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Insufficient Amounts or Usage of Mood Stabilizers or Atypical Antipsychotics

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Abstract

One factor that negatively affects the prognosis of bipolar disorder is incomplete pharmacotherapy. At present, bipolar disorder is recognized as "disorder of relapsing mood episodes that proceeds to a chronic condition". Therefore, maintenance therapy is usually administered after acute treatment of mood episodes to prevent deterioration of the prognosis. However, in the field of psychiatric care in Japan, despite maintenance therapy, the prognosis of patients with bipolar disorder may become poor due to the insufficient usage of mood stabilizers or atypical antipsychotics. For example, regarding maintenance therapy with lithium, the lowest blood concentration of lithium that can prevent recurrence is 0.4 mEq/L. However, there are many patients whose blood concentration is maintained at less than 0.4 mEq/L in Japan, and periodic blood concentration measurement may not be performed. A similar situation is observed for other mood stabilizers and atypical antipsychotics. It is unclear whether 50 mg/day of lamotrigine or quetiapine can prevent mood episodes; however, such prescriptions are common in clinical practice. In addition, clinical guidelines recommend maintenance therapy for several years, although there is no consensus on the duration, but there are patients whose mood episodes have recurred after reducing or withdrawing their medication after less than a year. A similar trend is observed in the treatment of acute mood episodes. When the effects of lithium are insufficient in the acute phase of a manic episode, the dose should be increased to 1.0 mEq/L. A follow-up period of 8 weeks is needed after reaching a blood concentration greater than 0.8 mEq/L in the acute phase

of a depressive episode. Atypical antipsychotics should also be used in a sufficient amount and for a sufficient period if their effects are not satisfactory.

Keywords: bipolar disorder, prognosis, pharmacotherapy, incompleteness, lithium

Introduction - Understanding the poor prognosis and inadequate pharmacotherapy of bipolar disorder

Bipolar disorder is a repetitive (recurrent) mental disorder, and its long-term prognosis is not favorable. Since the number of mood episodes experienced is associated with the long-term prognosis of bipolar disorder, prevention of recurrent mood episodes is key to improving the prognosis. However, there are a variety of factors that induce recurrent mood episodes, i.e., factors that worsen the prognosis of bipolar disorder.

One of the factors that may worsen the prognosis of various bipolar disorders is inadequate pharmacotherapy. Specifically, the use of mood stabilizers and atypical antipsychotics at insufficient doses and durations. The treatment guidelines of the Japanese Society of Mood Disorders 11) recommends the use of mood stabilizers and atypical antipsychotics at sufficient doses and for a sufficient duration for the acute treatment of mood episodes and prevention of recurrence in bipolar disorder, but these guidelines are often not followed in actual clinical practice.

The treatment of bipolar disorder includes (1) treatment for manic episodes, (2) treatment for depressive episodes (bipolar depression), and (3) prevention of recurrent mood episodes (maintenance therapy). Although there are many possible reasons for inadequate pharmacotherapy, the author suspects that the underlying cause is that many therapists do not properly understand that bipolar disorder is a chronic disorder with repeated mood episodes (recurrence).

Therefore, this article discusses the importance of maintenance therapy, the evidence for adequate dosage and duration of maintenance therapy, and the current status and problems in daily psychiatric practice in Japan, based on the changing global perception of bipolar disorder. In addition, the use of mood stabilizers and atypical antipsychotics at inadequate doses and durations in the acute phase of manic and depressive episodes has been reported, and the inadequacy of

pharmacotherapy in the acute phase will also be discussed.

I. Changing perceptions of bipolar disorder

In the past, when bipolar disorder was referred to as "manic-depressive illness" (before the 1980s), many psychiatrists had little awareness that this disorder was a chronic illness. In other words, the manic phase (manic episodes) was treated with medications for mania (often with lithium, carbamazepine, and typical antipsychotics), and the depressive phase (depressive episodes) was treated with medications for depression (often with antidepressants only). Maintenance therapy with mood stabilizers, such as lithium, was not often used, except in cases of frequent mood episodes.

