Invited Review CNPT11(2020)9-14

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

Pharmacotherapy of mania in Japan

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ABSTRACT

This review introduces the treatment guidelines of acute mania by the Japanese Society of Mood Disorders (JSMD) and compares it with that of the Canadian Network for Mood and Anxiety Treatments (CANMAT). Lithium alone for mild mania and the combination of lithium and some atypical antipsychotic drugs for more severe mania are recommended by the JSMD guidelines. This recommendation is different from that of the CANMAT. As maintenance treatment after treatment of the acute phase should be considered from the start of treatment and lithium is the most recommended drug for maintenance treatment in the JSMD guideline, lithium becomes the critical drug for the treatment of mania in the JSMD guidelines. The so-called "drug lag" accounts for the difference between the two guidelines. Safer drugs for extrapyramidal symptoms and cognitive function should be preferred, because these adverse effects interfere with the functional recovery of bipolar patients. The adverse effects of hypnotics or alcohol on cognitive function should be noted carefully, because cognitive impairment influences disabilities and quality of life (QOL) in bipolar patients. New understanding of the pathophysiology of bipolar disorder, that is circadian rhythm dysfunction, may lead to its new diagnosis and treatment.

Keywords: Mania, bipolar disorder, pharmacotherapy, lithium

Received February 11, 2020 / Accepted February 11, 2020 / Published March 30, 2020.

Introduction

Pharmacotherapy of bipolar disorder has made dramatic progress since the 2000s. In contrast to manic episodes, pharmacotherapy for depressive episodes and maintenance is underdeveloped. There have been several clinical trials into the manic episodes of bipolar disorder; a network meta-analysis was reported by Cipriani and his colleagues [1]. However, there is a gap in the number of approved drugs among countries. In general, there are fewer approved drugs in Japan than in the USA. On the other hand, some drugs approved for mania in Japan, which are old typical antipsychotic drugs including haloperidol and levomepromazine, are not approved for mania in the USA. The latter gap is not welcome because these old drugs can cause several severe side effects. Thus, this comparison of approved drugs between different countries gives us an important idea. Without possession of overseas information, we cannot ensure that the knowledge of pharmacotherapy is both correct and up-to-date, and any wrong understandings may not be noticed. In this article, we reviewed the pharmacotherapy of mania in Japan in comparison with those in the USA and Canada, along with the clinically important points for the treatment of mania.

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Table 1. Indication for bipolar disorder approved in the U.S.A.

Manic episode	Depressive episode	Maintenance
lithium	olanzapine+fluoxetine*	lithium
VPA	quetiapine (± XR)	lamotrigine
carbamazepine	lurasidone*±Li/VPA	olanzapine
chlorpromazine	cariprazine*	asenapine
olanzapine		aripiprazole ±Li/VPA
aripiprazole		quetiapine +Li/VPA
quetiapine (± XR)		ziprasidone* +Li/VPA
ziprasidone*		risperidoneLAI±Li/VPA
asenapine		
risperidone		
cariprazine*		
#haloperidol, #sultopride, #timiperone, #levomepromazine		

Indications of underlined drugs are approved in Japan
*not sold in Japan
the indication of mania for the drugs was not approved in the U.S.A.
VPA, valproic acid; Li, lithium

The state of approval for mania in Japan and USA

Table 1 shows the drugs approved for mania in Japan and the USA. Mood stabilizers (lithium, valproic acid, and carbamazepine) are approved for mania in both countries. Although two atypical antipsychotic drugs, aripiprazole and olanzapine, are approved in both countries, four other atypical antipsychotic drugs, quetiapine, ziprasidone, asenapine, and risperidone, are approved in the USA but not Japan. On the other hand, older typical antipsychotic drugs, such as haloperidol, are approved in Japan but not the USA. In general, more atypical antipsychotic drugs, which are clearly safer than typical antipsychotic drugs, are used clinically in the USA. This drug lag [2] should be resolved for bipolar patients. Older typical antipsychotic drugs approved for mania in Japan raise another problem by indicating that outdated treatment remains in Japan. Especially, extrapyramidal symptoms caused by typical antipsychotic drugs and cognitive disturbances caused by anticholinergic drugs frequently co-used with typical antipsychotic drugs may worsen the symptoms and quality of life of bipolar patients [3, 4].

How to choose antimanic drugs

Past clinical trials have shown that several drugs have a significant antimanic effect when compared with placebo [1]. It is noteworthy whether there are any clinical differences in efficacy and adverse effects between antimanic drugs, which leads to knowing how to choose antimanic drugs, i.e., compatible medications for each patient. A network meta-analysis study showed that, overall, antipsychotic drugs were more effective than mood stabilizers such as lithium, and that risperidone, olanzapine, and haloperidol were considered among the best of the available options for the treatment of manic episodes [1]. These antipsychotic drugs were superior to other antimanic drugs in both efficacy and acceptability. In their study, acceptability meant treatment discontinuation and was defined as the number of patients who left the study early for any reason during the first 3 weeks of treatment of the total number of patients randomly assigned to each treatment group [1]. Acceptability did not mean lack of adverse effects.

The Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) 2018 guidelines recommend lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine as first-line monotherapies for acute mania [5]. These guidelines recommend quetiapine, asenapine, aripiprazole, and risperidone in combination with lithium or divalproex as first-line combination therapies for acute mania. They do not recommend haloperidol and olanzapine as first-line, which have shown superior efficacy and acceptability in the network meta-analysis by Cipriani et al., [1] because safety and tolerability concerns relegated them to second-line options. Extrapyramidal symptoms induced by haloperidol and weight gain and diabetes mellitus induced by olanzapine are se-

Table 2. Treatment guidelines for manic episodes in the third edition of the Japanese Society of Mood Disorders for treatment of bipolar disorders [6] (https://www.secretariat.ne.jp/jsmd/iinkai/katsudou/data/180125.pdf)

• Most recommended treatment
When the manic condition is intermediate or severe:
Lithium and atypical antipsychotic drugs (olanzapine, aripiprazole, quetiapine, risperidone) in combination
In mild manic conditions:
Lithium
• Next recommended treatment
Valproic acid
Atypical antipsychotic drugs (olanzapine, aripiprazole, quetiapine, risperidone, paliperidone, asenapine)
Carbamazepine
Combination of valproic acid and an atypical antipsychotic drug
• Other recommended treatment
Combination of two or more mood stabilizers
Mood stabilizers and typical antipsychotic drugs (chlorpromazine, sultopride, haloperidol, levomepromazine, timiperone, zotepine) in combination
Electroconvulsive therapy
• Treatments that are not recommended
Lamotrigine
Topiramate
Verapamil

rious side effects that affect their choice.

Therefore, not only evidence from meta-analyses, but also comprehensive clinical judgment is needed for drug selection.

Treatment guidelines for acute mania in Japan

The Japanese Society of Mood Disorders (JSMD) established a committee for the treatment of mood disorders that created the first edition of a treatment guideline for bipolar disorders on March 10, 2011 and a revised second edition on March 31, 2012 [6]. In 2017, a third edition was revised and distributed through the home page of the JSMD in Japanese (https://www.secretariat.ne.jp/jsmd/iinkai/katsudou/data/180125.pdf). The recommendations for acute mania in the third edition (Table 2) are almost same as those in the second edition, which was published in an English journal [6]. This guideline recommends lithium monotherapy in mild manic conditions and lithium in combination with atypical antipsychotic drugs (olanzapine, aripiprazole, quetiapine, and risperidone) when the manic condition is intermediate or severe.

Although the CANMAT/ISBD guidelines recommend lithium, divalproex, or atypical antipsychotic drugs as first-line monotherapies, the Japanese guidelines do not recommend divalproex or atypical antipsychotic drugs as first-line monotherapies. The characteristic points of the Japanese guidelines are that the main drug for acute mania is lithium and that atypical antipsychotic drugs are used as adjuvant drugs to lithium. Such a combination of lithium and atypical antipsychotic drugs is also recommended as first-line combination therapies in the CANMAT/ISBD guidelines [5]. Therefore, the Japanese guidelines for acute mania overlap with the CANMAT/ISBD guidelines and the latter recommends more varied treatment options, especially with regards to monotherapies with atypical antipsychotic drugs.

The reason for the recommendation of monotherapy with atypical antipsychotic drugs for acute mania is associated with subsequent recommendations for maintenance treatment. As shown in Table 3, the Japanese guidelines recommends lithium as the most recommended treatment for maintenance. The CANMAT/ISBD guidelines recommend lithium, lamotrigine, divalproex, and atypical antipsychotic drugs as first-line treatments for maintenance. Following the treatment of acute mania, maintenance treatment should be started in all bipolar patients, because bipolar episodes recur frequently without maintenance treatment. Treatment options for maintenance may influence the treatment options for the acute mania.

Table 3. Treatment guidelines for maintenance treatment in the third edition of the Japanese Society of Mood Disorders for the treatment of bipolar disorders [6] (https://www.secretariat.ne.jp/jsmd/iinkai/katsudou/data/180125.pdf)

A. Drug therapy
• Most recommended treatment
Lithium
• Next recommended treatment
Lamotrigine
Valproic acid
Atypical antipsychotic drugs (olanzapine, aripiprazole, quetiapine, paliperidone)
Combination of lithium and lamotrigine
Combination of lithium and valproic acid
Combination of lithium/valproic acid and quetiapine
Combination of lithium and aripiprazole
• Other recommended treatment
Carbamazepine
Risperidone depot injection
Combination among mood stabilizers or a combination of mood stabilizers and atypical anti-psychotic drugs
Combination of lithium and thyroid hormones
Addition of ramelteon to the above recommended drugs
• Treatments that are not recommended
Use of antidepressants (in particular, tricyclic antidepressants)
Treatment with antidepressants alone
B. Psychosocial treatment (Combination with drug therapy in all cases)
• Most recommended treatment
Psychoeducation
• Next recommended treatment
Cognitive behavioral therapy
Interpersonal-social rhythm therapy
Family therapy
• Treatments that are not recommended
Treatment with psychosocial treatment alone without drug therapy

