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Efficacy of Olanzapine for Treating Depressive Episodes in Bipolar Disorder

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ABSTRACT

Purpose: We administered olanzapine to 24 outpatients with bipolar disorder who had experienced a depressive or mixed episode as their most recent episode to evaluate the efficacy and safety of olanzapine in clinical practice.
Methods: The duration of study treatment was 8 weeks. Symptoms in each subject were assessed using the Montgomery Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impressions-Severity of Illness, Bipolar Version (CGI-BP) at the start of treatment with olanzapine and at Week 4 and Week 8 of treatment.
Results: A total of 17 subjects underwent the assessments at Week 4, and 13 subjects completed the 8-week treatment regimen and the assessments at Week 8. The mean total score and each individual item score of the MADRS were significantly improved at Week 4 and Week 8 compared to those at the start of treatment. The mean CGI-BP Depression and CGI-BP Overall scores were significantly improved at Week 4 and Week 8, while the mean CGI-BP Mania score was not significantly different at Week 4 or Week 8 compared to that at the start of treatment. Adverse drug reactions were reported in 3 subjects during the study: hyperphagia in 2 subjects and light-headed feeling in 1 subject. No manic switches were observed.
Discussion: The results of this study confirmed the efficacy and safety of olanzapine in outpatients with bipolar depression in clinical practice.

Keywords: olanzapine, bipolar disorder, depressive episode, bipolar depression, Montgomery Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions-Severity of Illness, Bipolar Version (CGI-BP)

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INTRODUCTION

Bipolar disorder causes severe suffering for patients and caregivers, and constitutes a major health economic challenge for societies [1]. According to the most recent WHO global burden of disease study, bipolar disorder ranks among the top 20 causes of disability among all medical conditions worldwide, and ranks 6th among mental disorders [2]. The disease concept and treatment policy of bipolar disorder are still controversial. Although it is difficult to treat depressive episodes or bipolar depression in patients with bipolar disorder, the use of antidepressants is restricted because of the high risk of manic switching. In Japan, olanzapine is the only drug approved for the indication of bipolar depression in adults. Olanzapine was launched as a therapeutic drug for schizophrenia in 2001 and was also approved for the indication of manic symptoms of bipolar disorder in 2010. As a therapeutic drug for depressive symptoms of bipolar disorder, it was approved for marketing in February 2012 in Japan, but little evidence of its efficacy in clinical practice has been obtained. We administered olanzapine to adult outpatients with bipolar depression to evaluate its efficacy and safety in clinical practice.

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SUBJECTS AND METHODS

Subjects

Adult outpatients with bipolar disorder who presented to our mental clinic who had experienced a depressive or mixed episode as their most recent episode were recruited into this study. Patients were diagnosed based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Only patients who had not been treated with olanzapine were enrolled. During the period from March 2012 through March 2013, a total of 24 subjects gave informed consent and participated in this study. Before informed consent, each subject received a full explanation of the details of this study and the measures that would be taken to protect their personal information.

Methods

This study was a prospective, non-interventional, observational study of outpatients prescribed olanzapine for the treatment of bipolar disorder. We orally administered olanzapine to subjects as monotherapy or in combination with other drugs. The initial dose (2.5, 5, or 10 mg once daily) of olanzapine and the use and doses of concomitant drugs were left up to the discretion of the treating psychiatrist. During the study period, the dose of olanzapine was increased if the treating psychiatrist judged it necessary, and the concomitant drugs and their doses were not changed except when absolutely necessary. The duration of study treatment was 8 weeks. Symptoms in each subject were assessed using the Montgomery Åsberg Depression Rating Scale (MADRS) [3] and the Clinical Global Impressions-Severity of Illness, Bipolar Version (CGI-BP; Depression, Mania, and Overall) [4] at the start of treatment with olanzapine and at Week 4 and Week 8 of treatment. The safety of treatment with olanzapine was evaluated based on the reports of adverse drug reactions during the study.

STATISTICAL ANALYSIS

To evaluate the improvement of symptoms, the MADRS total and individual item scores and the CGI-BP (Depression, Mania, and Overall) scores at Week 4 and Week 8 were compared to those at the start of treatment with olanzapine using Wilcoxon signed-ranks tests. Multiplicity adjustment was not performed because of the relatively small sample size and the exploratory nature of the study.

