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Research paper

# Antidepressants and risk of cataract development: A population-based, nested case-control study

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ABSTRACT

*Background:* Previous studies demonstrated increased risk of cataract development among users of selective serotonin reuptake inhibitors (SSRIs). However, it remains unknown whether this risk also prevails with the use of other types of antidepressants. The aim of this study was to investigate whether use of antidepressants is associated with an increased risk of cataract development. Moreover, the relationship between binding affinities of serotonin transporter (SERT) of antidepressant and the risk of cataracts is examined.

*Methods:* We conducted a nested case-control study using National Health Insurance Research Database in Taiwan. A total of 14,288 patients were included; 7651 in the cataract group and 6637 in the control group. Antidepressant exposure was categorized by type, duration of use, and binding affinities of SERT. The association between antidepressant exposure and cataract development was assessed using conditional logistic regression analysis.

*Results:* The adjusted odds ratios (AORs) for developing cataracts among continuous users of SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), and other antidepressants were 1.26 (95% confidence interval (CI): 1.12–1.41, $p < 0.001$), 1.21 (95% CI: 1.02–1.43, p=0.027), and 1.18 (95% CI: 1.04–1.34, p=0.009) respectively. Specifically, continuous uses of fluoxetine (AOR: 1.21; 95% CI: 1.01–1.46, p=0.042), fluvoxamine (AOR: 1.47; 95% CI: 1.01–2.12, p=0.043), venlafaxine (AOR: 1.44; 95% CI: 1.19–1.74, $p < 0.001$) significantly increased the risk of cataract development. Moreover, continuous users of antidepressants with intermediate SERT binding affinities (AOR: 1.68; 95% CI: 1.10–2.56, p=0.017) were significantly associated with increased risks of cataract development.

*Limitations:* Several confounding factors such as obesity, multiple drug users, family history of cataracts, substance use, and environmental factors (such as sunlight or radiation exposure) were acquired.

*Conclusions:* We found increased risk of cataract development in patients continuously using antidepressants. Regular ocular evaluations in these patients are warranted.

## 1. Introduction

Cataracts are one of the leading causes of vision loss worldwide, and are a major public health problem (Pascolini and Mariotti, 2012). The actual mechanism of cataract development remains unknown, but many risk factors such as age (Mitchell et al., 1997), female sex (Mitchell et al., 1997), corticosteroid use (Ernst et al., 2006), diabetes mellitus (Rowe et al., 2000), hypertension (Richter et al., 2012),

*Abbreviations:* 5-HT, serotonin; AOR, adjusted odds ratio; CI, confidence interval; DDD, defined daily dose; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; IOP, intraocular pressure; kD, dissociation constant; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; RCIPD, Registry for Catastrophic Illness Patient Database; SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor

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intraocular surgery, ocular trauma, uveitis (Durrani et al., 2004), and smoking (Cumming and Mitchell, 1997) have been identified. In recent years, numerous studies have focused on the potential cataractogenic risk of prescription drugs.

Recently, several epidemiological studies have focused on the risk of cataractogenic effects of antidepressants, and several types of antidepressants have been found to be associated with increased risk of cataract development. In the Beaver Dam Eye study, amitriptyline, a tricyclic antidepressant, was found to be associated with an increased risk of cortical cataracts (Klein et al., 2001). In a nested case-control study using the administrative health insurance databases of the Canadian province of Quebec, Etminan et al. (2010) found an increased risk of future cataract diagnosis in current users of fluvoxamine and venlafaxine, as well as an increased incidence of cataract surgery in current users of paroxetine in those aged 65 years or older. Using the data of the Rochester Epidemiology Project, Erie et al. (2014) found that selective serotonin reuptake inhibitor (SSRI) use for 1 year or longer was associated with an increased risk of cataract surgery in people aged 50 years or older. Although the role of 5-HT in lens metabolism remains unclear, 5-HT receptors have been identified in the crystalline lens in animal models (Costagliola et al., 2004) and increased 5-HT levels have been shown to cause lens opacity in rats (Boerrigter et al., 1992).

