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Comparison of treatment effectiveness and medical costs for different long-acting injectable antipsychotics in patients with schizophrenia in Taiwan: A nationwide population-based cohort study

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ABSTRACT

Objective: To assess the comparative effectiveness and medical costs of five long-acting injectable (LAI) antipsychotics, flupentixol, fluphenazine, haloperidol, risperidone, and clopentixol/zuclopentixol, in patients with schizophrenia.
Method: We conducted a retrospective cohort study of patients with schizophrenia using data from Taiwan's National Health Insurance Research Database. Patients aged 15 years or older who began treatment with LAI antipsychotics between June 1, 2004 and December 31, 2008 were enrolled and followed for 1 year. We evaluated the medical costs and treatment effectiveness, which was assessed using the rates of treatment discontinuation, psychiatric hospitalization, and emergency department visits. Risperidone was used as a reference group.
Results: Compared to risperidone, flupentixol was associated with higher hazard ratios of treatment discontinuation and psychiatric hospitalization, fluphenazine was associated with higher hazard ratios of treatment discontinuation, and haloperidol was associated with higher rates of psychiatric hospitalization and emergence department visits. However, fluphenazine, flupentixol, and haloperidol were associated with lower medical costs compared to risperidone. Clopentixol/zuclopentixol was inferior to risperidone in treatment effectiveness and medical cost.
Conclusions: Our findings suggest that patients taking the LAI risperidone may be more effective in some but not all outcome measures; however, risperidone was also associated with higher medical costs in the Taiwanese healthcare setting.

1. Introduction

Schizophrenia is a chronic and severe psychiatric disorder. Antipsychotic medications can reduce psychotic symptoms and prevent relapse. Medication adherence plays a key role in treatment effectiveness, and previous studies have shown that nonadherence increases the risk of hospitalization and loss of function (Keith and Kane, 2003; Robinson et al., 1999). However, nonadherence is quite common; approximately 40% of patients with schizophrenia exhibit inconsistent medication adherence (Lacro et al., 2002). Long-acting injectable (LAI) antipsychotics could eliminate the need for daily doses of medication, resulting in improvements in treatment adherence and a decrease in hospitalization rates (Remington and Adams, 1995; Weiden et al., 2009). Despite that whether LAI antipsychotics were superior to oral antipsychotics remained inconclusive (Kishimoto et al., 2013b; Rosenheck et al., 2011), several treatment guidelines recommended that clinicians should consider LAI antipsychotics as a treatment of choice for patients who are noncompliant with orally administered medication (Hasan et al., 2012; Lehman et al., 2004).

Various LAI antipsychotics exist, and each differs in their individual pharmacokinetic and pharmacodynamic profile (Haddad and Sharma, 2007). The LAI risperidone was one of the first long-acting formulations of second-generation antipsychotics (SGAs), providing an alternative to depot first-generation antipsychotics (FGAs). Concerns have been raised regarding FGAs due to the related tardive dyskinesia and extrapyramidal symptoms. SGAs typically produce fewer adverse neurological effects, hence their use has increased, and they are currently favored over FGAs (Wu et al., 2012). In addition, SGAs have been associated with better medication compliance (Chang et al., 2012). However, a growing body of evidence shows SGAs carry higher metabolic adverse effects than FGAs (Leucht et al., 2009). It is also unclear whether SGAs are more effective than FGAs at treating the symptoms of schizophrenia (Kishimoto et al., 2013a; Lieberman et al., 2005). Furthermore, little is known about the comparative effectiveness of different LAI antipsychotics.

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This retrospective cohort study aimed to assess the effectiveness of different LAI antipsychotics. Data were collected from a large, nationwide cohort of patients with schizophrenia who recently began taking LAI antipsychotics in an outpatient setting. Treatment discontinuations, psychiatric hospitalizations, emergency department (ED), and direct medical costs visits were evaluated for all patients.

2. Materials and methods

2.1. Data source

The National Health Insurance Research Database (NHIRD), a database containing health information from approximately 22.6 million Taiwanese people (98% of the population) as of 2007, was used. The NHRID contains information about demographics, diagnoses, prescriptions, hospitalizations, and medical costs. The database has previously been used for pharmacoepidemiological research on several diseases, including schizophrenia (Wu et al., 2012). This study was approved by the Research Ethics Review Committee of Far Eastern Memorial Hospital. Given that information that could be used to identify beneficiaries and medical care providers is anonymized, the requirement for obtaining informed consent was waived.