RESULTS

Baseline Characteristics and Disposition of Subjects

The baseline and other characteristics of subjects are shown in Table 1. A total of 24 adult outpatients with bipolar I or II disorder who had experienced a depressive or mixed episode as their most recent episode were enrolled in this study. Before the assessment at Week 4, 7 subjects were withdrawn from the study because they had been lost to follow-up (4 subjects), they had experienced an adverse event (2 subjects), or they had asked to be withdrawn from the study (1 subject). The other 17 subjects underwent assessment at Week 4 and were included in the efficacy analysis set. Olanzapine was administered as monotherapy to 2 subjects, as add-on treatment to 14 subjects, and in combination with another drug whose treatment was initiated simultaneously with olanzapine in 1 subject. The following drugs were used in the subjects concomitantly with olanzapine: lamotrigine in 6 subjects, lithium in 5 subjects, valproate in 3 subjects, clonazepam in 4 subjects, aripiprazole in 3 subjects, the selective serotonin reuptake inhibitors (SSRIs) escitalopram, sertraline, or paroxetine) in 4 subjects, the serotonin and norepinephrine reuptake inhibitors (SNRIs) duloxetine or milnacipran in 4 subjects, mirtazapine in 2 subjects, and hypnotics (benzodiazepines or non-benzodiazepines) in 12 subjects. Before the Week 8 assessment, 4 subjects were withdrawn from the study because of an adverse event (1 subject), at the subject's request (2 subjects), or because of the resolution of symptoms (1 subject). These 4 subjects underwent assessment at discontinuation: at Week 5 in 1 patient, Week 6 in two patients, and Week 7 in one patient. The results of the assessments at discontinuation were analyzed together with the results at Week 8, according to the last-observation-carried-forward (LOCF) method of imputing data with dropouts. A total of 13 subjects completed the 8-week treatment course and the Week 8 assessments.

Results of the MADRS

The mean MADRS total scores at the start of treatment with olanzapine and at Week 4 and Week 8 (or at discontinuation) are shown in Figure 1. The mean MADRS total score was significantly improved at Week 4 ($p < 0.0001$) and Week 8 ($p < 0.0001$) compared to that at the start of treatment.

The mean scores of each individual MADRS item at the start of treatment with olanzapine and at Week 4 and Week 8 (or at discontinuation) are shown in

Figure 2. The mean score of each item was significantly improved at Week 4 and Week 8 compared to that at the start of treatment ($p < 0.05$ each).

Table 1. Baseline and Other Characteristics of Subjects

		All Enrolled Subjects	Efficacy Analysis Set
Number of subjects		24	17
Age (years)*		54.2 ± 14.8 (25 - 84)	55.4 ± 14.7 (29 - 84)
Sex	Male	9 (37.5%)	8 (47.1%)
	Female	15 (62.5%)	9 (52.9%)
Diagnosis	Bipolar I	14 (58.3%)	11 (64.7%)
	Bipolar II	10 (41.7%)	6 (35.3%)
Most recent episode	Depressive	22 (91.7%)	15 (88.2%)
	Mixed	2 (8.3%)	2 (11.8%)
Regimen	Monotherapy	3 (12.5%)	2 (11.8%)
	New combination therapy	2 (8.3%)	1 (5.9%)
	Add-on treatment	19 (79.2%)	14 (82.4%)
Concomitant drugs	Lamotrigine	6	6
	Lithium	6	5
	Valproate	4	3
	Clonazepam	4	4
	Aripiprazole	3	3
	SSRIs	6	4
	SNRIs	5	4
	Mirtazapine	2	2
	Hypnotics	16	12
Initial dose	2.5 mg	11 (45.8%)	7 (41.2%)
	5 mg	12 (50.0%)	9 (52.9%)
	10 mg	1 (4.2%)	1 (5.9%)
Final dose	2.5 mg	9 (37.5%)	5 (29.4%)
	5 mg	10 (41.7%)	7 (41.2%)
	7.5 mg	1 (4.2%)	1 (5.9%)
	10 mg	4 (16.7%)	4 (23.5%)

*Mean ± standard deviation (minimum - maximum)

Results of the CGI-BP

The mean CGI-BP (Depression, Mania, and Overall) scores at the start of treatment with olanzapine and at Week 4 and Week 8 (or at discontinuation) are shown in Figure 3. The mean CGI-BP Depression and CGI-BP Overall scores were significantly improved at Week 4 and Week 8 compared to those at the start of treatment ($p < 0.001$ each). The mean CGI-BP Mania score was not significantly different at Week 4 or Week 8 compared to that at the start of treatment.