However, the cataractogenic risk of new antidepressants remains unknown. Given that there are increasing trends in prescribing newer antidepressants such as bupropion, duloxetine, milnacipran, and mirtazapine in the United States and Taiwan (Pirraglia et al., 2003; Wu et al., 2012), an association between new antidepressant use and risk of cataract development would be useful to determine, and warrants further investigation. Moreover, previous studies did not consider the medical indication for the use of antidepressants as a possible confounding factor. In addition to depression, bipolar disorder, schizophrenia, or anxiety disorders, antidepressants can also be prescribed for diseases of the genitourinary system or various chronic and neuropathic pain disorders (Kuo et al., 2011); therefore, the dosage, dosing frequency, and duration of treatment may differ from those used in psychiatric diseases. Moreover, the relationship between 5-HT transporter (SERT) binding to antidepressant drugs and the risk of cataracts is still unclear. While studies were previously conducted in Western countries, whether the effects of antidepressants on cataract development among Asian populations are different from their effects in other populations is a topic worth further investigation.

The National Health Insurance program of Taiwan covers most of the population in the country (Chou et al., 2014). The National Health Insurance Research Database (NHIRD) is one of the largest insurance databases in the world. NHIRD contains all the claims ranging from ambulatory to inpatient care, and provides information for many epidemiological studies in psychiatry (Chen et al., 2012; Chien et al., 2007; Chou et al., 2011, 2015). Therefore, we aimed to conduct a nested case-control study to investigate associations between antidepressant use and cataract development in patients with schizophrenia and mood disorders using nationwide population-based medical claims dataset in Taiwan.

## 2. Methods

### 2.1. Data source

This study used data from the NHIRD in Taiwan. NHIRD is a claims database maintained by the Department of Health and the National Health Research Institutes of Taiwan. The National Health Insurance (NHI) program was launched in Taiwan in March 1995. By the end of 2010, over 23.07 million of Taiwan's 23.16 million residents were enrolled (Chou et al., 2013). In the Taiwanese NHI system, the government defines several diseases, such as schizophrenia and mood disorders, as "catastrophic illnesses" and offers insured affected individuals the opportunity to apply for a catastrophic illness certificate. This database provides scrambled patient identification numbers, and contains demographic information on dates of birth and sex, as well as clinical diagnoses coded according to the format of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Patients with catastrophic illness certification get free care for their illness or related conditions during the certificate's validity period. The data used in the present study was derived from a subset of the NHIRD, namely the Registry for Catastrophic Illness Patient Database **(RCIPD)**. The diagnosis and applications for patients with schizophrenia or mood disorders into the RCIPD are validated by psychiatrists' certification, with rigorous regulatory review and verification of medical records conducted by the National Health Insurance Bureau. The longitudinal health insurance database for people with catastrophic illnesses was used in this study. The database included all relevant information about the "catastrophic illness certificate" status, such as diagnosis, date of diagnosis, date of death, and outpatient/inpatient claims data for the beneficiaries with catastrophic illnesses during the period of 2000–2011. This study was approved by the ethical review board of the Taichung Veterans General Hospital (No. CE13151-1).

### 2.2. Study design

We conducted a nested case-control study design between 2000 and 2011 (Fig. 1). The period of study subject inclusion was from 2000 to 2005, and the observation period was from 2000 to 2011. To ensure that the diagnoses were of new-onset cataracts in adult populations, data from patients younger than 18 years of age, or from those who had received any diagnosis of cataract (ICD-9-CM code: 366) before 2000, were excluded. Additionally, we also excluded patients who underwent vitrectomy based on procedure code during the entire study period because of its high associations with cataract formation (Thompson et al., 1995).

### 2.3. Case definition

All patients with schizophrenia and mood disorders (ICD-9-CM code: 295 and 296) newly diagnosed with a cataract during the study period were identified. To increase the diagnostic accuracy, we defined new cataract cases by compatible ICD-9-CM codes (ICD=366, except 366.2 [traumatic cataract] and 743.3 [congenital cataract]) by at least one time hospitalization with a cataract diagnosis or a one-time outpatient diagnosis by an ophthalmologist. In the present study, we did not chose the rate of cataract surgery as an index of outcome because it is known that the decision to perform cataract surgery depends to a large extent on the willingness of the patient, his or her severities of symptoms, and his or her occupational needs (El Sanharawi et al., 2014). Therefore, the rate of cataract surgery in a population is not representative of the incidence of cataract in the same population. The date of the first cataract diagnosis was deemed the index date.

### 2.4. Control definition

Patients with no cataract diagnosis were selected as a control group in the present study. For each patient who had a cataract diagnosis, one control was selected from the same database and matched by age, sex, and index date (Fig. 1). We excluded control patients who died before the index date or whose index date was before the diagnosis of schizophrenia or mood disorder.

### 2.5. Antidepressant exposure

Data on antidepressant use were obtained from prescription files in the RCIPD. We investigated the effect of antidepressants based on use