2.2. Study population

We identified patients aged 15 years or older who initiated LAI antipsychotic treatment in an outpatient setting between June 1, 2004 and December 31, 2008. The start-date for this study was chosen because LAI risperidone was first introduced in Taiwan on June 1, 2004. During this period, there were five LAI FGAs (clopentixol, flupentixol, fluphenazine, haloperidol, and zuclopentixol) and one LAI SGAs (risperidone) marketed in Taiwan. To establish an incident user cohort, only patients who newly initiated LAI antipsychotic treatment in an outpatient setting were considered (n = 21.133). None of the included patients had been administered an LAI antipsychotic for at least 1 year prior. The index date was defined as the initial date of LAI antipsychotic prescription. We included patients with schizophrenia-spectrum disorder diagnoses, including various subtypes of schizophrenia (ICD-9 CM code: 295.0–295.3, 295.6, 295.8, and 295.9), schizophreniform disorder (ICD-9 CM code: 294.4), latent schizophrenia (ICD-9 CM code: 294.5), and schizoaffective disorder (ICD-9 CM code: 294.7). Those without schizophrenia-spectrum disorders in ambulatory or inpatient claims before the index date were excluded from this study (n = 4886). The exact date and duration of LAI antipsychotic treatment was not available for inpatient claims records; therefore, 3097 patients who started LAI antipsychotics while hospitalized were excluded. Patients younger than 15 years of age (n = 34), whose gender was not known (n = 5), and who were prescribed two or more LAI antipsychotics (n = 41) were also excluded. In total, 13,060 patients with schizophrenia-spectrum disorder were included in our study.

2.3. Effectiveness measures

We evaluated the association between LAI antipsychotics and treatment effectiveness, including the rate of all-cause treatment discontinuation, psychiatric hospitalization, and emergence department (ED) visits.

As the pharmacokinetic profiles of different LAI antipsychotics vary, the durations of effect were defined as follows: 14 days for risperidone; 21 days for flupentixol, fluphenazine, clopentixol, and zuclopentixol; and 28 days for haloperidol. The allowable gap between the end of effect of one LAI antipsychotic and the next LAI antipsychotic prescription was prespecified as 30 days. All-cause treatment discontinuation was defined as the period between LAI antipsychotic prescriptions that exceeded the allowable gap.

Psychiatric hospitalization was defined as admission of a patient to a psychiatric hospital or a general hospital's department of psychiatry. A psychiatric ED visit was defined as a visit of the patient to the ED of a psychiatric hospital, or a general hospital, with a recorded diagnosis of schizophrenia. The first psychiatric hospitalizations or ED visits after the index date were the study endpoints in the analysis.

2.4. Cost measures

Total medical costs were calculated from the actual claims records during the first year after initiation of the LAI antipsychotic treatment, regardless of whether the patient discontinued treatment. Total medical costs included those of hospitalization, health-care professional consultation, medications, laboratory tests, imaging, surgery, and medical procedures in both psychiatric and non-psychiatric setting. We divided total medical costs into psychiatric and non-psychiatric costs. Psychiatric costs were further divided into outpatient, inpatient, and ED costs. All costs were reported in New Taiwan dollars (NT$) and the exchange rate of the NT$ against the US dollar was 31.54 in 2008.

2.5. Patient characteristics and potential confounders

Demographic variables, including age at index date, gender, and year of index date, were assessed. Clinical variables were assessed 1 year prior to the index date. Comorbid psychiatric conditions included mood disorders (ICD-9-CM: 296.2, 296.3, 300.4, and 311.x), anxiety disorders (ICD-9-CM: 300.x except 300.4), sleep disorders (ICD-9-CM: 307.4 and 780.5), alcohol abuse (ICD-9-CM: 291.x, 303.x, 305.0, 357.5, 425.5, 535.3, 571.0, 571.1, 571.2, and 571.3), and substance abuse (ICD-9-CM: 292.x, 304.x, 305.2–305.9). Use of concomitant psychotropic agents, including oral antipsychotics, antidepressants, mood stabilizers, and anxiolytic or hypnotic medications, was noted. Medication adherence before the index date was measured using the medication possession ratio, which was calculated using the ratio of the cumulative duration of oral antipsychotic use in the year prior to the index date to 365 days. Comorbid medical conditions included hypertension (ICD-9-CM: 401–405), diabetes mellitus (ICD-9-CM: 250), and dyslipidemia (ICD-9-CM: 272). A Charlson comorbidity index score was calculated using the sum of the weighted scores of 19 comorbid conditions; this was used to control for potential confounding factors (Deyo et al., 1992). Psychiatric service utilization measures included the number of outpatient visits, hospitalizations, and ED visits in the preceding year.

2.6. Statistical analysis

Patients were classified into groups according to the specific LAI antipsychotic drug that was prescribed at the index date. Clopentixol and zuclopentixol were collapsed into a clopentixol/zuclopentixol group due to small patient numbers and similar pharmacological profile. We used a “first exposure carried forward” analysis, analogous to intent-to-treat in clinical trial, to reduce potential bias due to informative switching or discontinuation. Patients were followed-up for 365 days, or until the study end point, whichever occurred first. Kaplan–Meier event-free survival curves were used to compare the following outcomes: treatment discontinuations, hospitalizations, and ED visits. Cox proportional hazards regression models were used to estimate the treatment effectiveness of antipsychotics. We included all patient characteristics and potential confounders in an exposure propensity score to control for indication bias without variable selection (Cepeda et al., 2003). The propensity score of each antipsychotic drug was calculated pairwise against risperidone, the reference drug. We used inverse probability weighting, based on estimated exposure propensity scores, to balance differences between antipsychotic drugs in our primary analysis (Curtis et al., 2007). In brief, patients with a high probability (propensity score) of a given antipsychotics would receive a lower weight (inverse propensity score), compared with those with a low probability.

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