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Research paper

Bipolar disorder and the risk of fracture: A nationwide population-based cohort study

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ABSTRACT

Background: The co-primary aims are: 1) to compare the risk of fracture between adults with bipolar disorder and those without bipolar disorder; and 2) to assess whether lithium, anticonvulsants and antipsychotics reduce risk of fracture among individuals with bipolar disorder.

Methods: The analysis herein is a population-based retrospective cohort study, utilizing the National Health Insurance (NHI) medical claims data collected between 1997 and 2013 in Taiwan. We identified 3705 cases with incident diagnoses of bipolar disorder during study period and 37,050 matched controls without bipolar diagnoses. Incident diagnosis of fracture was operationalized as any bone fracture after the diagnosis of bipolar disorder or after the matched index date for controls.

Results: Bipolar patients had significantly higher risk of facture when compared to matched controls (17.6% versus 11.7%, respectively $p < 0.001$). The hazard ratio (HR) was 1.33 (95% confidence interval [CI] = 1.23–1.48, $p < 0.001$) after adjusting for covariates. Persons with bipolar disorder and a prior history of psychiatric hospitalization were had higher risk for bone fracture than those without prior history of psychiatric hospitalization when compared to match controls. Higher cumulative dose of antipsychotics or mood stabilizers did not increase the risk of fracture.

Limitations: The diagnoses of bipolar disorder were not confirmed with structured clinical interview. Drug adherence, exact exposure dosage, smoking, lifestyle, nutrition and exercise habits were unable to be assessed in our dataset.

Conclusions: Bipolar disorder is associated with increased risk of fracture, and higher cumulative dose of mood stabilizers and antipsychotics did not further increase the risk of fracture.

1. Introduction

Bone Fracture is a major public health priority, particularly among the aging demographic. For example, in 2010, approximately 21 million men and 137 million women aged 50 years and older were at high risk for fracture, which can result in serious disability, disease

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burden, and mortality (Oden et al., 2015; Sambrook and Cooper, 2006). For example, more than half of individuals with hip fracture were unable to return to pre-morbid levels of functioning and mortality rates increase by up to 33% within one year (Bass et al., 2007; Forsen et al., 1999; Trombetti et al., 2002). The increased mortality rate within one year was most prominent in the elderly (Bass et al., 2007; Forsen et al., 1999; Trombetti et al., 2002).

Mood stabilizers, including lithium and anticonvulsants (e.g. sodium valproate, carbamazepine, and lamotrigine), are approved by the U.S Food and Drug Administration (FDA) for the treatment of bipolar disorder. Previous studies suggest that anticonvulsant use may be associated with an increased risk for fracture (Cummings et al., 1995; Jette et al., 2011; Nicholas et al., 2013; Perreault et al., 2008; Shiek Ahmad et al., 2012). For example, results from a recent meta-analysis indicates that the use of antiepileptic drugs was highly associated with increased risk of fracture, and a greater risk was noted with anticonvulsant agents with known liver-enzyme inducing effects (Shen et al., 2014). However, interpretation of the foregoing findings are limited by the heterogeneity of study samples, which infrequently included subjects with elevated risk for fracture (e.g. elderly, women, or patients with epilepsy). Moreover, there have been relatively few studies that have evaluated the risk of fracture specifically among individuals with bipolar disorder.

The potential moderating effects of lithium on incident bone fracture have resulted in mixed and contradictory findings. For example, lithium is associated with bone loss in healthy rats after three months of exposure (Lewicki et al., 2006). In addition, a clinical study in psychiatric populations reported that one year of maintenance therapy with lithium was associated with elevated bone mass (Zamani et al., 2009). Other clinical studies have not identified an effect of chronic lithium use on bone mineral density and two large population-based case-control studies have reported a decreased fracture risk with lithium use (Bolton et al., 2008; Vestergaard et al., 2005). However, results from a study using the UK General Practice Research Database evaluating the possibly protective effect of lithium on risk of fracture did not support the foregoing hypothesis. Although the authors did not find significant data, they concluded that a mental disorder was much more critical to the risk for fracture than was any possible iatrogenic effect (Wilting et al., 2007).

Evidence suggestive of higher risk of fracture in psychiatric populations is also heterogeneous. For example, some studies have reported that depression is associated with an increase in risk for fracture (Mezuk et al., 2008; Mussolino, 2005; Whooley et al., 1999), while results from other studies have not supported the foregoing observation (Amsterdam and Hooper, 1998; Reginster et al., 1999; Whitson et al., 2008). Studies have also reported that schizophrenia is not associated with increased risk of fracture however, schizophrenic drug prescription of prolactin-elevating antipsychotics have been reported to be independently associated with increased risk of hip fracture (Howard et al., 2007).