However, it is known that untreated patients with bipolar disorder tend to experience a total of 10 or more mood episodes in their lifetime, and that as the number of mood episodes increases, the duration of the inter-episode period (from the remission of one mood episode to the beginning of the next) tends to decrease 1). At the beginning of the century, a follow-up study of patients suffering from bipolar I disorder for an average of 12.8 years reported that 31.9% had depressive symptoms, 8.9% had manic/hypomanic symptoms, 5.9% had rapid alternation/mixed symptoms, and only 52.7% had remission 7). Similarly, in a follow-up study of patients suffering from bipolar II disorder for an average of 13.4 years, 50.3% had depressive symptoms, 1.3% had hypomanic symptoms, 2.3% had rapid cycling/mixed symptoms, and only 46.1% were in remission 8). In other words, the long-term prognosis of bipolar disorder is poor, and it is highly likely that mood episodes will reappear even after the remission of a previous mood episode, even if there is an intermittent period. In addition, around the same time, it was reported that patients' quality of life (QOL) decreased as the number of mood episodes increased.

Based on these results, it is now recognized that bipolar disorder, whether Type I or Type II, is a "disorder with repeated (recurrent) mood episodes and a chronic course". Therefore, with few exceptions, even after acute treatment of mood episodes, it is believed that maintenance therapy should be used to prevent the recurrence of future mood episodes.

II. Inadequate maintenance therapy

As mentioned above, bipolar disorder is a "chronic disorder with repeated (recurrent) mood episodes", indicating the importance of maintenance therapy. It is known that a high number of recurrences leads to a worse prognosis

in bipolar disorder 10). Therefore, it is important to provide maintenance therapy to prevent the prognosis of bipolar disorder from worsening even after the acute treatment of mood episodes.

However, in psychiatric practice in Japan, there are some situations in which the use of mood stabilizers and atypical antipsychotics at inadequate doses and durations, despite maintenance therapy, may lead to recurrent mood episodes and worsen the prognosis of patients with bipolar disorder.

The most common failure of maintenance therapy is due to lithium concentrations below the minimum required for prevention of relapse. Other mood stabilizers and atypical antipsychotics are also being used at doses far below the level that evidence has shown them to be effective at preventing mood episodes.

III. Inadequate maintenance therapy with lithium

Regarding the dosage and efficacy of medications for the maintenance treatment of bipolar disorder, the most is known about the relapse-preventive effects of lithium.

First, it is known that a high blood concentration of 0.8-1.0 mEq/L (mmol/L) is more effective in preventing relapse (but also has stronger side effects) than a low blood concentration (0.4-0.6 mEq/L) 5). According to the results of a meta-analysis 12), the minimum blood concentration at which lithium is effective in preventing relapse in maintenance therapy is 0.4 mEq/L, and a rapid decrease in blood concentration above 0.2 mEq/L is associated with an increased risk of relapse. Therefore, lithium dose reduction may increase the risk of recurrence if blood levels fall below 0.4 mEq/L or if there is a sudden drop in blood levels of 0.2 mEq/L or more.

Despite this, many patients in Japan are maintained at blood levels below 0.4 mEq/L. These patients may not be benefiting from the preventive effects of lithium on recurrent mood episodes. Considering the risks of weight gain, renal dysfunction, hypothyroidism, and hyperparathyroidism (hypercalcemia) associated with long-term lithium use 15)17), maintenance therapy at blood levels below 0.4 mEq/L may not be desirable in terms of the risk-benefit ratio.

In some patients, regular measurement of blood concentration of lithium is not performed. In this case, it is not known whether an effective blood concentration has been maintained or not, and considering the risk of lithium poisoning 15)17) and the fact that adverse drug reactions are not covered by the Adverse Drug Reaction Relief

System as inappropriate use 14)16), it is probably out of the question.

