Journal of Affective Disorders 205 (2016) 360–364

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Clinical outcomes of long-acting injectable risperidone in patients with bipolar I disorder: A 1-year retrospective cohort study

Hsue-Wei Chan [a,b], Chin-Yu Huang [a], Wen-Jui Feng [d,e], Yung-Chieh Yen [a,c,*]

[a] Department of Psychiatry, E-Da Hospital, Kaohsiung, Taiwan
[b] Graduate Institute of Health Care Administration, School of Medicine, I-Shou University, Kaohsiung, Taiwan
[c] School of Medicine, I-Shou University, Kaohsiung, Taiwan
[d] Departments of Administrative Management, China Medical University Hospital, Taichung, Taiwan
[e] Department of Health Services Administration, College of Public Health, China Medical University, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form
4 August 2016
Accepted 14 August 2016
Available online 17 August 2016

Keywords:
Bipolar disorder
Emergency service
Long-acting injection
Rehospitalization
Risperidone

ABSTRACT

Objectives: We explored the effect of risperidone long-acting injection (LAI) treatment on patients with bipolar I disorder in a real-world setting.
Methods: In this retrospective cohort study, 469 patients with bipolar I disorder were enrolled and treated with risperidone LAI and different oral antipsychotics and followed for 1 year. Concomitant medications, such as mood stabilizers, antidepressant, anxiolytics, hypnotics, or anticholinergics, were administered. On the basis of risperidone LAI use and treatment compliance, the patients were classified into 4 groups: the first long-acting injectable antipsychotics (LAI1) group (compliant patients receiving risperidone LAI treatment) (N=44), the second long-acting injectable antipsychotics (LAI2) group (non-compliant patients receiving risperidone LAI treatment) (N=33), the first non-LAI (NLAI1) group (compliant patients receiving oral medications) (N =337), and the second non-LAI (NLAI2) group (non-compliant patients receiving oral medications) (N=55). The rate of re-hospitalization, length of hospital stay, and rate of emergency room visit were assessed.
Results: Compared with the non-LAI groups, the LAI groups had longer mean duration of illness (8.5 years, $P=0.0001$), higher rate of admission due to mood episodes ($P<0.0001$), depressive episodes ($P<0.0001$), or manic episodes ($P=0.0002$), and higher rate of emergency room visit ($P=0.0003$) before enrollment. After a 1-year follow-up, re-hospitalization rates were significantly lower in the LAI1 group than that before enrollment for any episodes ($P=0.0001$), manic episodes ($P=0.005$), and depressive episodes ($P=0.002$). The rates of emergency room visit were significantly lower in the LAI1 ($P=0.0001$), LAI2 ($P=0.013$), and NLAI1 ($P=0.0001$) groups compared with those before enrollment.
Conclusions: Risperidone LAI reduces the clinical severity of bipolar I disorder.

1. Introduction

Bipolar disorder is a severe and disabling psychiatric disorder characterized by mood elevation, mood fluctuation during manic or hypomanic episodes, and vivid depression during major depressive episodes. Patients with bipolar I disorder experience manic episodes, and nearly all such patients experience major depressive episodes, whereas patients with bipolar II disorder experience episodes of hypomania and major depression (Ketter, 2010). The lifetime prevalence is 1.0% for bipolar I disorder and 1.1% for bipolar II disorder in the U.S. population (Merikangas et al., 2007). During a manic episode, mood elevation or instability leads to recklessness or even destructive behavior (Nourse et al., 2014; Volavka, 2013), whereas during a major depressive episode or a mixed episode, the risk of suicide (Dilsaver et al., 2005; Rihmer, 2007; Rihmer and Gonda, 2013) is high and cannot be ignored. Lack of insight is observed not only in patients with psychosis, such as schizophrenia (Lehrer and Lorenz, 2014; Schennach et al., 2012), but also in patients with bipolar disorder, especially during a manic episode (de Assis da Silva et al., 2015). Poor insight leads to medical nonadherence, which consequently results in deterioration of mental health. The high risk of violence in patients experiencing manic episodes or that of suicide in patients experiencing mixed or depressive episodes cause physical and mental harm not only to the patients but also to their family members who care for them. In addition to interfering with the personal life of the patient, mood instability strongly affects the

* Corresponding author at: Department of Psychiatry, E-Da Hospital, 1 Yi-Da Road, Yan-Chau District, Kaohsiung 824, Taiwan.
E-mail address: jackycyen@yahoo.com (Y.-C. Yen).