Adverse Drug Reactions

Adverse drug reactions were reported in 3 subjects during the study: hyperphagia in 2 subjects and light-headed feeling in 1 subject. The 2 subjects who experienced hyperphagia were withdrawn from the study due to the adverse event on Day 2 and Day 15 of treatment, respectively. The subject who experienced a light-headed feeling was withdrawn from the study due to the adverse event on Day 29 of treatment (the subject underwent the Week 4 assessments). No manic switches were observed.

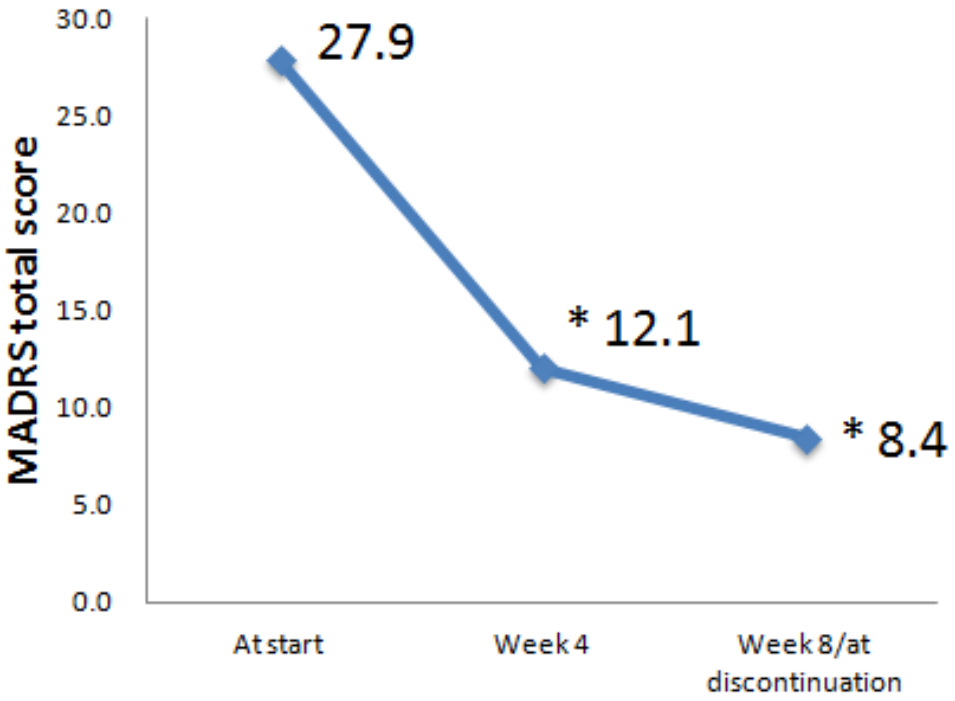

Figure 1. Change over time in the mean MADRS total score
*p < 0.0001 vs. the score at treatment initiation (Wilcoxon signed-ranks test)
MADRS: Montgomery Åsberg Depression Rating Scale