IV. Inadequate maintenance therapy with drugs other than lithium

Although there has been little investigation of drugs other than lithium, a meta-analysis of olanzapine 12) found that the rate of recurrent depressive episodes was significantly increased in patients treated with less than 10 mg/day compared with those treated with 10 to 20 mg/day. Therefore, it should always be considered that a reduction of olanzapine to less than 10 mg/day during maintenance therapy may increase the risk of relapse.

For most drugs other than lithium and olanzapine, there are only data on the effect of fixed doses on relapse prevention. According to these data, the doses that have been shown to be effective in preventing recurrence of mood episodes are 15 mg/day or 30 mg/day for aripiprazole 9), 300-800 mg/day for quetiapine (most data are for 300 mg/day and 600 mg/day) 13)18), and 200 mg/day for lamotrigine 2)4).

Maintenance therapy with 50 mg/day of lamotrigine or quetiapine is a common prescription in daily clinical practice, but we are not aware of any evidence that these inadequate doses are effective in preventing mood episodes.

In any case, caution should be exercised because maintenance therapy at doses (or blood levels) that have not been proven to prevent mood episodes may worsen the prognosis of bipolar disorder.

V. Inadequate duration of maintenance therapy

Even after the mood episodes of bipolar disorder are in remission, maintenance therapy is still important considering that bipolar disorder is a “chronic disorder with recurrent mood episodes”. A major contributing factor to recurrence is the duration of maintenance therapy. If it is true that repeated recurrences lead to a worse long-term prognosis, then maintenance therapy should be continued as long as possible.

The treatment guidelines of the Japanese Society of Mood Disorders 11) emphasizes the importance of maintenance therapy, but does not include specific information on its recommended duration. The World Federation of Societies of Biological Psychiatry (WFSBP) 6) states that the duration of long-term maintenance therapy after completion of early maintenance therapy is "variable", but may last up to a lifetime. Ultimately, the duration of maintenance therapy should be determined by the patient and on a case-by-case basis, depending on the severity of the patient's previous mood

episodes, the number of previous episodes, and the length of the most recent intermittent period.

Although there is no consensus on the duration of maintenance therapy, the treatment guidelines of the Japanese Society of Mood Disorders 11) recommend that it should be conducted on a yearly basis. Unfortunately, we have occasionally seen cases of recurrence of mood episodes due to dose reduction or discontinuation after less than one year.

Indeed, most clinical trials of maintenance therapy with mood stabilizers (including atypical antipsychotics) have been short (6 months) or long (2 years). Therefore, there is little evidence of the efficacy and safety of maintenance therapy beyond 2 years. Despite this, discontinuation of maintenance therapy after less than one year is not advisable, given the nature of bipolar disorder. Early termination of maintenance therapy may increase the risk of recurrence of mood episodes, which in turn may worsen the patient's prognosis.

VI. Inadequate pharmacotherapy in the acute phase of manic episodes

Prolonged manic episodes can increase a patient's risk of loss of social confidence and prolong hospitalization. Therefore, an important aspect of the treatment of manic episodes is to relieve the manic state as early as possible.

One of the most important points to keep in mind when using drugs is to use sufficient doses. It is not advisable to use inadequate doses of medication because it may lead to prolonged mania.

As stated in the treatment guidelines of the Japanese Society of Mood Disorders 11), the dose of lithium should be increased promptly until a blood level of 1.0 mEq/L is reached if there is no effect. Since lithium is not fast-acting, it makes sense to combine it with atypical antipsychotics, which are expected to be fast-acting, as recommended by the treatment guidelines of the Japanese Society of Mood Disorders 11).

The dose of valproic acid should also be increased promptly until a blood concentration of 70 μg/mL (100 μg/mL if no effect) is reached 11).

Atypical antipsychotics should be started at higher doses as well. For aripiprazole, start at 24 mg/day and increase to 30 mg/day if there is no effect. For olanzapine, start at 10 mg/day and increase to 20 mg/day if there is no effect. Other antipsychotics should be used in the same manner as aripiprazole and olanzapine, starting at high doses or starting at low doses and increasing rapidly. Sequential titration from low doses is unlikely to produce immediate effects.

