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Comparison of the effectiveness of brand-name and generic antipsychotic drugs for treating patients with schizophrenia in Taiwan

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ABSTRACT

The purpose of this nationwide population-based study is to compare the long-term effectiveness of brand-name antipsychotics with generic antipsychotics for treating schizophrenia. We identified patients with schizophrenia who were prescribed antipsychotics from a random sample of one million records from Taiwan's National Health Insurance database, observed between January 1, 2000 and December 31, 2012. Only those with no prior use of antipsychotics for at least 180 days were included. We selected patients who were prescribed brand-name risperidone (N = 404), generic risperidone (N = 145), brand-name sulpiride (N = 334), or generic sulpiride (N = 991). The effectiveness of the treatments researched in this study consisted of average daily doses, rates of treatment discontinuation, augmentation therapy, and psychiatric hospitalization. We found that compared to patients treated with generic risperidone, those treated with brand-name risperidone required lower daily doses (2.14 mg vs. 2.61 mg). However, the two groups demonstrated similar rates of treatment discontinuation, augmentation, and psychiatric hospitalization. On the other hand, in comparison with patients prescribed generic sulpiride, those treated with brand-name sulpiride not only required lower daily doses (302.72 mg vs. 340.71 mg) but also had lower psychiatric admission rates (adjusted hazard ratio: 0.24, 95% confidence interval: 0.10–0.56). In conclusion, for both risperidone and sulpiride, higher daily doses of the respective generic drugs were prescribed than with brand-name drugs in clinical settings. Furthermore, the brand-name sulpiride is more effective at preventing patients from hospitalization than generic sulpiride. These findings can serve as an important reference for clinical practices and healthcare economics for treating schizophrenic patients.

1. Introduction

Schizophrenia is a serious mental disorder, and schizophrenic patients often require inpatient treatment when the acute disease is exacerbated (van Os and Kapur, 2009). Patients with schizophrenia are often treated using antipsychotic drugs (De Oliveira and Juruena, 2006), which are usually classified as either first or second generation antipsychotics (Meltzer et al., 1989). Continuous antipsychotic treatment can successfully improve patients' psychotic symptoms and prevent them from relapse (Harvey and Keefe, 2001; Leucht et al., 2009; Lieberman et al., 2005; Masi and Liboni, 2011). Once the patents of the original antipsychotic compounds expired, corresponding generic formulations entered the market as competing prescription options (Borgheini, 2003). Therefore, understanding the long-term treatment effectiveness of both generic drugs and their original compounds for schizophrenic patients is crucial for clinical practice and health-care economics.

Currently, several studies have measured blood concentration and hemodynamics between brand-name and generic antipsychotics (Boonleang et al., 2010; Chen et al., 1989; Elshafeey et al., 2009; Khorana et al., 2011; Liu et al., 2013; Mahatthanatrakul et al., 2008; van Os et al., 2007) and have generally demonstrated that generic drugs exhibit bioequivalence, similar tolerability, and comparable safety profiles with the original compound (brand-name drugs) (Frank, 2007; Gyorgy et al., 2008). However, these studies have small sample sizes, and the study populations were restricted to healthy subjects. Therefore, the results of such pharmacodynamics or pharmacokinetic studies may not be applicable to the field of clinical practice (Desmarais et al., 2011). In clinical studies, the findings related to potential differences in treatment effects between brand-name and generic antipsychotics

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have been mixed. Regarding second generation antipsychotic drugs, some studies have reported that generic clozapine had similar efficacy and safety profiles with generic clozapine, but the daily doses of generic clozapine were generally higher than the brand-name drug (Bobo et al., 2010; Healy et al., 2005; Italiano et al., 2015; Oluboka et al., 2010; Paton, 2006). (Gyorgy et al., 2008) indicated that both generic and original quetiapine demonstrated therapeutic equivalence. One study of New Zealand's Pharmaceutical Management Agency records found that for patients switching from brand-name to generic olanzapine, their clinical outcomes did not worsen (Lessing et al., 2015). However, switching from brand-name to generic risperidone has been reported to be associated with a loss of efficacy or the occurrence of side effects (Hardan et al., 2010). With regard to first generation antipsychotics, (Verster et al., 1998) observed no significant differences in the symptom changes between schizophrenia patients treated with brand-name and generic fluphenazine decanoate. Although manufacturers claim that generic drugs generate savings with regard to medical expenditures (Haas et al., 2005), whether generic antipsychotics provide long-term effectiveness equivalent with the brand-name drugs in the real world remains unclear.

To fill the research gap, we used a claims database consisting of a representative nationwide sample to determine the long-term treatment outcomes of schizophrenic patients. The aim of this retrospective cohort study was to compare the effectiveness of generic antipsychotics and their original compounds (brand-name drug), using average daily doses, rates of treatment discontinuation, augmentation therapy, and psychiatric hospitalization as indicators of clinical effectiveness.