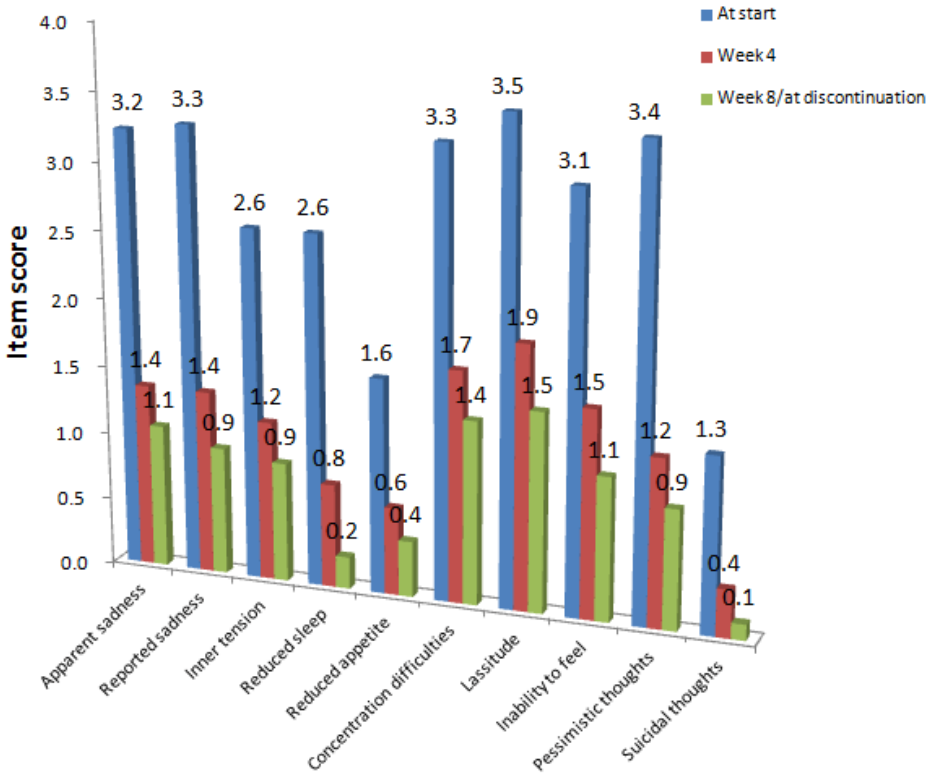

Figure 2. Changes over time in mean scores of MADRS question items
MADRS: Montgomery Åsberg Depression Rating Scale

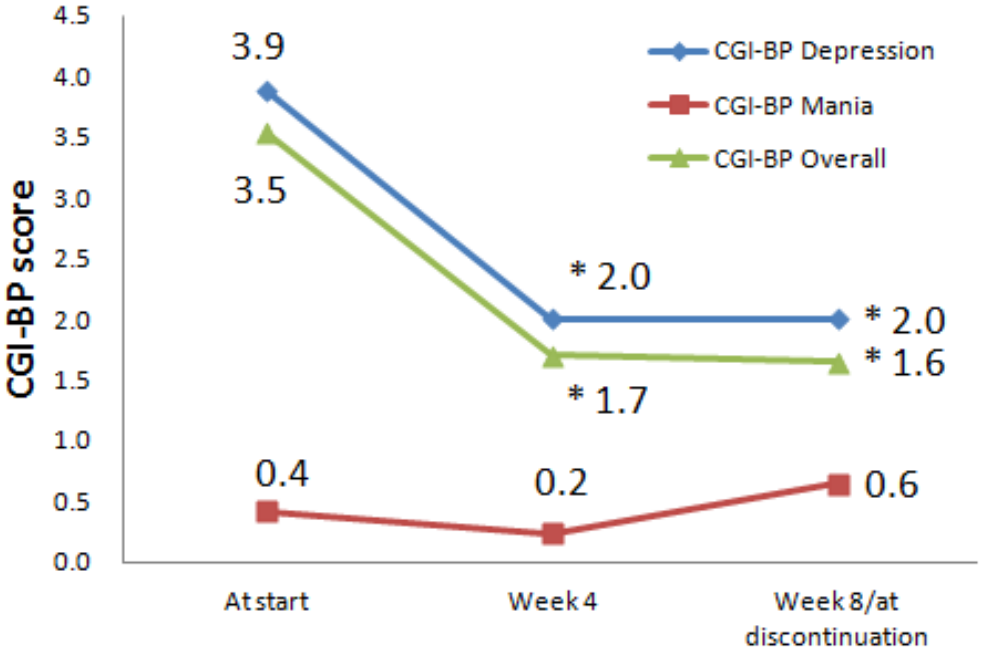

Figure 3. Changes over time in mean CGI-BP scores
*p < 0.001 vs. the score at treatment initiation (Wilcoxon signed-ranks test)
CGI-BP: Clinical Global Impressions-Severity of Illness, Bipolar Version

