PSYCHIATRIA ET NEUROLOGIA JAPONICA

Special Feature Article

The Pros and Cons of Antidepressant Use for Bipolar Disorder

Teruaki TANAKA
Department of Psychiatry, KKR Sapporo Medical Center
Psychiatria et Neurologia Japonica 122: 212-220, 2020

Abstract

Bipolar disorder commonly develops during a depressive episode, and as patients are more often in a depressive state than (hypo) mania, clinicians often treat depressed patients. However, therapeutic options for bipolar depression are currently limited compared with those for acute mania, and its clinical treatment remains unclear. Clinical guidelines recommend mood stabilizers and atypical antipsychotics, such as lithium, lamotrigine, quetiapine, and olanzapine, as the first-line treatment for depressive episodes in bipolar disorder. The use of antidepressants, which used to be commonly administered for bipolar depression, is controversial, and they have become less common due to concern over risks for manic switch, destabilization, and rapid cycling. Pharmacotherapy for bipolar disorder has changed markedly compared with approximately 20 years ago. However, antidepressants are widely used to treat acute bipolar depression in clinical settings, and may be effective for some patients. Although there are risks, antidepressant treatment, especially SSRIs or bupropion, may be effective in combination with atypical antipsychotics or mood stabilizers, as recommended by the International Society for Bipolar Disorders (ISBD) Task Force. Recent meta-analyses also demonstrated that modern antidepressants combined with mood stabilizers had a small but significant effect and did not increase the risk of manic switch during short-term treatment of bipolar depression. Several studies have reported that adjunctive antidepressant therapy is associated with a lower rate of rehospitalization

and relapse of mood episodes without increasing the risk of new (hypo) manic episodes. Indeed, there is insufficient evidence for antidepressant use for bipolar depression, but it may be helpful rather than harmful in some cases. Antidepressants should be prescribed appropriately for bipolar depression after considering the clinical picture, diagnosis, specifiers, comorbidities, and drug classes, instead of discussing the pros and cons of antidepressants as a whole.

Keywords: depressive episode, antidepressants, combination therapy, manic switch, continued use

Introduction.

Many patients with bipolar disorder demonstrate a chronic course with recurrent episodes. The interphase interval shortens with recurrence, often with rapid alternation, instability, and resistance to treatment. Patient's long-term prognosis is often not good, and social functioning is impaired to a greater degree than in other chronic diseases such as hypertension and diabetes mellitus. According to a WHO report, bipolar disorder ranks among the top 10 diseases for Years Lived with Disability (YLDs, years of healthy life impaired by disability). Since relapse worsens the prognosis of bipolar disorder, it is important that treatments also act to prevent relapse.

In recent years, the pharmacotherapy of bipolar disorder has changed dramatically with the introduction of new agents, mainly second-generation antipsychotics. Lithium has remained the first-line drug of choice, but the classic mood stabilizers valproic acid and carbamazepine have fallen behind quetiapine, and olanzapine and lamotrigine have established themselves as primary treatments. On the other hand, while antidepressants have long been used to treat depressive episodes in bipolar disorder as well as unipolar depression, the pros and cons of their use are still controversial. Initially, the mainstream opinion was in favor of the efficacy of antidepressants, but the side effects of antidepressants, such as mania and destabilization, have gradually become a concern, and the results of a large-scale randomized controlled trial reported in 2007 (RCT) (STEP-BD) 16) became a decisive factor in the argument against the use of

antidepressants. However, as the results of recent meta-analyses 9)10) show, the efficacy of antidepressants has begun to be re-recognized and re-evaluated, although not as much as before, and the position of antidepressants in the treatment of bipolar disorder is changing again.

This article discusses the ability of antidepressant treatments to alter the prognosis of bipolar disorder and reconsiders their merits and demerits in light of recent findings.