To our knowledge, only one study by Kilbourne et al. has investigated the relationship between bipolar disorder and fracture. Kilbourne et al. reported that the diagnosis of bipolar disorder was associated with a 20% increase in risk for fracture, independent of medication prescription (Mezuk et al., 2010). Our study herein aimed to investigate whether an association exists between bipolar disorder and the incidence of fracture as part of a nationwide population-based retrospective cohort study. An addition aim of our study is to determine whether the prescription of mood stabilizing agents is associated with lower risk of fracture among individuals with bipolar disorder. Our hypotheses were: (I) patients with bipolar disorder have significantly greater risk of fracture when compared to a matched controls; (II) patients with severe bipolar disorder (i.e. as operationalized by history of psychiatric hospitalization) are at greater risk of fracture than those with less severe bipolar disorder (i.e. no prior history of psychiatric hospitalization); (III) prescription of mood stabilizing agents (i.e. anticonvulsant, lithium) and antipsychotics influences the risk of fracture among individuals with bipolar disorder.

2. Methods

2.1. Study protocol

This was a population-based retrospective cohort study based on the National Health Insurance (NHI) medical claims dataset in Taiwan. The NHI program was established in 1995 and is a government-run single-payer insurance system. It offers comprehensive healthcare in Taiwan and covers 99.9% of the national population as of 2014 (National Health Insurance Administration, 2015). The NHI dataset includes, but is not limited to, data on outpatient visits, ambulatory and inpatient care, dental care, medical procedures and drug prescriptions.

The data analyzed was obtained from the National Health Research Institute database (NHRID). The NHRID provided longitudinal data from 1997 to 2013 on 1,000,000 individuals randomly selected from the complete NHRID using a systemic sampling method. The foregoing sample population provided by the NHRID is comparable to approximately 5% of the national population in Taiwan. There were no statistically significant differences in sex, age, or healthcare utilization between our sample population and the complete sample population.

Bipolar disorder was operationalized as having an inpatient diagnosis with bipolar disorder and/or at least two medical records of outpatient care within one year for bipolar disorder. The International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes 296.0, 296.4, 296.5, 296.6, 296.7, 296.80 and 296.89 were used to determine a diagnosis of bipolar disorder. In order to evaluate the risk of fracture among individuals with an incident diagnosis of bipolar disorder, we excluded those who were diagnosed with bipolar disorder before 1998. The index date was defined as the day of incident diagnosis of bipolar disorder. Other exclusion criteria included epilepsy, pathological fracture, fracture due to traffic accidents, insufficient data (i.e. only one medical record in one year during the study period), and prescription of an anticonvulsant, such as lithium and/or an antipsychotic within one year preceding the index date. Each bipolar patient was sex- and age-matched to 10 controls, and both bipolar patients and matched controls were followed from the index date to the incidence of a fracture or death or terminating on December 31, 2013 Incidence of fracture was operationalized using ICD-9-CM codes 800–829.

Medications commonly used in bipolar disorder such as anticonvulsants (i.e. valproic acid, carbamazepine, lamotrigine), lithium, antipsychotics, antidepressants, benzodiazepines (BZD), hypnotics (i.e. Z drugs, including zopiclone, zolpidem, and zaleplon) were identified using Anatomical Therapeutic Chemical (ATC) system of the World Health Organization (WHO) (index, 2016a). In addition, antipsychotics were divided into two groups, either prolactin-elevating or prolactin-sparing (Madhusoodanan et al., 2010; Peuskens et al., 2014). Typical antipsychotics, risperidone, paliperidone and amisulpride were classified as prolactin-elevating antipsychotics. Most atypical antipsychotics such as olanzapine, quetiapine, clozapine, zotepine, ziprasidone and aripiprazole were classified as prolactin-sparing antipsychotics. Dosage was operationalized using the defined daily dose (DDD)(index, 2016b) and we classified it into three categories: none-use, $0 <$ cumulative dose < 28 DDD, and cumulative dose ≥ 28 DDD.

Other covariates considered in the analysis include area of residence, income, general physical condition assessed by Charlson Comorbidity Index (CCI) (D'Hoore et al., 1993), previous prednisolone, benzodiazepine (BZD) or hypnotics (Z drugs) use, and other comorbidities (e.g. osteoporosis, hypertension, diabetes mellitus, rheumatoid arthritis, senile dementia, substance abuse, extrapyramidal symptoms (EPS) and alcohol-related disorders) recorded within one year prior to the index date. Based on a previous study, there is no specific diagnostic code in ICD-9-CM (Yang et al., 2007). Therefore, we collected those