



Research paper

Bipolar patients treated with long-acting injectable risperidone in Taiwan: A 1-year mirror-image study using a national claims database



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ABSTRACT

Objective: Bipolar disorder (BD) is burdensome for patients and healthcare systems. This study evaluated changes in concomitant medication patterns, healthcare utilization, and costs after the initiation of risperidone long-acting injection (RLAI) treatment among BD patients.

Method: 287 BD patients receiving regular RLAI treatment for 1 year were identified from the Taiwan National Health Insurance Research database during 2007–2012. The bootstrapping procedure was performed to create 1000 samples to generate normally distributed data. The paired t-tests with a correction for multiple comparisons using Bonferroni correction were used to compare the proportion of patients of concomitant psychiatric medication and resource use and costs between pre- and post-RLAI periods. Rapid and non-rapid cycling *stratification* was performed based on the number of change-in-mood episodes within 1 year prior to the index date.

Results: The mean annual dose of RLAI was 638.41 mg, which was equal to an average dose of 24.6 mg every 2 weeks. The prevalence of concomitant use of conventional antipsychotics, atypical antipsychotics, lithium, and antidepressants decreased from the pre-RLAI period to the post-RLAI period by 23.75%, 31.91%, 1.29%, and 7.08%, respectively. RLAI use decreased emergency room (ER) visits, hospital admissions, length of hospital stay, and non-medication costs (all $P < 0.0001$). The cost savings with RLAI were attributed to lower hospitalization costs in spite of higher medication costs. Moreover, rapid cycling patients ($n = 36$) demonstrated greater reduction in ER and inpatient services with RLAI than non-rapid cycling patients ($n = 251$).

Limitations: Of the patients who initiated RLAI, 15% of them who had regular treatment were included. Furthermore, data on measures of symptom severity, side effects, and *hyperprolactinemia* were not available.

Conclusion: BD patients had lower inpatient and ER utilization, and non-medication costs after using RLAI. In addition, RLAI use decreased the number of change-in-mood episodes in rapid cycling patients; which provides additional insights into the treatment of rapid cycling BD patients.

1. Introduction

Bipolar disorder is a severe, chronic, and often life-threatening illness (Anderson et al., 2012; Belmaker, 2004). Previous studies have shown that patients with bipolar disorder incur higher medical costs and vasculometabolic comorbidities than matched controls (Bai et al., 2013; Hsieh et al., 2012a, 2012b; Stensland et al., 2007; Swartz and Fagiolini, 2012; Tang et al., 2010). Currently, effective treatment includes antipsychotics, alone or in combination with mood stabilizers (Anderson et al., 2012; Belmaker, 2004; Grunze et al., 2013). However,

treatment adherence is a significant problem in patients with bipolar disorder; approximately half such patients are partially or completely nonadherent to recommended treatments, with poor adherence being one of the most common causes of relapse (Sajatovic et al., 2006). Long-acting injectable forms of atypical antipsychotics ensure transparency of medication delivery and could potentially improve adherence (Bond et al., 2007; El-Mallakh, 2007; Gigante et al., 2012; Littlejohn et al., 1994; Malempati et al., 2008; White et al., 1993). Risperidone long-acting injection (RLAI) is the first depot antipsychotic indicated for the treatment of bipolar disorder and is first-line treatment for maintenance

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therapy (Yatham et al., 2013). Randomized controlled trials have demonstrated that RLAI monotherapy or adjunctive therapy with lithium or divalproex can delay the time to the recurrence of mood episodes in affected patients (Macfadden et al., 2011, 2009; Vieta et al., 2012, 2008).

Rapid cycling bipolar disorder refers to the occurrence of four or more discrete mood episodes during a 1-year period. Rapid cycling patients have been reported to have more severe depressive symptoms, greater functional impairment, and poorer adherence to treatment, as well as a higher risk of suicide (Coryell, 2005; Gao et al., 2009; Lee et al., 2010; Schneck, 2006; Schneck et al., 2004). *Aside from limiting antidepressant exposure* (Pacchiarotti et al., 2013), compared with non-rapid cycling, there is no consensus on the optimal pharmacological management of rapid cycling and its association with poorer treatment response (Fountoulakis et al., 2013; Tondo et al., 2003). McFadden et al. (2009) administered a 52-week, double-blind, placebo-controlled study in frequently relapsing bipolar I disorder and randomized patients with adjunctive RLAI (25–50 mg every two weeks) plus treatment as usual (TAU) (n = 65) or switched to adjunctive placebo injection plus TAU (n = 59). It showed that adjunctive RLAI significantly delayed time to relapse in patients with bipolar disorder type I who relapse more than four mood episodes in the 12 months prior to study entry. *In addition*, Bobo et al. conducted a 12-month randomized open comparison of RLAI plus TAU versus TAU alone in 20 versus 25 rapid cycling patients; they reported that RLAI might reduce the need for urgent care (defined as psychiatric hospitalization, emergency room [ER] visit, or referral for respite care or intensive outpatient treatment due to worsening mood symptoms) and/or the frequency of medication adjustments to prevent relapse in patients with rapid cycling bipolar disorder (Bobo et al., 2011).