I. Current status of antidepressant use

Many academic organizations around the world have published guidelines for the treatment of bipolar disorder, and although there is general agreement on the general principles, the specific principles (the position of each therapeutic agent) vary. The same can be said for the use of antidepressants. Most guidelines do not recommend the "use of tricyclic antidepressants" or "monotherapy with antidepressants," and the Japanese Society for the Study of Depression's Guidelines for the Treatment of Bipolar Disorder 12) lists them as "not recommended" for depressive episodes and maintenance treatment. The same guidelines acknowledge that combination therapy with mood stabilizers and second-generation antipsychotics is often used in clinical practice, but states, “However, the efficacy of combination therapy with mood stabilizers and antidepressants has not been reported to a high level of evidence.”

The use of antidepressants for the treatment of bipolar disorder is still common in clinical practice, despite the publication of various guidelines. This is true not only in Japan, but also in North America, Europe, and Asia. According to a recent survey, about one-third of patients with bipolar disorder in Spain and Korea were prescribed antidepressants in combination with other treatments, and in Denmark, antidepressants were prescribed at a high level of around 40-60% 3)5)23). In Sweden, about 35% of 3,240 patients selected from a national registry were reported to be treated with antidepressant monotherapy 21).

Antidepressants have not always been reported to be effective as pharmacotherapeutics for bipolar disorder. Rather, they are routinely prescribed (worldwide) despite concerns about problems including mania, rapid cycling, and suicide. Certainly, it is not clear that this applies equally to all antidepressants, and it has been suggested that bipolar I and II may respond differently. They may be more effective in combination with mood stabilizers. Although a great deal of evidence has been reported in recent years, we have not yet reached a stage where we can overcome the complexity

and individuality of bipolar disorder. At this point, we have no choice but to assess the findings case by case, conduct a careful assessment with consideration for individuality, avoid risks as much as possible, and try to provide safer antidepressant treatment.

II. Efficacy and safety of antidepressant treatment (Figure 1, Figure 2)

Neither the use of tricyclic antidepressants nor antidepressant monotherapy for bipolar disorder is commonly recommended in any guidelines. Most clinical studies have examined the use of novel antidepressants in combination with mood stabilizers or second-generation antipsychotics. Therefore, this discussion will focus on the combinatory use of novel antidepressants with mood stabilizers or second-generation antipsychotics.

A 2016 meta-analysis reported on the combination therapy of novel antidepressants (second-generation antidepressants) such as selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs), excluding the classical tricyclic antidepressants and MAO inhibitors (Figure 1) 10). The meta-analysis of six trials (total of 1,383 patients) examined the effect these novel antidepressants in combination with mood stabilizers or second-generation antipsychotics (administered over 6 to 26 weeks) on depressive episodes of bipolar disorder, and found a small but significant difference compared with a placebo group [Standardized mean difference 0. The mean standardized difference was 0.165 (95% CI 0.051-0.278), P=0.004]. However, there was no difference in treatment response or remission rates between placebo and antidepressant groups [Combined odds ratio 1.158 (95% CI 0.840-1.597), P=0.371; 1.220 (95% CI 0.874-1.703), P=0.243]. Furthermore, the same analysis also investigated drug-induced mania, which is a concern with antidepressant use, and found an odds ratio of 0.926 (95% CI 0.576-1.491, P=0.753) in the acute phase, which was not significantly different from the placebo group. However, there was found to be an increased risk of mania [odds ratio of 1.774 (95% CI 1.018-3.091, P=0.043)] when the administration period was extended to 52 weeks. Although we cannot make conclusions from these results alone, the use of antidepressants for depressive episodes in bipolar disorder is not necessarily ineffective, and may indeed be expected to reduce symptoms, although it may not lead to remission or increase treatment responsiveness.

A meta-analysis on the preventive efficacy and safety of antidepressant treatment (monotherapy or

combination of mood stabilizers) has also been reported (Figure 2) 9). Risk ratios for the occurrence of new mood episodes during treatment and NNT (number needed to treat)/NNH (number needed to harm) were calculated for 11 randomized controlled trials (N=629) that evaluated the use of antidepressant treatment of bipolar disorder for more than 4 months. Despite a moderate risk of bias, antidepressant use did not increase the risk of new manic or hypomanic episodes and reduced new depressive episodes compared with the placebo. The results were similar for antidepressants alone and in combination with mood stabilizers, and the trend was more evident for bipolar II than for bipolar I in subgroup analyses. Although many guidelines recommend that antidepressants should be used for a short period of time and discontinued when depressive symptoms improve, this meta-analysis suggests that long-term treatment with antidepressants is more effective.

