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Research paper

Risks of road injuries in patients with bipolar disorder and associations with drug treatments: A population-based matched cohort study

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ABSTRACT

Objective: Using a nation-wide, population-based dataset, we aimed to investigate the risk of road injury among individuals with bipolar disorder (BD) compared to individuals without BD. In addition, we investigated the putative moderating effects of prescription for lithium, anticonvulsants, antidepressants, and/or first- or second-generation antipsychotic agents on the association between BD and risk of road injury.

Method: As part of an16-year longitudinal cohort study, we compared the risk of road injuries among study subjects aged 16 and above with a diagnosis of BD, with ten age- and sex-matched sample of individuals without BD. Individuals were compared on measures of incidence on road injuries using medical claims data based on the ICD-9-CM codes: E800~807, E810~817, E819~830, E840~848. Time dependent Cox regression models were used to adjust for time-varying covariates such as age, and medication uses. Hazard ratios before and after adjusting for age, sex, other comorbidities, and drug use were calculated.

Results: 3953 people with BD were matched with 39,530 controls from general population. Adjusted hazard ratios revealed a 1.66-fold (95% CI 1.40–1.97) increase in risk of road injuries among bipolar subjects when compared to controls. Female gender, older age (i.e. over 80), residence in areas of highest levels of urbanization, and use of antidepressants were associated with a lower risk of road injuries.

Conclusions: In this large, national, population-based cohort, BD was associated with an elevated risk of road injuries. However, prescriptions of antidepressants might help mitigate the foregoing risk.

1. Introduction

Bipolar disorder (BD), affecting approximately 1% (48.8 million) of the global population, is a leading cause of disability and associated with increased healthcare utilization, premature mortality, and reductions in psychosocial functioning and quality of life (Global Burden of Disease Study, 2015). Traffic accidents are also associated with premature mortality, disability, and economic burden to affected individuals and their families. With the number of people injured or disabled from motor vehicle crashes at around 50 million each year (GBD DALYs et al., 2015; McGee et al., 2003), traffic accident-related injury is the third leading cause of death among children and adults under age 41 (Peden, 2001), and has been accounted for 12% of the global burden of disease (Global Burden of Disease Study, 2015). For instance, it was described that patients from road traffic injury comprised around 13–31% of all injury-related attendees in hospitals, and 48% of bed occupancy in surgical wards (GBD DALYs et al., 2015). Previous literature has reported that youth, males, pickup truck drivers, urban dwellers, and the elderly are at higher risk for road injury morbidity and mortality (Schlundt et al., 2004). Behavioral factors

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moderating higher risk included not wearing seat belts (or helmets in the case of cyclists and motorcyclists), driving under the influence of alcohol, fatigue, distracted driving, speeding, or aggressive driving (Schlundt et al., 2004).

Previous case-control studies among drivers involved in motor vehicle accidents have reported increased risks of traffic injuries and driving under influences of alcohol (Taylor et al., 2010) or drugs (Corsenac et al., 2012; Etminan et al., 2004; Orriols et al., 2013a,b; Orriols et al., 2012), with odds ratios ranged from 1.2 to 2.2. Results from cross-sectional studies have reported higher prevalence of BD among individuals with a record of driving under influence (DUI) when compared to individuals without a DUI record (Albanese et al., 2010; Freeman et al., 2011; Shaffer et al., 2007). In addition, recent studies using case crossover designs have reported higher rates of exposure to antidepressants and anticonvulsants before incident traffic accidents (Orriols et al., 2012, 2013a,b; Bramness et al., 2009). However, no population-based cohort studies have explored the directionality of associations between BD, treatments with lithium, anticonvulsants, antidepressants, or antipsychotic agents, and traffic accident-related injuries. Whether taking psychotropic medications is associated with an increase or decrease in the risk of causing motor vehicular accidents remains unclear.

Using a nation-wide, population-based dataset, we aimed to investigate the risk of road injury among individuals with BD compared to individuals without BD. In addition, we investigated the possibly moderating effects of treatment with mood stabilizers, anticonvulsants, antidepressants, and/or first- or second-generation antipsychotic agents on the association between BD and risk of road injury.