In March 1995, Taiwan launched a single-payer National Health Insurance (NHI) program. Since then, over 98% of Taiwan's 22.96 million population has been enrolled in this program (Institute.). Several studies on schizophrenia and major depressive disorders have been performed using the Taiwan NHI Research Database (NHIRD, 2015), which contains registration files and original claim data for reimbursement (Chang et al., 2012, 2009; Chen et al., 2014; Hsieh et al., 2012a, 2012b; Lin et al., 2014; Su et al., 2009; Tang et al., 2010; Wu et al., 2014, 2013a). Our previous studies showed that annual medical costs associated with relapses among patients with bipolar disorder were approximately 7.6 times the average per capita NHI expenditure in Taiwan and that bipolar disorder was associated with both poor medication adherence rates and frequent recurrences (Hsieh et al., 2012a, 2012b; Tang et al., 2010).

To understand real-world clinical practice, many mirror-image studies or analyses have been performed to evaluate the impact of long-acting injectable medication on patients with various psychiatric disorders (Born et al., 2009; Chang et al., 2012, 2009; Hayhurst et al., 2002; Niaz and Haddad, 2007; Nielsen et al., 2012; Serra et al., 2015; Su et al., 2009). Previous studies using mirror-image analysis assessed RLAI in the UK (Niaz and Haddad, 2007; Young and Taylor, 2006) and Taiwan (Chang et al., 2012, 2009; Su et al., 2009). However, most of the studies focused on schizophrenia, and none recruited patients with bipolar disorder alone. The objective of the present mirror-image study was to examine the characteristics of BD patients treated with RLAI, as well as *changes in their concomitant medication patterns*, resource use, and healthcare service costs using the national insurance claims data NHIRD in Taiwan.

2. Methods

2.1. Data sources

The data used were obtained from the NHIRD, covering the period from January 1, 2007 to December 31, 2012. The NHIRD, released by the National Health Research Institute (NHRI) for research purposes, is

a nationwide population-based claims database that contains comprehensive health care data for the more than 22 million enrollees of the Taiwan NHI program, representing approximately 98.4% of the Taiwan population (National Health Insurance Research Database).

The NHIRD provides comprehensive information on healthcare utilization, including enrollees' demographic data, primary and minor diagnosis codes, details of inpatient and ambulatory care orders (e.g., physician services, medications, medical materials and procedures, and ward care). The study was approved by the NHRI, and all the data were de-identified. Confidentiality assurances were addressed by abiding by data regulations of NHI Administration.

2.2. Study patients

This study was a mirror-image study with the study period defined as 1 year before RLAI initiation (the pre-RLAI period) and 1 year after RLAI initiation (the post-RLAI period). The inclusion criteria for the study are as follows:

- Patients diagnosed with bipolar disorder (ICD-9-CM code 296.xx) who have received at least one RLAI *during* 2007–2012.
- Patients whose date of initiation of RLAI, defined as the index date, occurred after January 1, 2008, or before December 31, 2011, to ensure complete observation during both the pre- and post-RLAI periods.

Patients who had diagnoses of ICD-9-CM codes 296.2 or 296.3 only during the mirror image study period were excluded to increase the validity of patients with bipolar disorder. To ensure that only patients with regular RLAI treatments were included in the study, those who did not receive at least one dose of RLAI every 3 months for 1 year after the index date were excluded. In addition, considering the impact of prolonged hospitalization on healthcare resource use, patients who were hospitalized for more than 90 days during the mirror-image study period were excluded. Consequently, 287 patients were eligible for inclusion in the study.

Patients were further classified as either rapid cycling or non-rapid cycling, according to the frequency of their change-in-mood episodes. Thirty-six patients were defined as rapid cycling because they had at least four change-in-mood episodes within 1 year before the index date. A change-in-mood episode was defined as any one of the following events:

- (i) medication pattern in outpatient visits for bipolar disorder treatment changed from either antipsychotics or antiepileptics to antidepressants or vice versa
- (ii) interval between a hospitalization or an ER visit and the next hospitalization or ER visit for treatment of bipolar disorder was longer than 60 days
- (iii) symptoms of bipolar disorder changed from mania/mix (ICD-9-CM codes 296.0, 296.1, 296.4, 296.6) to depression (ICD-9-CM codes 296.2, 296.3, 296.5, 300.4, 311) or vice versa.

The process of identifying study patients is outlined in Fig. 1.

2.3. Outcome measurement

First, changes in concomitant psychiatric medication, classified into the five drug categories of conventional antipsychotics, atypical antipsychotics, antiepileptics, lithium, and antidepressants, were also compared by drug category in terms of proportion of medication users within 1 year before and after the initial RLAI. *Second*, the frequency of outpatient and ER visits, admissions, and hospitalization days for bipolar disorder, and their associated service costs between the pre- and post-RLAI periods *were compared*. Service costs were further classified into medication and nonmedication costs. Nonmedication

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