The long-term use of antidepressants for bipolar disorder is not currently recommended due to concerns about the disadvantages of mania, destabilization, and rapid cycling, rather than their efficacy. Hooshmand et al. 4) reported that depressive episodes recurred earlier in the antidepressant group than in the non-antidepressant group in a 2-year retrospective study. However, methodologically, a causal relationship between the two cannot be proven and confounding factors cannot be excluded. Tundo et al. 19) conducted evidence-based long-term treatment plan of 266 outpatients over 4 years and compared relapse rates before and after the intervention. Although the intervention method was unstructured and the study was a prospective observational study based on general practice, they found that appropriate use of antidepressants according to the recommendations of the International Society for Bipolar Disorders (ISBD) 14) (see below for details) did not increase relapse.

III. Antidepressant Treatment and Readmission

As mentioned above, the benefits of antidepressant treatment (mainly in combination with mood stabilizers and second-generation antipsychotics) for bipolar disorder have been reaffirmed in recent years. Appropriate antidepressant use may alleviate depressive symptoms and prevent depressive episodes without leading to manic episodes. On the other hand, a large database-based study (N=190,894) 11) found that monotherapy with SSRIs (citalopram, fluoxetine, sertraline) and SNRIs (duloxetine, venlafaxine) was associated with a higher risk of hospitalization

than lithium monotherapy (risk ratio 1.17 to 1.24). Only three drugs had a lower risk of hospitalization than lithium: valproic acid, aripiprazole, and bupropion (all with a risk ratio of 0.80), but not antidepressants alone. However, few patients in this study were able to remain on monotherapy for more than 4 months, and the majority completed less than 60 days.

A large Finnish study 7) followed 18,018 patients diagnosed with ICD-10 bipolar affective disorder for an average of 7.2 years and compared the risk of rehospitalization among medications. The adjusted hazard ratio (HR) was used as a measure. Nine thousand seven hundred and twenty-one patients (54.0%) were readmitted one or more times, and although the overall HR for antidepressants was 1.07, lower than that for benzodiazepines (HR=1.19), the risk of readmission was higher than that for mood stabilizers (HR=0.91). Although individual data for antidepressants were not presented, the HRs for the major medications were risperidone-LAI (0.58) < lithium (0.67) < carbamazepine (0.74) < lamotrigine (0.78) < valproic acid (0.88). With the exception of risperidone-LAI (HR=0.86 for regular risperidone), there was a general trend toward lower readmission risk with mood stabilizers than with second-generation antipsychotics. The results of these two large studies refute the (re)preventive effect of antidepressants themselves, but what about their combination with mood stabilizers and second-generation antipsychotics? Although insufficient data are available, a small retrospective study using inpatient medical records (N=98) 17) reported that the rate of readmission was significantly lower in the antidepressant combination group than in the non-antidepressant group at 6 months (9.2% vs. 36.4%) and at 1 year (12.3% vs. 42.4%). Concomitant use of antidepressants prolonged the time to rehospitalization and did not increase the rate of rehospitalization for new manic episodes. However, this was a backward-looking study of medical records, and the results cannot be generalized. The results can be interpreted as limited to patients in whom long-term use of antidepressants is effective and safe.

