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Research paper

Change in 1-year hospitalization of overall and older patients with major depressive disorder after second-generation antipsychotics augmentation treatment

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ABSTRACT

Background: Studies on second-generation antipsychotics (SGA) augmentation treatment for older adults with major depressive disorder (MDD) remain limited. We aimed to investigate the effectiveness of SGA augmentation for overall and older patients with MDD inpatient history by assessing the change in 1-year hospitalization before and after SGA augmentation using the latest National Health Insurance Research Database (NHIRD) in Taiwan.

Methods: The samples were MDD patients (ICD-9 CM code: 296.2 and 296.3) who had psychiatric inpatient history. A total of 2602 MDD patients including 430 elderly subjects (age ≥ 60 years) who received SGA augmentation for 8 weeks between January 1998 and December 2012 were included in this 1-year mirror-image study. Outcome measures included number and length of psychiatric and all-cause hospitalizations.

Results: After 8-week continuous SGA augmentation in the study subjects, the total number and days of psychiatric hospitalizations among overall patients reduced by 33.57% ($p < .0001$) and 18.24% ($p < .0001$), respectively; the total number and days of psychiatric hospitalizations among older patients (age ≥ 60) reduced by 44.52% ($p < .0001$) and 27.95% ($p < .0001$), respectively. Similarly, the total number and days of all-cause hospitalizations were significantly reduced.

Limitations: MDD patients without inpatient history were not included due to data limitation; hence, the results may not be generalized to all patients.

Conclusions: The results support that SGA may be effective in reducing psychiatric and all-cause hospitalization among overall and elderly MDD patients. More studies focusing on the safety of SGA among older MDD patients is warranted.

1. Introduction

Major depressive disorder (MDD), the most striking psychiatric disease with a high rate of treatment resistance, burdens the individuals, families, and society (Kasper and Montgomery, 2013, Kessler et al., 2003, Rush et al., 2006). Clinical trials (Bauer et al., 2009, Berman et al., 2009, 2007, Mahmoud et al., 2007, McIntyre et al., 2007, Rapaport et al., 2006) have revealed that antidepressants augmented with second-generation antipsychotics (SGA) result in better treatment responses for difficult-to-treat MDD patients (Komossa et al., 2010, Nelson and Papakostas, 2009). Our previous population-based study (Lin et al., 2014) revealed that use of key psychiatric services due to MDD was reduced after SGA augmentation. The subjects were MDD patients with psychiatric inpatient history before 2008, and patients with new onset inpatient history after January 1, 2008 were not included due to data limitation (Lin et al., 2014). With SGA augmentation in MDD becoming an alternative treatment option, patients with inpatient history after 2008 merit investigation when the updated database is available.

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Importantly, MDD is common across an individual's life span. In older population with MDD, comorbid conditions account for a major portion of disability (Greenberg et al., 2015). Although treatment of MDD often includes use of multiple medications (Nelson and Papakostas, 2009, Rush et al., 2006), pharmacotherapy for older adults with MDD requires careful consideration (Steffens et al., 2011). While older patients bring unique challenges, evidence for effectiveness of SGA augmentation treatment is more limited among the elderly than in the general population (Alexopoulos et al., 2008, Lenze et al., 2015, MacQueen et al., 2016, Steffens et al., 2011). Thus, analysis on health service utilization among older patients would provide clinicians with more information on the benefits and risks of SGA augmentation in this population.

Hospitalization can serve as a valid outcome indicator (Wingård et al., 2017) because it indicates relapse of severe symptoms and functional impairment of MDD patients, while shorter length of hospitalization represents better treatment response of the illness. In this 1-year mirror image study, MDD patients with continuous SGA augmentation for 8 weeks were identified for assessing the change of hospitalization service utilization before and after SGA augmentation treatment.

2. Methods

2.1. Data source

In Taiwan, 99% of the entire population is enrolled in the National Health Insurance (NHI) program which covers all illness (National Health Insurance Adminstration, 2017). The National Health Insurance Research Database (NHIRD) contains healthcare data from the NHI program and has been successfully used for pharmaco-epidemiological research and studies on psychiatric disorders (Hsu et al., 2017, Lin et al., 2013, 2016). The sample in this study was derived from the NHIRD and included 266,328 patients who received inpatient psychiatric service from January 1, 1996 to December 31, 2013. Demographic data and both psychiatric and all-cause inpatient and outpatient health care utilization information including diagnostic codes, as well as details of procedures, surgeries and pharmacy records of the enrolled patients from January 1, 1996 to December 31, 2013 were collected and analyzed.