VII. Inadequate pharmacotherapy in

the acute phase of depressive episodes

One of the problems in treating depressive episodes in bipolar disorder is that there are only four drugs with established efficacy (quetiapine, lithium, olanzapine, and lamotrigine). In daily clinical practice, many patients do not show sufficient treatment efficacy because medications are not being administered at effective doses, potentially explaining why depressive episodes often do not go into remission.

According to the treatment guidelines of the Japanese Society of Mood Disorders 11), the effective doses for treatment of depressive episodes are 300 mg/day or 600 mg/day for quetiapine, blood levels above 0.8 mEq/L for lithium, 5-20 mg/day for olanzapine, and 200 mg/day for lamotrigine. It has also been reported that lamotrigine at 50 mg/day was as effective as a placebo in improving depressive episodes.

One of the problems in the treatment of acute depressive episodes is that many drugs are not expected to have an immediate effect. It is believed that lithium requires more than 6 to 8 weeks after reaching a blood concentration of more than 0.8 mEq/L to produce an effect on depressive episodes 11)19). Lamotrigine requires at least 5 weeks to reach a dose of 200 mg/day (in the absence of concomitant medications such as valproate) that is effective in reducing the risk of severe drug eruptions.

Although lithium and lamotrigine are effective in preventing recurrence of bipolar disorder, they are difficult to use for the treatment of depressive episodes because they are not fast-acting. Therefore, the use of quetiapine and olanzapine, which are fast-acting drugs, seems to make more sense. The dose of quetiapine should be increased to 300 mg/day as soon as possible. The author has previously increased the dose to 300 mg/day on day 7, especially in hospitalized patients. In daily clinical practice, it is common to see patients who are so concerned about the side effect of drowsiness that they do not increase the dose to the effective dose or increase it slowly from a low dose. This often results in suffering from side effects without the effective treatment effects of the medicine. Of course, psychoeducation should be given to the patient, but the dose should be increased with the understanding that the patient will be drowsy regardless.

Concomitant use of antidepressants may also be used in refractory cases. However, it goes without saying that antidepressants should be used with great caution to avoid mania and hypomania. Upon consideration of this risk, the dose of drugs such as quetiapine, lithium, olanzapine, and lamotrigine should be increased to

sufficient levels before resorting to antidepressants.

Conclusion - To avoid worsening the prognosis of bipolar disorder

In view of the current situation in Japan, where inadequate pharmacotherapy is relatively common not only in the maintenance treatment of bipolar disorder, but also in the acute phase of manic episodes and depressive episodes (bipolar depression), in this article I have outlined the effectiveness of pharmacotherapy, and its correct methodological application, for preventing the prognosis of bipolar disorder from worsening.

As mentioned above, bipolar disorder is a “chronic disorder with recurrent mood episodes”, and an increase in the number of recurrent mood episodes leads to a worsening of the prognosis of bipolar disorder. Therefore, in order to prevent this from occurring, it is important to provide sufficient doses and duration of evidence-based pharmacotherapy in maintenance treatment.

One of the questions that always arises in such discussions is, "If acute mood episodes are remitted with a low dose of a drug, can we continue with maintenance therapy at the same low dose?”. In clinical trials, even placebos have been shown to remit acute episodes at a significant rate, so this may well be the case in clinical practice. It is true that there may be resistance to increasing the dose of a drug to a sufficient level for a patient who has been in remission with a low dose. However, given that relapse prevention (maintenance therapy) is one of the factors that keeps the long-term prognosis of bipolar disorder from worsening, especially in patients with a history of frequent mood episodes, the dose should be increased to a sufficient level even if the patient is currently in remission to prevent the recurrence of another mood episode. The author's suggestion is that adequate psychoeducation of the patient is essential. We understand that some readers may disagree with this answer, and we would be grateful if readers could share their opinions with us by submitting a "Discussion" or "Member's Voice" to this journal (Psychiatria et Neurologia Japonica).

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