IV. Antidepressant Treatment and Suicide-Related Events

In addition to questions about the efficacy of antidepressant treatment for bipolar disorder, there have been concerns about problems such as mania, destabilization, and rapid alternation. As a related phenomenon, the so-called "mixed state" has attracted attention and has recently been considered to be a background factor for antidepressant-induced suicidal behavior. In fact, it is

said that about 20% of bipolar patients experience mixed states, and the risk of suicide is high under such states. However, there are no prospective studies that demonstrate this fact. Several retrospective studies 13)20)22) have indicated that suicidal behavior is increased in bipolar patients taking antidepressants compared with those taking mood stabilizers, and that antidepressant use correlates with increased suicidal behavior in mixed episodes (DSM-IV). On the other hand, Leon et al. 8) reported that the risk of suicidal behavior in patients with bipolar disorder was significantly reduced during antidepressant treatment (bipolar I: HR=0.46, bipolar II: HR=0.65) based on the results of a 27-year long-term observational study. Persons et al. 15) conducted a longitudinal, long-term observational study and found that although a history of mixed states is certainly a risk factor for suicidal behavior, the predominantly depressive course of the illness is more associated with suicide risk than the mixed states themselves.

The issue of mixed states and suicide has been discussed in the context of activation syndrome. Suicide-related behaviors increased in some young patients in the early stages of antidepressant treatment, and this problem has become a worldwide concern and a social issue that is often discussed in the mass media in Japan. We also investigated 104 untreated depressed patients aged 13-24 years who first visited the Department of Psychiatry, Hokkaido University Hospital, and reported that activation syndrome occurring within 8 weeks after antidepressant administration was associated with subsequent diagnostic changes, including bipolar disorder. Recently, a prospective observational study of 106 young untreated depressed patients at risk for bipolar disorder 6) was also conducted. However, high or low risk did not affect treatment response, and the mania rate was generally low regardless of risk.

V. Appropriate use of antidepressants

In recent years, the use of antidepressants for bipolar disorder has been discouraged because of uncertainty about their efficacy and concern over their side effects. Nevertheless, antidepressants are still routinely prescribed in clinical practice. Pharmacotherapy for depressive episodes of bipolar disorder is more limited than that for manic episodes and maintenance treatment. It is not uncommon to encounter difficulties in treatment in daily practice. When a patient is suffering from depressive symptoms, the therapist will consider all possible treatment options to provide rapid relief. Therefore, they may

prescribe antidepressants, hoping for their acute effects, despite the lack of solid evidence and knowing the risks of mania and rapid alternation.

As discussed previously, recent meta-analyses 9)10) suggest that concomitant use of antidepressants may reduce depressive symptoms and suppress the occurrence of depressive episodes without causing new manic episodes. Long-term use may also be beneficial in some patients. Indeed, in clinical practice, we have occasionally encountered patients who have benefited from concomitant use of antidepressants without problems such as mania or destabilization. Several long-term observational studies 1)17) have reported that continued use of antidepressants reduced recurrence and relapse of depressive episodes and decreased rehospitalization rates. However, it should be noted that patients were able to remain on antidepressants for a long time. In other words, if concomitant use of antidepressants does not cause adverse effects such as mania, destabilization, and rapid alternation, and if clinical effects on depressive symptoms can be confirmed, subsequent long-term use may be a safe and effective treatment. Of course, continuous observation and evaluation are important in the use of antidepressants, and attention should always be paid to the appearance of minor (subthreshold) mood swings and mixed states, as well as to changes such as despair and phase instability.

Of course, this does not apply to all patients or all antidepressants, and appropriate use and caution are required in prescribing them. The ISBD Task Force on the Use of Antidepressants for Bipolar Disorder (Table 1) 14) recommends the use of antidepressants in combination with mood stabilizers. In the acute phase, concomitant use of antidepressants is acceptable if the patient has responded to treatment in the past, and if the depressive episode recurs after discontinuation of antidepressant treatment, concomitant use of mood stabilizers can be considered as a maintenance treatment. On the other hand, the use of antidepressants should be avoided in the case of psychomotor agitation or rapid alternation with more than one manic symptom. Monotherapy should also be avoided in bipolar I disorder and in the presence of more than one manic symptom, but not necessarily in bipolar II disorder and pure depression. The guidelines also state that antidepressants should be discontinued promptly at the first sign of mixed states or mania with careful observation. In addition, it is suggested that antidepressants should be avoided in patients with a history of mania or mixed states, mood instability, rapid

alternation, or mixed states at present. As for the type of antidepressants, it is recommended to avoid tricyclic and tetracyclic antidepressants and to start with newer antidepressants excluding than SNRIs.