2. Methods

2.1. Data source

Data for this study were obtained from the ambulatory claims database of the National Health Insurance Research Database (NHIRD). NHIRD comprises the reimbursement medical claims of the National Health Insurance (NHI) program in Taiwan, which started on March 1, 1995. The Bureau of NHI is the sole payer for healthcare services under the NHI program and covers 93% of all of Taiwan's healthcare providers. Participating medical care institutions are required to electronically submit monthly claim documents related to medical expenses by the 20th day of the following month. Such documents include such information as patient demographic data, diagnostic codes, medical institutions visited, dates of prescriptions, drugs prescribed, and claimed medical expenses. Individual and hospital identifiers are unique to the NHIRD and cannot be used to trace individual patients or medical care institutions. The reliability of diagnostic codes in the NHIRD has been proven by a previous study (Multhoff et al., 2014). The protocol for this study conformed to the Helsinki Declaration, and was approved by the Institutional Review Board (IRB) of Chang Gung Memorial Hospital (IRB No: 103-0637B). Patient records/information was anonymized and de-identified prior to analysis, and the need for written informed consent was waived by the IRB.

2.2. Study subjects

We included all patients in the NHIRD who had been diagnosed with schizophrenia-spectrum disorder and were prescribed at least one dose of antipsychotic drug between January 1, 2000 and December 31, 2012. A patient with schizophrenia-spectrum disorder was defined as a patient with at least one inpatient or outpatient record pursuant to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 295.x. After excluding patients whose gender was not recorded (N = 24), our study sample consisted of 9651 patients. The prescription of antipsychotic drugs whose brand-name and generic forms are both available in Taiwan was traced from NHI claim records, including amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and sulpiride.

The remaining patients were classified according to the antipsychotic agent that was prescribed to them as of the index date. To eliminate the confounding effect of drug interactions, we established the following exclusion criteria: (1) patients who had been prescribed another antipsychotic agent within 180 days before using the selected antipsychotic; (2) the observation period after the initial prescription of the selected antipsychotic was <180 days; (3) patients aged <18 years or ≥65 years at the index date of the selected antipsychotic prescription; (4) patients who were prescribed more than one antipsychotic agent at the index date; (5) patients who had used the long-acting injectable form of risperidone (only the brand-name drug but no generic drug with a long-acting injectable form was available in Taiwan); and (6) patients who were first prescribed risperidone prior to June 01, 2004 (the time at which the first generic risperidone appeared on the market in Taiwan).

Using the aforementioned selection criteria, the case numbers of patients who had been prescribed at least one dose of antipsychotic drug with brand-name and generic forms are provided in the Supplementary Table 1. We found that patients treated with risperidone (N = 727) and sulpiride (N = 1916) were sufficient for comparing the effectiveness between the brand-name and generic drugs. Of the selected patients, 178 received both brand-name and generic risperidone prescriptions, and 591 patients received both brand-name and generic sulpiride prescriptions. To eliminate the cross-over effect and the confounding effect of the disease's course (e.g., most patients with mixed drug use were initially prescribed a brand-name drug and were subsequently switched to a generic drug), we excluded patients with mixed drug use. We ultimately obtained 404 patients who only used brand-name risperidone (risperidone-B group) and 145 patients who only used generic risperidone (risperidone-G group), 334 patients who only used brand-name sulpiride (sulpiride-B group), and 991 patients who only used generic sulpiride (sulpiride-G group) for further analysis. Fig. 1 is a flow chart of the detailed patient selection procedure.

2.3. Demographics and comorbidities

In addition to age and gender, we listed the year of initial use of the selected antipsychotic agent, employed the Charlson Comorbidity Index (CCI) before the initial use of the selected drug to determine general health status (Deyo et al., 1992), and evaluated the comorbidity of psychiatric disorders before initial use of the selected medication. The CCI was calculated using diagnostic codes from outpatient records and discharge codes from hospitalization records, a method that is widely used for confounders in epidemiological research (Schneeweiss et al., 2001). The psychiatric comorbidities were defined as any ICD-9-CM from the same medical records and include alcohol use disorders (ICD-9-CM: 291.x, 303.x, 305.0, 357.5, 425.5, 535.3, and 571.0–571.3), substance use disorders (ICD-9-CM: 292.x, 304.x, and 305.2–305.9), mood disorders (ICD-9-CM: 296.2, 296.3, 300.4, and 311.x), anxiety disorders (ICD-9-CM: 300.x except 300.4), and sleep disorders (ICD-9-CM: 307.4 and 780.5).

2.4. Outcome variables

In this study, the outcome measures of treatment effectiveness were average daily dose, medication discontinuation, augmentation therapy with another antipsychotic drug, and psychiatric hospitalization. All subjects were observed from the index date (on which the selected antipsychotic was initially prescribed) to the discontinuation date or December 31, 2012. The average daily dose was defined as the dose of antipsychotic on the day of medication discontinuation or the end of follow-up. Medication discontinuation was defined as cessation of risperidone-B, risperidone-G, sulpiride-B, or sulpiride-G for 60 days or longer. We defined augmentation therapy as when a patient treated with

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