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Association between antipsychotic drug use and cataracts in patients with bipolar disorder: A population-based, nested case-control study

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ABSTRACT

Background: No previous study has focused on the association between use of antipsychotic drugs and the development of cataracts in patients with bipolar disorder (BD); hence, we aimed to examine this association in the present study.

Methods: We conducted a retrospective nested case-control study using data from the National Health Insurance Database of Taiwan between 2000 and 2011. A total of 3292 BD patients, 1684 with cataracts and 1608 controls matched for age, sex, and index date, were included. Antipsychotic drug exposure was categorized by type of drug and duration of use. A conditional logistic regression analysis was used to analyze the association.

Results: Among BD patients, we found significantly reduced odds ratio (OR) of cataract development among past (adjusted OR (AOR), 0.74; 95% confidence interval (CI), 0.62–0.89; p=0.001) and continuous users (AOR, 0.71; 95% CI, 0.59–0.85; p < 0.001) of atypical antipsychotics. No association was found between the odds of cataract development and typical antipsychotics. Besides, concomitant use of antidepressants (AOR, 1.23; 95% CI, 1.06–1.43; p=0.007) and mood stabilizers (AOR, 1.23; 95% CI, 1.06–1.42; p=0.007) were associated with increased odds of cataract development.

Limitations: Some important contributors to cataract development such as family history of cataract, smoking and alcohol exposure could not be measured from the claims data and this may confound the results.

Conclusions: Reduced odds of cataract were found in patients with BD taking atypical antipsychotics. However, given that BD patients often have risk factors for developing cataract, regular ocular evaluations are recommended for those treated with antipsychotics drugs.

1. Introduction

Bipolar disorder (BD) is a chronic illness characterized primarily by manic, hypomanic, and depressive mood episodes (American Psychiatric Association, 2013a). Diagnostic and statistical manual of mental disorders (5th ed.). Arlington). The life time prevalence is approximately 1% globally (Yatham et al., 2013). Due to high rates of hospitalization, suicide, and comorbidity, it is one of the most disabling illnesses worldwide (Whiteford et al., 2013; Yatham et al., 2013). Individual episodes of depression and mania can usually be successfully treated, but relapse is common. Prevention of relapse is therefore important to reduce the disability caused by recurrent illness.

Abbreviations: AAPs, atypical antipsychotics; AOR, adjustedodds ratio; BD, bipolar disorder; CCI, Charlson comorbidity index; CIs, confidence intervals; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; IFN-γ, interferon-gamma; IL, interleukin; NHI, National Health Insurance; NHIB, National Health Insurance Bureau; NHIRD, National Health Insurance Research Database; OR, odds ratio; RCIPD, Registry for Catastrophic Illness Patient Database; TAPs, typical antipsychotics

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According to international treatment guidelines, mood stabilizers, typical antipsychotics (TAPs), atypical antipsychotics (AAPs), and antidepressants, used either as monotherapy or as adjuncts to other medications, are recommended for treatment of BD patients (National Institute of Health and Care Excellence (NICE). Bipolar disorder: the assessment and management of bipolar disorder in adults; Yatham et al., 2013). In recent years, growing evidence has shown that AAPs are effective in the treatment of bipolar mania, bipolar depression, and in the maintenance phase (National Institute of Health and Care Excellence (NICE). Bipolar disorder: the assessment and management of bipolar disorder in adults; Vieta et al., 2013; Yatham et al., 2013). AAPs have a more favorable profile than TAPs and mood stabilizers, as they cause fewer extrapyramidal side effects and are efficacious in management of psychotic symptoms (Seeman, 2002). In addition, mood stabilizers (such as lithium or valproic acid) used in combination with AAPs have better efficacy than when used as monotherapy (Smith et al., 2007). Therefore, the use of AAPs, either as monotherapy or adjunctive therapy, has become increasingly common. Indeed, 75% of the experts in Taiwan prefer to use mood stabilizers and AAPs in combination to treat acute mania, and up to 80% of experts would like to administer combination treatment in bipolar depression (Bai et al., 2013). A study using data from the National Health Insurance Research Database (NHIRD) in Taiwan found that the trend of using AAPs in treating BD rose markedly from 2001 to 2010 (Chang et al., 2016).