http://dx.doi.org/10.1016/j.jad.2016.08.023
0165-0327/

caregivers and the society (Miller et al., 2014), both in terms of direct cost (e.g., in-patient care, frequent rehospitalization, and medical expenditure) (Jaramillo-Gonzalez et al., 2014) and indirect cost (e.g., loss of productivity). Cognitive functional decline in patients with bipolar disorder is another problem that requires attention, because long-term mood instability can cause functional decline in such patients. Studies have suggested that long-term mood instability can impair neurocognitive functions, such as working memory, processing speed, inhibition, attention, vigilance, and executive function, all of which slow down the overall reaction in patients with bipolar disorder; moreover, impairment of occupational function, interpersonal relationships, global functions, and social adjustment have been recently reported in such patients (Burdick et al., 2010; Daglas et al., 2015; Mann-Wrobel et al., 2011; Marotta et al., 2015; Martino et al., 2015; Nenadic et al., 2015; Pålsson et al., 2013; Rosa et al., 2010; Torres et al., 2007). Additionally, a study revealed that neurocognitive deficits are present across the bipolar spectrum and that they are slightly severer in bipolar I disorder (Sole et al., 2012). Antipsychotic agents are one of the first-line drugs used for treating bipolar disorder (Yatham et al., 2013) and are used in monotherapy or combination treatment with mood stabilizers (Baek et al., 2014; Paterniti and Bisserbe, 2013). Second-generation antipsychotic agents have been found effective in treating bipolar mania (Young et al., 2008), and some of them, such as quetiapine (Thase, 2008) and olanzapine (Tohen et al., 2013), are being used to treat bipolar depression. Long-acting injection (LAI) of antipsychotic agents was developed for treating patients with poor medical adherence who would not accept long-term oral treatment. LAI formulations are used as the first-line treatment (Chou et al., 2015). Among the LAIs of antipsychotics, second-generation antipsychotic agents, such as risperidone LAI (RLAI), have been proven effective and to have fewer side effects compared with first-generation antipsychotics (Chengappa et al., 2010). The safety and efficacy of RLAI in treating bipolar patients have been examined, mostly through randomized trials (Bobo et al.; 2011; Chengappa et al., 2010; Macfadden et al., 2009; Vieta et al.,. 2012) and open-label studies (Boarati et al., 2013; Bräunig et al., 2008; Malempati et al., 2011; Quiroz et al., 2010). In addition, a prospective naturalistic observational study examined the effect of RLAI on bipolar patients (Vieta et al., 2008). In randomized controlled trials, patients are screened using specific inclusion and exclusion criteria, which is quite different from the real-world experience. Therefore, in this study, we clarify the effect of RLAI treatment on bipolar disorder in a real-world setting. We recruited patients with bipolar disorder who were being treated with either oral antipsychotic or RLAI and compared the rates of emergency room visit and rehospitalization during the treatment.

2. Methods

2.1. Study design

This study was approved by the Institutional Review Board of E-Da Hospital. Data were obtained from a retrospective cohort study conducted during June 2010–September 2014. We collected the medical records of patients with bipolar I disorder treated at E-Da Hospital. The patients were categorized into 4 groups: Patients who had continuously received RLAI for 3 months were recruited as the first long-acting injectable antipsychotics (LAI1) group. Patients who had irregularly received RLAI treatment were recruited as the second long-acting injectable antipsychotics (LAI2) group. Patients who did not receive RLAI treatment throughout the treatment course (minimum treatment duration 6 months) were recruited as the first non-LAI (NLAI1) group. Patients who had irregularly received oral drug treatments were recruited as the second non-LAI (NLAI2) group. This was an observational study in the setting of a general hospital, in which patients received psychiatric treatment in the outpatient department, emergency department, or acute psychiatric unit depending on their clinical conditions. We determined the clinical outcomes of the recruited patients and their relation with different pharmacological treatments during a 1-year followup.

2.2. Inclusion and exclusion criteria

Patients aged 18 years and older were recruited from a single hospital where they received their psychiatric treatment. All patients were diagnosed as having bipolar I disorder according to DSM-IV-TR criteria. Patients with bipolar I disorder who had received treatment for physical illness and pregnant or breast-feeding women were excluded.

2.3. Characteristics and clinical outcomes

Characteristics of patients, including age, age of onset, sex, physical conditions, and previous history of psychiatric treatment of bipolar I disorder, were collected retrospectively. During the 1-year followup, we recorded the antipsychotic agents used, the dosage and interval of each drug, and the concomitant oral medications. We also recorded remission of manic and depressive episodes of the patients and their length of their subsequent hospital stay. The rate of admission to acute psychiatric unit, length of hospital stay, and rate of emergency service utilization were followed for 1 year after patient recruitment.

2.4. Treatment options

Recruited patients received their psychiatric treatments mostly through ambulatory care visits and from acute psychiatric units and emergency departments when necessary. The antipsychotic agents and mood stabilizers or antimanic drugs and their dosage were determined by psychiatrists according to their evaluation of the clinical condition of the patients. If RLAI was selected for a patient, the medication was injected when the patient returned to the outpatient department for followup.

2.5. Statistical analyses

Patients were categorized according to their medication. Demographic data, baseline characteristics, and clinical outcomes were compared between the groups. The means of two continuous variables were compared between the groups by using the *t*-test, and Fisher's exact test was used to compare the distributions of categorical variables between the groups.

3. Result

This study recruited 469 patients with bipolar I disorder who received treatment from June 2010 to September 2014. Among these 469 patients, 77 patients in the LAI groups (i.e., LAI1 and LAI2) used RLAI, and patients in the NLAI groups (i.e., NLAI1 and NLAI2) received oral antipsychotic treatment. The NLAI group comprised 136 men and 256 women (mean age 42 years), and the LAI group comprised 30 men and 47 women (mean age 39 years); the mean age ($P=0.055$) and sex ($P=0.515$) differed non-significantly between the groups (Table 1). Before the patients were enrolled in this study, the LAI groups had a mean duration of illness of 8.5 years, significantly longer ($P=0.0001$) than the 5.5 years in the NLAI groups. An analysis of the medical records of