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Research paper

Comparative effectiveness of long-acting injectable risperidone vs. long-acting injectable first-generation antipsychotics in bipolar disorder

Chi-Shin Wu [a,b], Ming H. Hsieh [a], Chao-Hsiun Tang [c], Ching-Jui Chang [a,d,e,*]

[a] Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan
[b] Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan
[c] School of Health Care Administration, Taipei Medical University, Taipei, Taiwan
[d] Department of Psychiatry, Cathay General Hospital, Taipei, Taiwan
[e] School of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan

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ABSTRACT

Objective: The aim of this study was to compare the treatment effectiveness between long-acting injectable risperidone and long-acting injectable first-generation antipsychotics among patients with bipolar disorder.
Method: We conducted a retrospective cohort study using Taiwan's National Health Insurance Research Database. Patients with bipolar disorder aged 15 years or higher, who were newly administered long-acting injectable antipsychotics between June 1, 2004 and December 31, 2011 were included. The clinical outcome indexes were hospitalization for any mood, manic/mixed, or depressive episodes. In addition, the all-cause discontinuation of long-acting injectable antipsychotic treatment was also assessed.
Results: A total of 3916 patients with bipolar disorder were extracted. Compared with risperidone, the use of first-generation antipsychotics was associated with a higher rate of hospitalization for any mood episode and major depressive episode. However, there was no statistically significant difference in treatment discontinuation rate between risperidone and first-generation antipsychotics.
Limitations: Information for the severity of mood symptoms, social support, life style, neurological and metabolic adverse effect was not available in this database. In addition, we only measured severe mood episodes with hospitalization as our outcome index. It may not be possible to generalize our findings to mild mood episodes.
Conclusions: Our findings suggested that patients treated with long-acting injectable risperidone might be superior to first-generation antipsychotics in the rate of psychiatric hospitalization.

1. Introduction

Bipolar disorder is a severe and chronic psychiatric disorder. In a worldwide mental health survey, the lifetime prevalence was 0.6% for bipolar I disorder, 0.4% for bipolar II disorder, 1.4% for subthreshold bipolar disorder, and 2.4% for the overall bipolar disorder spectrum (Merikangas et al., 2011). Patients with bipolar disorder suffer from recurrent mood episodes, especially depressive ones. Mood stabilizers and second-generation antipsychotics (SGAs) are standard pharmacological treatment of bipolar disorder. Use of SGAs increased markedly in this last decade. Most of SGAs are recommended in all guidelines for the treatment of acute and preventive manic episodes; quetiapine are also recommended for treatment of depressive episodes and their prophylaxis (Yatham et al., 2013). First-generation antipsychotics (FGAs) are only recommended in the acute treatment of manic episode (Yatham et al., 2013). However, even with medication treatment, the relapse rate is higher than 70% over 5 years (Coryell et al., 1995). Medication adherence is one of the important predictors for recurrent mood episodes (Suppes et al., 1991). Previous studies have shown that overall medication non-adherence ranges from 20% to 66% (Lingam and Scott, 2002). Patients with poor adherence had an increased risk of mood episodes and psychiatric hospitalization (Scott and Pope, 2002).

Long-acting injectable (LAI) antipsychotics could improve medication adherence (El-Mallakh, 2007; Vieta et al., 2008), with a

* Corresponding author at: Department of Psychiatry, Cathay General Hospital, 280 Renai Rd. Sec.4, Taipei, Taiwan.
E-mail address: ccj061@gmail.com (C.-J. Chang).

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growing body of evidence demonstrating their effectiveness in the treatment of schizophrenia (Kishimoto et al., 2013; Mauri et al., 2009). Currently, only LAI risperidone is approved for the maintenance-treatment of bipolar disorder in some countries, including United State, Taiwan, and most European countries. Three randomized, double-blind, and placebo-controlled studies have demonstrated that LAI risperidone could prevent relapse of mood episodes in stable bipolar I patients (Macfadden et al., 2009; Quiroz et al., 2010; Vieta et al., 2012). LAI aripiprazole and LAI olanzapine are approved in the United States for schizophrenia, but have not been studied in bipolar disorder in controlled trials. In addition, LAI paliperidone is approved in the US for schizophrenia and schizoaffective disorder, but not bipolar disorder. Indeed, any formulation of paliperidone lacks any bipolar indication in the US, despite having been assessed in multiple controlled trials (Berwaerts et al., 2011, 2012a, 2012b; Vieta et al., 2010).