Tundo et al. 18) conducted an observational study of 255 self-tested patients to examine the usefulness of the ISBD recommendations for antidepressant use. Based on their own clinical experience, they examined the safety and expanded indications for the use of antidepressants, particularly when recommendations 1 (antidepressant combination is acceptable for acute depressive episodes in bipolar I/II if there has been a previous response to antidepressant treatment) and 4 (antidepressant monotherapy should be avoided for bipolar I disorder) were applied. For 154 patients with unipolar depression (UP), 49 patients with bipolar I disorder (BP-I), and 52 patients with bipolar II disorder (BP-II), the response rate to antidepressant treatment was 64.9% for UP, 75.5% for BP-I, and 75.0% for BP-II, respectively. The dropout rate was 18.2% for UP, 2.0% for BP-I, and 7.7% for BP-II. One patient in the bipolar group had a suicide attempt (1.0%) and three patients had a manic episode (2.9%). Thus, according to ISBD recommendations 1 and 4, combination antidepressant therapy for depressive episodes of bipolar disorder may be as safe and effective as antidepressant therapy for unipolar depression.

Conclusion.

Although guidelines and evidence-based treatment are recommended in the treatment of bipolar disorder, there are many situations in which the acute treatment of depressive episodes is difficult. In recent years, antidepressant therapy for bipolar disorder has been avoided, but with the accumulation of new evidence, safe and effective methods have been proposed. Although the use of antidepressants requires caution, clinical efficacy can be expected if safety is considered and application is strictly applied. The diagnosis of bipolar disorder has become more precise than in the past, and the accumulation of knowledge and experience has reduced the use of antidepressants, which may reduce the number of cases of mania, destabilization, and rapid alternation. The use of antidepressants in combination with mood stabilizers and second-generation antipsychotics is expected to reduce the risk and increase the efficacy of bipolar disorder treatment. In fact, some patients may benefit from the use of antidepressants. The ISBD recommendations may be useful criteria for the use of antidepressants in bipolar disorder.

Pharmacotherapy for bipolar disorder is now away from antidepressant avoidance and towards appropriate use.

There are no conflicts of interest to be disclosed in relation to this paper.

References

1) Altshuler, L., Suppes, T., Black, D., et al.: Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry, 160 (7); 1252-1262, 2003

2) Ghaemi, S. N., Wingo, A. P., Filkowski, M. A., et al.: Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks. Acta Psychiatr Scand, 118 (5); 347-356, 2008

3) Grande, I., de Arce, R., Jiménez-Arriero, M. Á., et al.: Patterns of pharmacological maintenance treatment in a community mental health services bipolar disorder cohort study (SIN-DEPRES). Int J Neuropsychopharmacol, 16 (3); 513-523, 2013

4) Hooshmand, F., Do, D., Shah, S., et al.: Differential prevalence and demographic and clinical correlates of antidepressant use in American bipolar I versus bipolar II disorder patients. J Affect Disord, 234; 74-79, 2018

5) Kessing, L. V., Vradi, E., Andersen, P. K.: Nationwide and population-based prescription patterns in bipolar disorder. Bipolar Disord, 18 (2); 174-182, 2016

6) Koirala, P., Hu, B., Altinay, M., et al.: Sub-threshold bipolar disorder in medication-free young subjects with major depression: clinical characteristics and antidepressant treatment response. J Psychiatr Res, 110; 1-8, 2019

7) Lähteenvuo, M., Tanskanen, A., Taipale, H., et al.: Real-world effectiveness of pharmacologic treatments for the prevention of rehospitalization in a Finnish nationwide cohort of patients with bipolar disorder. JAMA Psychiatry, 75 (4); 347-355, 2018