In our opinion, maintenance treatment should be started alongside the acute mania treatment to prevent a switch to depression following acute mania, rapid cycling, or mixed state [7]. The third edition of the JSMD guidelines for treatment of bipolar disorders recommend psychosocial treatment in combination with pharmacological treatment for maintenance treatment; the most recommended psychosocial treatment of bipolar disorder is psychoeducation. First, patients should have psychoeducation for manic or hypomanic states as well as a mixed state, because these states of bipolar disorder are difficult for patients and their families to understand. The authors used the Manic Episode Screening Questionnaire (MES) to explain the symptoms that constitute manic or hypomanic syndromes (states) to the patients and their families [8]. Understanding the clinical concepts of (hypo) manic states and mixed states may lead to enough insight into bipolar disorder and therefore, good adherence to long-term maintenance treatment.

Cognitive impairment in bipolar disorder

A recent clinical topic in psychiatry is cognitive impairment in endogenous psychiatric diseases, including bipolar disorder. Executive function and processing are the cognitive domains affected in euthymic bipolar outpatients, and such deficits are maintained over time for at least 2 years [9]. In euthymic bipolar patients, both subjective and objective cognitive function predict quality of life [10], even after controlling for the influence of mood symptoms [11]. The International Society for Bipolar Disorders Targeting Cognition Task Force recommends the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) as a screening tool for subjective cognitive impairment, in addition to an objective cognitive assessment in a clinical context [12]. Clinically, a self-reported

questionnaire is more convenient for the screening of cognitive impairment and evaluation of its improvement or worsening.

Recently, attention has focused on the effects of drugs for bipolar disorder on cognitive function [13]. There is some evidence that while lithium improves some cognitive domains, it impedes others. Antipsychotics may be deleterious to cognition, although this may relate to the patient population in which they were prescribed. Sodium valproate is also associated with worse cognitive outcomes, while the impact of other antiepileptics is unclear. Overall the quality of evidence is poor and is derived from a relatively small number of studies that often do not account for the significant heterogeneity of the disorder or common comorbidities.

At this time, it seems that anticholinergics and benzodiazepine anxiolytics or hypnotics should be avoided as much as possible in the treatment of bipolar disorder because these classes of drug impair cognitive function [3, 14, 15]. These drugs are expected to adversely affect the cognitive function of bipolar disorder and thus quality of life (QOL). Treating cognitive impairment in bipolar disorder is an attractive idea. However, it is more important to eliminate factors such as drugs and alcohol that cause cognitive impairment before that.

Circadian rhythm sleep-wake disorders

Another topic in the diagnosis and treatment of bipolar disorder is comorbidity of the circadian rhythm sleep-wake disorders. Irregularity of the sleep-wake rhythm, eveningness chronotype, abnormality of melatonin secretion, vulnerability of clock genes, and the irregularity of social time cues have also been well-documented in bipolar disorder [16]. Circadian rhythm dysfunction is more prominent in BD when compared with that in major depressive disorders and acts as a predictor for the early onset age of BD and the relapse of mood episodes [16]. Hence, treating circadian rhythm dysfunction in bipolar disorder is a new therapeutic target. Melatonin and agonists of melatonin receptors, light therapy and dark therapy, and interpersonal social rhythm therapy, which is recommended as psychosocial maintenance treatment by the JSMD bipolar disorder treatment guidelines, hold promise for the treatment of circadian rhythm dysfunction.

For the treatment of acute mania, adjunctive darkness therapy is reportedly effective. Furthermore, the use of blue‐blocking glasses, a kind of sunglass, is also effective in acute mania [17].

Conclusion

The present review introduced the treatment guidelines for bipolar mania by the JSMD and approved drugs in Japan and compared those with those of the CANMAT and approved drugs in the USA. The so-called ‘drug lag’ accounts for the difference in the guidelines and treatment statuses of bipolar disorder between countries. Safer drugs are preferred in modern psychiatric treatment. More recently, the adverse effect of antimanic drugs, hypnotics, or alcohol should be noted carefully because cognitive impairment influences disabilities and QOL in bipolar patients. New understanding of the pathophysiology of bipolar disorder, that is circadian rhythm dysfunction, may lead to its new diagnosis and treatment.

CONFLICT OF INTEREST

Takeshi Inoue has received personal fees from Pfizer, Takeda Pharmaceutical, Kyowa Pharmaceutical Industry, MSD, and Dainippon Sumitomo Pharma. The authors report no other conflicts of interest in this work.

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