The effectiveness of LAI FGAs in the treatment of bipolar disorder was rarely investigated. Lowe and Batchelor reported treating 12 patients with bipolar disorder using depot haloperidol for 23 months (Lowe and Batchelor, 1986). Four patients dropped out during the study period because of adverse effects (n=2) or relapse (n=2). The remaining patients did not have manic relapses during depot therapy. Ahlfors et al. (1981) conducted two studies to assess the effect of depot flupentixol on bipolar disorder. The first study consisted of a small-scale randomized, active-comparator trial. The authors found that the mean number of mood episodes did not differ between lithium and depot flupentixol-treated groups. The second study was an open label trial in patients who had switched to depot flupentixol due to the adverse or unsatisfactory prophylactic effects of lithium. The results showed a reduction in the number of manic episodes; however, the number of depressive episodes and the time ill with depression increased after switching to depot flupentixol. Esparon et al. conducted a double-blind, placebo-controlled, crossover trial and found that there was no difference in the length of hospitalization between the placebo and depot flupentixol groups (Esparon et al., 1986). Currently, LAI FGAs are not recommended for the maintenance treatment of bipolar disorder due to little evidence (Llorca et al., 2013). However, LAI FGAs are still frequently used for treating bipolar disorder. The effectiveness and therapeutic profile of LAI FGAs for maintenance treatment of bipolar disorder remain unclear.

To the best of our knowledge, there is no study comparing the effectiveness of LAI risperidone with LAI FGAs in patients with bipolar disorders. Therefore, we explored the comparative effectiveness of LAI FGAs vs. LAI risperidone in such patients.

2. Methods

2.1. Data source

This retrospective cohort study utilized the National Health Insurance Research Database (NHIRD), which is derived from the reimbursement claims submitted to the National Health Insurance program in Taiwan. The National Health Insurance program is a single-payer and compulsory health insurance program launched in 1995. Approximately 98% of the 23 million inhabitants in Taiwan are included. The NHIRD includes demographic characteristics, clinical diagnoses, and prescription records in outpatient and inpatient care claims. The database has been used for pharmacoepidemiological studies and research for psychiatric disorders, including bipolar disorder (Wu et al., 2015).

2.2. Study population

LAI risperidone was introduced in Taiwan in June 1, 2004; therefore, we set this date as the starting point for this study. There are five LAI FGAs available in Taiwan: clopentixol, flupentixol, fluphenazine, haloperidol, and zuclopentixol during the study period. We identified all patients with bipolar disorder (ICD-9-CM code: 296.0, 296.1, 296.4-296.9) newly initiated on LAI antipsychotic drugs in outpatient settings between June 1, 2004 and December 31, 2011 (n=8268). The index date was defined as the date of the first LAI antipsychotic prescription. These new LAI users were to be free from any LAI prescription records in the one-year period prior to the index date. We excluded patients having recorded diagnoses with both schizophrenia and bipolar disorder (n=4317). We further excluded those aged less than 15 years (n=24) and those using multiple LAIs on the index date (n=11). Ultimately, 3916 patients were extracted in this study. Patients were classified into risperidone or FGAs group based on the first LAI prescribed. We further categorized LAI FGAs into clopentixol, flupentixol, fluphenazine, haloperidol, and zuclopentixol. Clopentixol and zuclopentixol were collapsed into a clopentixol/zuclopentixol group due to small patient numbers and similar pharmacological profile.

2.3. Outcome

The primary outcome was time to psychiatric hospitalization for any mood episodes. We defined psychiatric hospitalization for any mood disorder as an admission to psychiatric hospitals or the department of psychiatry in a general hospital with a diagnosis of any mood episode (ICD-9-CM code: 296.x). We further categorized psychiatric hospitalization into manic/mixed episodes (ICD-9-CM code: 296.0, 296.1, 296.4, or 296.6), major depressive episodes (ICD-9-CM code: 296.2, 296.3, or 296.5), and unspecific mood episodes (ICD-9-CM code: 296.7, 296.8, or 296.9). Only the first hospitalization after LAI antipsychotic use were included.

In addition, treatment discontinuation with LAI antipsychotics were also assessed. Given the reasons for treatment discontinuation, such as ineffectiveness, adverse effects, physician's evaluation, or patient's options were not available, only all-cause discontinuation were included in our analysis. Each LAI antipsychotic exhibits a different pharmacokinetic profile. Therefore, the treatment intervals were pre-specified as follows: 14 days for risperidone; 21 days for flupentixol, fluphenazine, clopentixol, and zuclopentixol; and 28 days for haloperidol (Gigante et al., 2012; Taylor, 2009). We defined treatment discontinuation as the occurrence of a gap period of more than 30 days between the expected date of next LAI prescription (the prescription date plus pre-specified treatment interval of index drug) and the actual date of the next prescription.

2.4. Potential confounding factors

Several potential confounding factors that might be associated with the clinical outcome and choice of LAIs were assessed. Patients' demographic variables included age on the index date, gender, and the calendar year of index date. To assess the severity and complexity of bipolar disorder, we used multiple proxy measures, including index mood episode (manic/mixed, major depressive, or unspecified mood episode on the index date) and concomitant psychotropic treatment (oral antipsychotics, antidepressants, and mood stabilizers [lithium, valproic acid, carbamazepine, and lamotrigine]). Based on the claims records in the year preceding the index date, we assessed patients' psychiatric comorbidity (alcohol use disorder, substance use disorder, anxiety disorder, and sleep disorder), the length of psychiatric