Cataracts and associated opacities cause visual impairment and are one of the leading causes of blindness. Blindness due to cataracts affects nearly 20 million people worldwide, especially in Asia (Wong et al., 2006). By the mid-1960s, the association between TAPs (particularly chlorpromazine and phenothiazines) and the development of cataracts had already been reported. The proposed mechanism for causing cataracts is believed to be that phenothiazines cause lenticular and corneal pigmentation by combining with melantin to form a photosensitive product (Thaler et al., 1985). More recently, studies have been reported on the cataractogenic risks of AAPs, although the findings are inconsistent (Chou et al., 2016; Lieberman et al., 2005; Pakzad-Vaezi et al., 2013; Shahzad et al., 2002; Ucok and Gaebel, 2008). Initial evidences for the cataractogenic tendency of AAPs came from animal studies. A study reported that cataracts developed in beagle puppies given four times the recommended human dose of AAPs, but this risk was not demonstrated in another study using monkeys (Shahzad et al., 2002). Some human studies have reported no elevated cataractogenic risks related to the use of AAPs (Chou et al., 2016; Lieberman et al., 2005; Shahzad et al., 2002; Ucok and Gaebel, 2008); one even reported a possible protective effect (Pakzad-Vaezi et al., 2013). For example, our previous nested case-control study found no association between specific AAPs used and the risk of cataracts in patients with schizophrenia (Chou et al., 2016). However, the cataractogenic risks of AAPs might be confounded by medical indication, as AAPs could be used in other disorders, such as depression (Nelson and Papakostas, 2009), anxiety disorders (Pies, 2009), and BD. The dose of antipsychotic drug and the duration of use may vary among patients with different psychiatric disorders; hence, the side effects may differ among different patient groups. Currently, there is no study investigating the possible cataractogenic effects of AAPs in patients with BD, who are prone to having risk factors for cataract development, such as smoking, hypertension, hyperglycemia, dyslipidemia, and type II diabetes (Young and Oldani, 2013). Therefore, we thought the issue deserved more attention, since the AAPs are commonly prescribed for this population.

The National Health Insurance (NHI) program of Taiwan covers most of the population, and most medical institutions in the country (Chou et al., 2013). It is, therefore, one of the largest insurance databases in the world. The NHIRD contains all claims data from ambulatory and inpatient care, and has provided valuable information for a variety of epidemiological studies (Chien et al., 2007; Chou et al., 2011, 2014). The database is maintained by the Department of Health and the National Health Research Institutes of Taiwan. The aim of this study was to investigate the association between different types of AAPs and the risks of cataract development in patients with BD by using data obtained from the NHIRD.

2. Methods

2.1. Data source

Data were obtained from the NHIRD in Taiwan. The NHI program was initiated in Taiwan in March 1995. By the end of 2010, almost all (23.07 million of Taiwan's 23.16 million) residents were enrolled (Chou et al., 2012). The NHIRD provides scrambled patient identification numbers and contains demographic information on dates of birth, sex, and clinical diagnoses, coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). In the Taiwanese NHI system, the government defines several psychiatric diseases, such as schizophrenia and mood disorders, as “catastrophic illnesses” and provides regulations for insured affected individuals to apply for a catastrophic illness certificate. These individuals are included in a subset of the NHIRD, the Registry for Catastrophic Illness Patient Database (RCIPD). Patients with catastrophic illness certification receive free medical care for the duration of the certificate's validity. Diagnosis of schizophrenia and admission of patients diagnosed with schizophrenia to the RCIPD are validated by board-certified psychiatrists via rigorous regulatory review, and with medical record verification by the National Health Insurance Bureau (NHIB). The longitudinal health insurance data used in the present study were obtained from the RCIPD population subset of the NHIRD. Similar to the NHIRD, the RCIPD includes all relevant information regarding “catastrophic illness certificate” status, such as diagnosis, date of diagnosis, date of death, and outpatient/inpatient claims data for the beneficiaries of individuals with catastrophic illnesses during the period 2000–2011.

2.2. Study design

We used a retrospective nested case-control design study to analyze data from 2000 to 2011 (Fig. 1). The period of study subject inclusions was from 2000 to 2005 and the observation period was from 2000 to 2011. Our exclusion criteria were as follows: first, to ensure that diagnoses were from new-onset cataracts in an adult population, we excluded data from patients younger than 18 years of age and from patients with a diagnosis of cataract (ICD-9-CM code: 366) received before 2000. Second, we excluded patients who underwent vitrectomy (procedure code) because of the high association between this procedure and cataract formation (Thompson et al., 1995). Finally, we excluded patients who did not receive any antipsychotic medications.

2.3. Case definition

All BD patients (ICD-9-CM code: 296.0X, 296.1X, 296.4X to 296.8X) newly diagnosed with a cataract during the study period were identified. To increase diagnostic validity, we defined new incident cases of cataract using compatible ICD-9-CM codes: ICD-9=366, excluding 366.2 (traumatic cataract) and 743.3 (congenital cataract). The compatible code had to be applied to a patient for at one hospitalization with a cataract diagnosis or a one outpatient diagnosis by an ophthalmologist. The date of the first cataract diagnosis was considered the index date.

2.4. Control definition

BD patients without a diagnosis of cataract were selected as the control group. For each BD patient with a diagnosis of cataract, one