8) Leon, A. C., Fiedorowicz, J. G., Solomon, D. A., et al.: Risk of suicidal behavior with antidepressants in bipolar and unipolar disorders. J Clin Psychiatry, 75 (7); 720-727, 2014

9) Liu, B., Zhang, Y., Fang, H., et al.: Efficacy and safety of long-term antidepressant treatment for bipolar disorders: a meta-analysis of randomized controlled trials. J Affect Disord, 223; 41-48, 2017

10) McGirr, A., Vöhringer, P. A., Ghaemi, S. N., et al.: Safety and efficacy of adjunctive second-generation antidepressant therapy with a mood stabiliser or an atypical antipsychotic in acute bipolar depression: a systematic review and meta-analysis of randomised placebo-controlled trials. Lancet Psychiatry, 3 (12); 1138-1146, 2016

11) Nestsiarovich, A., Mazurie, A. J., Hurwitz, N. G., et al.: Comprehensive comparison of monotherapies for psychiatric hospitalization risk in bipolar disorders. Bipolar Disord, 20 (8); 761-771, 2018

12) 日本うつ病学会気分障害の治療ガイドライン作成委員会: 日本うつ病学会治療ガイドライン I. 双極性障害 2017. 2018 (https://www.secretariat.ne.jp/jsmd/iinkai/katsudou/data/180125.pdf) (参照 2019-10-11)

13) Pacchiarotti, I., Valentí, M., Colom, F., et al.: Differential outcome of bipolar patients receiving antidepressant monotherapy versus combination with an antimanic drug. J Affect Disord, 129 (1-3); 321-326, 2011

14) Pacchiarotti, I., Bond, D. J., Baldessarini, R. J., et al.: The International Society for Bipolar Disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am J Psychiatry, 170 (11); 1249-1262, 2013

15) Persons, J. E., Coryell, W. H., Solomon, D. A., et al.: Mixed state and suicide: is the effect of mixed state on suicidal behavior more than the sum of its parts? Bipolar Disord, 20 (1); 35-41, 2018

16) Sachs, G. S., Nierenberg, A. A., Calabrese, J. R., et al.: Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med, 356 (17); 1711-1722, 2007

17) Shvartzman, Y., Krivoy, A., Valevski, A., et al.: Adjunctive antidepressants in bipolar depression: a cohort study of six- and twelve-months rehospitalization rates. Eur Neuropsychopharmacol, 28 (3); 353-360, 2018

18) Tundo, A., Calabrese, J.R., Proietti, L., et al.: Short-term antidepressant treatment of bipolar

depression: are ISBD recommendations useful in clinical practice? J Affect Disord, 171; 155-160, 2015

19) Tundo, A., Musetti, L., Benedetti, A., et al.: Predictors of recurrence during long-term treatment of bipolar I and II disorders. A 4 year prospective naturalistic study. J Affect Disord, 225; 123-128, 2018

20) Valentí, M., Pacchiarotti, I., Rosa, A. R., et al.: Bipolar mixed episodes and antidepressants: a cohort study of bipolar I disorder patients. Bipolar Disord, 13 (2); 145-154, 2011

21) Viktorin, A., Lichtenstein, P., Thase, M. E., et al.: The risk of switch to mania in patients with bipolar disorder during treatment with an antidepressant alone and in combination with a mood stabilizer. Am J Psychiatry, 171 (10); 1067-1073, 2014

22) Yerevanian, B. I., Koek, R. J., Mintz, J., et al.: Bipolar pharmacotherapy and suicidal behavior Part 2. The impact of antidepressants. J Affect Disord, 103 (1-3); 13-21, 2007

23) Yoon, W., Shon, S. H., Hong, Y., et al.: Antidepressant prescription patterns in bipolar disorder: a nationwide, register-based study in Korea. J Korean Med Sci, 33 (46); e290, 2018