DISCUSSION

Before the marketing approval of olanzapine for the treatment of bipolar depression, the first-line medications recommended for the acute phase of bipolar depression by the practice guidelines in Japan [5, 6] were lithium or quetiapine, as monotherapy (both are off-label therapies). In the practice guidelines published after olanzapine was approved for the treatment of bipolar depression in Japan [7], the recommended first-line medications are quetiapine, lithium, olanzapine, or lamotrigine, as monotherapy, although all of these other than olanzapine are off-label therapies. The efficacy and safety of olanzapine monotherapy have been demonstrated in multinational randomized placebo-controlled studies in adult patients (age ≥ 18 years) with bipolar I disorder and a depressive episode [8-10]. A subpopulation analysis in Japanese adult patients with a depressive episode of bipolar I disorder also supported the efficacy and safety of olanzapine monotherapy in Japanese patients [11]. In these studies, efficacy was evaluated using the MADRS and the CGI-BP, as was done in this study. In addition, a meta-analysis demonstrated the efficacy of olanzapine for improving the MADRS total score [12]. The pharmacological mechanism of action of olanzapine for treating depression is thought to be based on an increase in dopamine and noradrenaline release in the prefrontal cortex [13] and on 5-HT2A and 5-HT2C receptor antagonistic activity [14].

In this study, we administered olanzapine to adult outpatients with bipolar depression to evaluate the efficacy and safety of olanzapine in clinical practice. Treatment with olanzapine rapidly improved the MADRS total score and individual item scores and the CGI-BP Depression and Overall scores, confirming the effect of olanzapine on bipolar depression. In particular, the finding that suicidal ideation as measured by the MADRS rapidly disappeared suggests the usefulness of olanzapine in clinical practice. Treatment with olanzapine was well-tolerated, and no manic switching was observed. The majority of the subjects in this study received olanzapine concomitantly with other drugs, and no special adverse events occurred. The results of this study demonstrated the efficacy and tolerability of olanzapine in outpatients with bipolar depression in clinical practice.

The discontinuation rate of 45.8% (11/24) in the present study is comparable to or higher than those in trials of other agents for bipolar depression, such as quetiapine, lithium and lamotrigine, that used the same treatment period of 8 weeks. The discontinuation rates in trials of quetiapine for bipolar depression were 45.6% (82 of 180 subjects) [600 mg] and 33.3% (60 of 181 subjects) [300 mg] in the report by Calabrese et al. [15] and 41.4% (70 of 169 subjects) [600 mg] and 41.5% (71 of 171 subjects) [300 mg] in the report by

Thase et al. [16], although lower rates of 24.5% (65 of 265 subjects) [300 mg] and 23.5% (63 of 268 subjects) [600 mg] were reported by Young et al. [17]. The discontinuation rate for lithium was 25.0% (34 of 136 subjects) [600-1800 mg] in the report by Young et al., and 15% (9 of 60 subjects) [plasma concentration: 0.6-1.2 mmol/L] in the report by Van der Loos et al. [18]. The discontinuation rate of lamotrigine in a 7-week treatment period was 34.6% (71 of 205 subjects) [150-200 mg] in the report by Brown et al. [19], and 34.8% (23 of 66 subjects) [50 mg] and 28.6% (18 of 63 subjects) [200 mg] in a report by Calabrese et al. [20]. The rate in combination therapy with lithium [0.6-1.2 mmol/L] and lamotrigine [titrated to 200 mg] for 8 weeks was 18.8% (12 of 64 subjects) in the report by van der Loos et al. [18]. The above-mentioned trials were all randomized controlled trials with protocols and sample sizes different from those of open trials such as the present study. There are, to the authors' knowledge, no other reports of open trials of olanzapine for bipolar depression reporting a clear discontinuation rate. Further studies with a larger sample size and tighter control would be necessary to resolve concerns over the discontinuation rate more convincingly.

Patients with bipolar II disorder and those having a mixed episode were included in this study. Olanzapine is expected to be effective in treating bipolar II disorder and mixed episodes. Furthermore, it is expected to be useful in treating bipolar spectrum disorder as proposed by Ghaemi et al. [21], as well as so-called soft bipolarity. However, this study has some limitations. First, since the sample size of this study was small, interpretation of the results is limited. Second, the use of LOCF has been severely criticized recently because it is almost certain to create bias, although the method has been used for many years in several therapeutic areas, and is sometimes justified on the grounds that it is conservative; in other words, it tends to underestimate treatment effects [22]. It will be necessary to obtain more data on treatment and in randomized controlled trials with olanzapine to evaluate the efficacy and safety of olanzapine in patients with bipolar depression in clinical practice.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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