2.2. Study subjects

Ethical approval was obtained from the Institutional Review Board of Tsaotun Psychiatric Center for this study. The flowchart of study sample selection is shown in Fig. 1. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes of the diseases and the medicines analyzed in the study are shown in Supplementary Table 1 and Supplementary Table 2, respectively. The MDD subjects were assessed according to ICD-9 CM records. A total of 58,539 patients whose initial hospitalization to a psychiatric ward with the diagnosis of MDD (ICD9-CM code 296.2 or 296.3) occurred between January 1, 1996 and December 31, 2013 were identified. In addition, for ascertaining the diagnostic stability of unipolar depression (Lin et al., 2014, Sadock and Sadock, 2003), 19,393 patients with records of psychiatric inpatient stays with a diagnosis of MDD (ICD9-CM code 296.2 or 296.3) were identified.

The claims for prescription drugs were employed to confirm the use of antidepressants, SGA, and other medicines. According to previous clinical trials (Komossa et al., 2010, Nelson and Papakostas, 2009) with a mean treatment duration of 8 weeks, the subjects were MDD patients in Taiwan who received antidepressants plus SGA, including amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone, or zotepine, continuously for at least 8 weeks. The index date was the day when the subjects started SGA augmentation. For accurate calculation of outcome measures, patients who could not be observed for service utilization of an entire year before and after the index date were further excluded. Thus, the present study comprised a final sample of 2602 MDD patients, among which 430 were elderly subjects (age ≥ 60) (Fig. 1).

2.3. Outcome measures

This study used a mirror-image study design to compare number and length of psychiatric and all-cause hospitalizations before and after SGA augmentation treatment (pre- and post-SGA periods) among 2602 MDD patients. The number and length of hospitalizations were measured using inpatient records in NHIRD. If a patient was readmitted to the same hospital or transferred to another hospital within 3 days with the same diagnosis, the subsequent admission was counted as part of the previous hospitalization. In addition to measuring hospitalization service utilization, changes in concomitant treatment after SGA augmentation were compared.

2.4. Ascertainment of other variables

The demographic and clinical information of the study subjects including age, gender, comorbidities that frequently influence the outcome of MDD, antidepressant treatments, and other augmentation treatments were analyzed (American Psychiatric Association, 2010, Kornstein and Schneider, 2001). Physical comorbidities included neurologic disorders, cardiac diseases, endocrine disorders, and chronic liver disorders. Psychiatric comorbidities included anxiety, dysthymia and alcohol/substance uses. The comorbidity was coded as one if it appeared in the inpatient register once or in the outpatient register 3 times prior to the index day. Uses of antidepressants, first-generation antipsychotics (FGA), lithium, anticonvulsants, stimulant, thyroid hormone, or electroconvulsive therapy (ECT) were defined on the basis of at least one dispensation for a year prior to the index date. Antidepressant dosages were converted into imipramine-equivalent milligrams (Bollini et al., 1999) and antipsychotics dosages were converted into chlorpromazine-equivalent milligrams (Gardner et al., 2010).

2.5. Statistical analysis

The data were expressed as mean (± standard deviation) for continuous variables and frequency (%) for categorical data. Chi-square test or independent t-test was employed to test the differences between patients with continuous SGA treatment and those never treated with any SGA. Since data of inpatient service utilization are usually non-normal distributed and skewed, Wilcoxon sign-rank test was utilized to assess the differences including number and length of hospitalizations between pre- and post-SGA period of the subjects in the 1-year mirror-image study. McNemar's test was employed to compare the 1-year difference of concomitant treatments beyond SGA including FGA, lithium, anticonvulsants, stimulant, thyroid hormone and ECT (Nielsen et al., 2012).

All analyses were performed using the SAS system (version 9.2; SAS Institute, Cary, NC) and the STATA 11th edition (Stata Corporation, College Station, TX, USA) and $p < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

For overall patients and those older than 60 y/o, the number of patients who received SGA had grown steadily by year (Nelson and Papakostas, 2009, Papakostas et al., 2007), revealing a trend of increasing usage of SGA (Supplementary Table 3). Quetiapine (n = 1461), risperidone (n = 350), aripiprazole (n = 264) and olanzapine (n = 237) are the leading SGA administered to MDD patients with