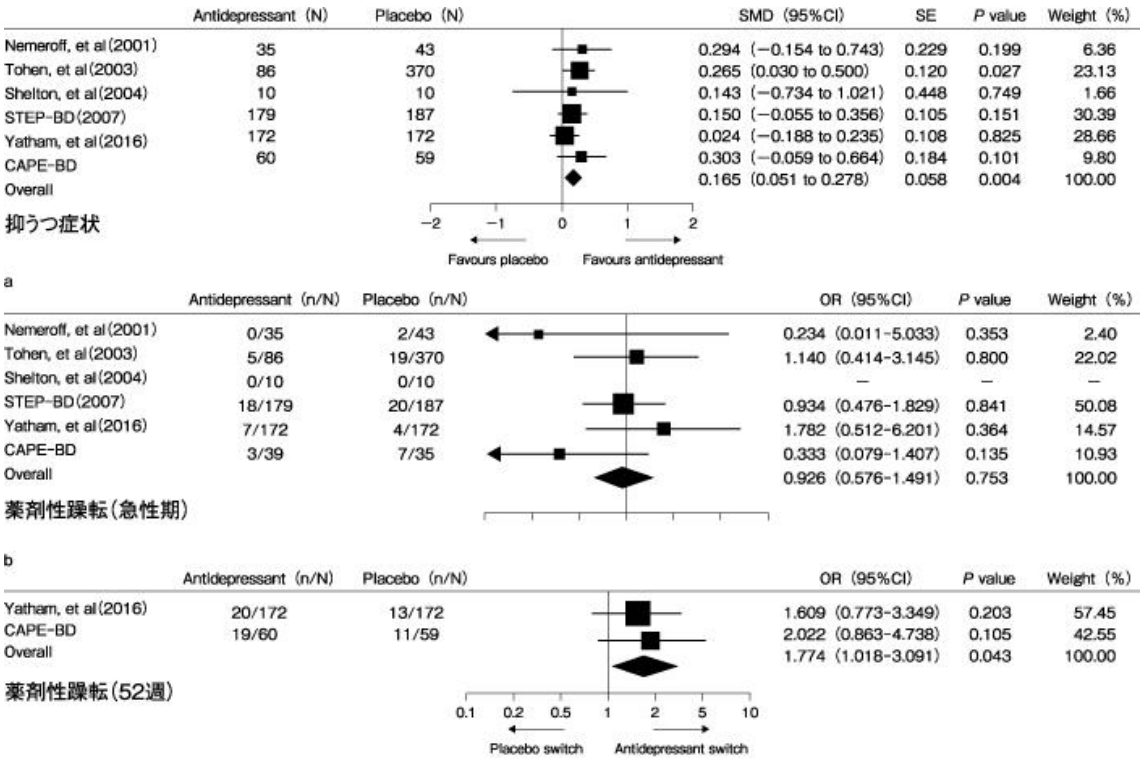

図1　第二世代抗うつ薬の併用：急性期

SMD：standardised mean difference，CI：confidence interval，SE：standard error，OR：odds ratio

