assessed, such as whether they reduce the occurrence of mood episodes, after at least six months of observation, and that medications that are not effective be discontinued to avoid unnecessary multidrug therapy. Moreover, patients should be monitored for at least six months to determine the effect of medication such as whether it reduces the occurrence of mood episodes.

The CANMAT/ISBD guidelines published in 2018 report an association between rapid alternans and hypothyroidism, antidepressant use, and psychoactive substance abuse, and state that treatment should include assessment of thyroid function and tapering, and discontinuation of antidepressants, psychostimulants, and psychoactive substances 37). Thyroid function should be assessed and antidepressants, psychostimulants, and psychoactive substances should be tapered off. There is no evidence that any particular drug is superior in either

the depressive or manic phases of rapid cycling, and we recommend selection based on efficacy in the maintenance phase of bipolar disorder.

The treatment guidelines of the Japanese Society for the Study of Depression published in 2017 report that discontinuation of antidepressants, efficacy of quetiapine, and the possibility that thyroid hormone agents may be effective 27).

Conclusion.

Pharmacotherapy for treatment-resistant bipolar depression should begin with a careful review of the diagnosis, followed by a review of the adequacy of treatment for bipolar disorder. Periodic monitoring of blood levels is also important to confirm that mood stabilizers were used in sufficient doses and for a sufficient period of time, and that adherence was good. If quetiapine has not been used in the past, then treatment with quetiapine should be attempted. If the patient does not respond to monotherapy with quetiapine, lithium, or lamotrigine, or to combination therapy with lithium and lamotrigine, other mood stabilizers or antipsychotics (olanzapine, carbamazepine, valproate, aripiprazole) may be added or modified, or pramipexole may be added. If the patient does not respond to any of these medications, modified electroconvulsive therapy may be considered.

On the other hand, when rapid cycling in clinical situations is identified and treated, the treatment history is usually more than one year. The initial phase may be mania/hypomania, depression, or remission, and treatment priorities may differ. It may be necessary to tentatively determine that the medications used in the previous course were ineffective in preventing mood episodes. Coexisting psychoactive substance use, hypothyroidism, and poor medication adherence should be addressed as appropriate. It is important to comprehensively examine the efficacy of the depressive, manic, and maintenance phases of bipolar disorder (including non-rapid cycling) when selecting medications (Table 6). As a result, the evidence-based options for the treatment of rapid-cycling bipolar disorder include lithium, quetiapine, olanzapine, and valproate. Although monotherapy is ideal, combination therapy with lithium or valproate and quetiapine or olanzapine may be an effective treatment option in some cases. Persistent injectable antipsychotics may also be considered in patients with rapid-onset bipolar I disorder with extreme nonadherence and frequent relapses after withdrawal.

In the treatment of both, antidepressants should be avoided, and benzodiazepines should be used only in

small doses or on a limited basis because of their dependence and adverse effects.

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Table 1
表 1　軽躁病エピソードと混合性の特徴の要件

双極Ⅱ型障害 軽躁病エピソード	抑うつ障害群の特定用語 混合性の特徴
気分高揚，開放的，易怒的	気分高揚，開放的
活動性や活力の亢進	
自尊心の肥大，誇大	自尊心の肥大，誇大
睡眠欲求の減少	睡眠欲求の減少
多弁，会話への促迫	多弁，会話への促迫
観念奔逸，複数の考えの競い合い	観念奔逸，複数の考えの競い合い
注意散漫	
目標指向性の活動増加，精神運動焦燥	目標指向性の活動増加
困った結果になる可能性が高い活動への熱中	困った結果になる可能性が高い活動への熱中

（文献 2 より著者作成）

Table 2
表 2　双極性うつ病の短期治療における抗うつ薬の効果と安全性

Outcome	Mood Stabilizer＋ Antidepressant (N＝179) number (percent)	Mood Stabilizer＋ Placebo (N＝187) number (percent)	*P* Value
Transient remission	32 (17.9)	40 (21.4)	0.40
Durable recovery (primary outcome)	42 (23.5)	51 (27.3)	0.40
Transient remission or durable recovery	74 (41.3)	91 (48.7)	0.23
Treatment-effectiveness response	58 (32.4)	71 (38.0)	0.27
Treatment-emergent affective switch	18 (10.1)	20 (10.7)	0.84
Discontinuation of study medication because of adverse event	22 (12.3)	17 (9.1)	0.32

・効果は抗うつ薬とプラセボで有意差なし
・躁転も有意差なし
（文献 28 より引用）

Table 3
表 3　海外の主なガイドライン，双極性うつ病について

	CANMAT/ISBD（2018）		CINP	BAP	WFSBP
	双極 I 型障害	双極 II 型障害	(2017)	(2016)	(2013)
1st line	QTP lurasidone＋Li/VPA Li LTG lurasidone LTG（adj）	QTP	QTP lurasidone OLZ＋fluoxetine	QTP lurasidone OLZ OLZ＋fluoxetine	QTP

adj：adjunctive, Li：lithium, LTG：lamotrigine, OLZ：olanzapine, QTP：quetiapine, VPA：valproate

Table 4
表 4　急速交代型双極性障害の治療：CINP ガイドラインより

薬剤名	躁病相	うつ病相	維持期
Aripiprazole	3	—	3
Carbamazepine	—	—	2（Li＋CBZ）
Lamotrigine	—	—	5
Lithium	4	3	2（Li, Li＋CBZ）
Olanzapine	3	—	—
Paroxetine	—	5	—
Quetiapine	3	2	2（QTP＋Val/Li）
Risperidone, long-acting injectable	—	—	2（RLAI＋TAU）
Valproate	4	4	—

—：no data
CBZ：carbamazepine, Li：lithium, QTP：quetiapine, RLAI：risperidone long-acting injectable, TAU：treatment as usual, Val：valproate
（文献 12 より引用）

Table 5

表 5　推奨レベル：CINP ガイドライン

		安全性/忍容性		
		Level 1	Level 2	Level 3
有効性	Level 1	1	2	4
	Level 2	1	2	4
	Level 3	3	3	4
	Level 4	4	4	4
	Level 5	5	5	5

推奨 Level 1＝最も推奨される，推奨 Level 5＝推奨されない
（文献 12 より著者作成）

Table 6
表 6　双極性障害治療ガイドライン（単剤療法）

	躁病相			うつ病相			維持療法		
	BAP 2016	CANMAT/ ISBD 2018	CINP 2017	BAP 2016	CANMAT/ ISBD 2018	CINP 2017	BAP 2016	CANMAT/ ISBD 2018	CINP 2017
Aripiprazole	3	1	1	—	NR	3	3	1	1
Asenapine	3	1	1	—	—	—	3	1	—
Carbamazepine	3	2	2	—	3	4	2	2	2
Lamotrigine	NR	NR	NR	2	1	4	2	1	3
Lithium	3	1	2	3	1	2	1	1	1
Olanzapine	1	2	2	1	3	4	2	2	1
Quetiapine	1	1	1	1	1	1	2	1	1
Risperidone	1	1	1	—	—	—	3	—	1
Valproate	2	1	1	—	2	2	2	1	2

NR：not recommended
BAP：British Association for Psychopharmacology, CANMAT：Canadian Network for Mood and Anxiety Treatments, CINP：The International College of Neuro-Psychopharmacology, ISBD：International Society for Bipolar Disorders
（文献 12，17，37 より著者作成）