（文献 10 より抜粋，一部改変）

Figure 1

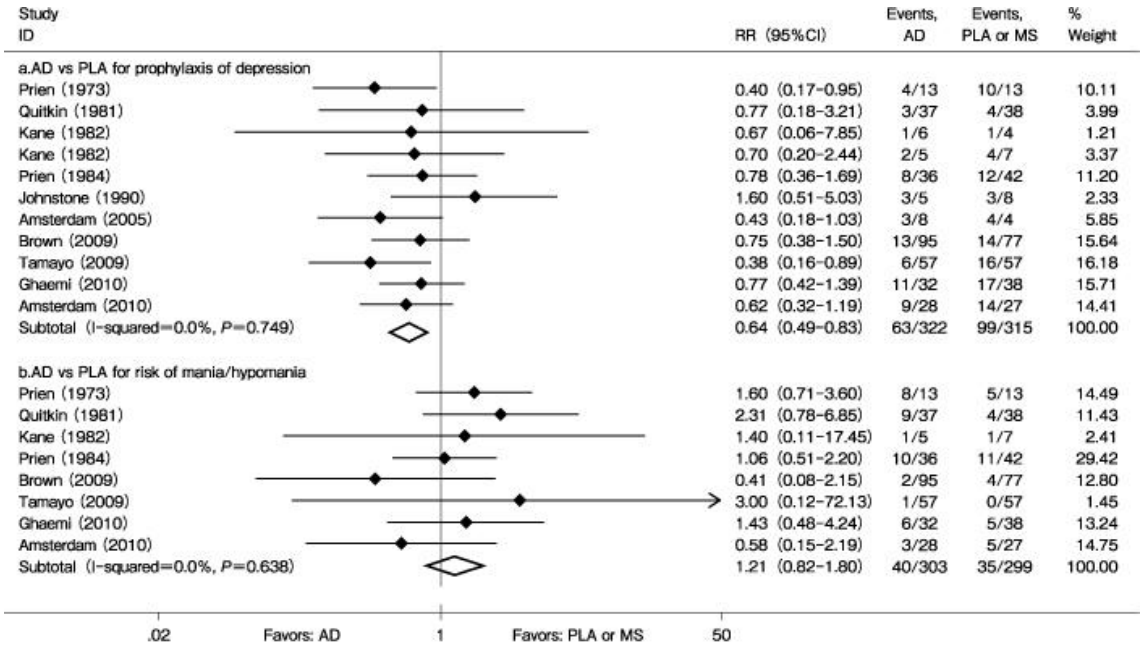

図2　予防効果と安全性に関するメタ解析

a：新規抑うつエピソードの予防に関する抗うつ薬（AD）とプラセボ（PLA）との比較

b：新規（軽）躁病エピソード発生のリスクに関する抗うつ薬（AD）とプラセボ（PLA）との比較

AD：antidepressants，PLA：placebo，RR：risk ratio，CI：confidence interval，MS：mood stabilizers

（文献9より抜粋，一部改変）

Figure 2

Table 1

表1　抗うつ薬使用に関する国際双極性障害学会（ISBD）タスクフォースの勧告

急性期治療	1. 過去に抗うつ薬への反応がみられた場合，急性期の双極Ⅰ型/Ⅱ型抑うつエピソードで抗うつ薬の併用は許容される
	2. 急性期の双極Ⅰ型/Ⅱ型抑うつエピソードにおいて，精神運動焦燥や急速交代化が存在する状況で，2つ以上の中核的な躁症状が混在している場合，抗うつ薬の追加は避けるべきである
維持治療	3. 抗うつ薬治療の中止によって抑うつエピソードが再燃する場合，維持治療での抗うつ薬併用は考慮される
単剤治療	4. 抗うつ薬単剤治療は，双極Ⅰ型障害では避けるべきである
	5. 双極Ⅰ型/Ⅱ型抑うつエピソードに2つ以上の中核的な躁症状が混在している場合，抗うつ薬単剤治療は避けるべきである
躁病，軽躁病，混合状態への移行と急速交代化	6. 抗うつ薬を開始した双極性障害患者に関しては，（軽）躁病の兆候や精神運動焦燥の増加を注意深く監視し，そのような場合には抗うつ薬を中止すべきである
	7. 抗うつ薬治療中に（軽）躁病や混合性エピソードを呈した既往がある場合，抗うつ薬の使用は思いとどまるべきである
	8. 気分不安定性が高い場合（頻回の気分エピソードなど）や急速交代化の既往がある場合，抗うつ薬の使用は避けるべきである
混合状態での使用	9. 混合性の特徴を伴う躁病・抑うつエピソードに対して，抗うつ薬は避けるべきである
	10. 混合状態が優勢な双極性障害患者に対して，抗うつ薬の使用は避けるべきである
	11. 現時点で混合状態を呈している患者に対しては，以前から処方されている抗うつ薬は中止すべきである
薬の種別	12. SNRIや三環系・四環系抗うつ薬の追加は，他の抗うつ薬を試した後に初めて検討すべきであり，躁転や不安定化のリスクが高まることから，使用に際しては注意深い観察が必要である

（文献14より作成）