2. Methods

2.1. Data source

The National Health Insurance (NHI) program is a single-payer medical insurance system that was launched in 1995 and insures over 99.8% of total residents in Taiwan (approximately 22.8 million individuals of the national Taiwanese population of 23 million). The National Health Insurance Research Database (NHIRD) is comprised of all medical claims data (e.g. ambulatory, emergency, inpatient, outpatient care) from all residents in Taiwan. Data within the NHIRD are anonymized and scrambled twice such that individual identification is not possible. From the NHIRD, one million beneficiaries were randomly selected to form the Longitudinal Health Insurance Database (LHID) (NHIRD, 2009) that contains insurance claims from the NHIRD between 1998 and 2013 (NHIRD, 2006). There are no significant differences in distributions of age, gender, and healthcare utilization between the LHID, the NHIRD, and the general population in Taiwan (NHIRD, 2009).

In order for healthcare providers to claim drug prescriptions or record prescribed therapeutic interventions, appropriate disease diagnoses must be recorded and codified based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM).

2.2. Sampled participants

Individuals from the LHID, 16 years old or older, with a diagnosis of BD (ICD-9-CM 296. XX, excluding major depressive disorder: ICD-9-CM 296.2X~296.3X) and at least two outpatient visits within one year or at least one hospitalization between 1998 and 2013 were included in our study cohort. The severity of BD was operationalized as either 'greater severity' (i.e. having at least one hospitalization with BD as the main discharge diagnosis) or 'lesser severity'(i.e. haven't been severe enough to be hospitalized due to bipolar condition, and only followed up in ambulatory care). The index date was operationalized as the date of the first diagnosis of BD.

In order to control for age-related unspecific cognitive decline, for each BD subject, we have randomly selected ten age-, sex-, year of diagnosis (the years of bipolar diagnoses were used as the index dates)-matched controls without BD, who have never received lithium, anticonvulsants, or psychotropic drugs before index dates, from LHID. The primary outcome of interest was defined as the incidence of road injuries involving drivers(ICD-9-CM codes: E800~807, E810~817, E819~830, E840~848). All subjects were followed from the index date until the date of incident road injury, loss to follow up, or the end of 2013. Both cohorts excluded those with history of BD or road injuries before 1998, those with less than twice on the diagnosis of BD, and those with records of road injury preceding the diagnosis of BD.

2.3. Comorbidities and medications

We calculated Charlson Comorbidity Index (CCI) scores using medical data from within one year preceding the index date as a measure of baseline medical comorbidity (Charlson et al., 1987). Diabetes mellitus (ICD-9-CM 250, A181) (Signorovitch et al., 2013), hypertension (ICD-9-CM 401 – 405, A260, A269) (Vingilis and Wilk, 2012), rheumatoid arthritis (ICD-9-CM 714.0) (Vingilis and Wilk, 2012), senile dementia (ICD-9-CM 290.0) (Gorrie et al., 2008), alcohol-related illness (ICD-9-CM 291, 303, 305, 357.5, 425.5, 571.0, 571.1, 571.2, 571.3, 980.0, and V11.3) (Taylor et al., 2010), use of benzodiazepine (BZD), non-benzodiazepine sedative hypnotics (NBSH) of zolpidem, zolpiclone, Zaleplon, antihistamine, anticholinergics, or corticosteroids during the follow up period (Vingilis and Wilk, 2012) were also included as covariates because they were associated with our independent and outcome variables.

We further identified and counted follow-up periods in the use of anticonvulsants (carbamazepine, divalproex, lamotrigine, clonazepam, topiramate, gabapentin), lithium, first- and second-generation antipsychotic agents, and antidepressants within the follow-up period using Anatomical Therapeutic Chemical (ATC) system of the World Health Organization (WHO, 2009). In order to explore the associations between drug use and cumulative dose among our study subjects and risk of road injuries, the cumulative 'Defined Daily Dose' (DDD; i.e. the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO, 2009)), previously applied in this kind of research (Wu et al., 2015), was used to standardize comparisons between average doses. Levels of utilizations in anticonvulsant, lithium, antidepressants, and antipsychotic agents were defined as 'non-use', 'used for 1–27 days' (less than 28DDD in the total prescribed doses), or 'use for more than 28 days' (at least 28 DDD in the total prescribed doses).

2.4. Statistical analysis

Chi-squared tests were used to compare distributions of age, sex, CCI, comorbidities, and medications between our study and comparison subjects. Cumulative incidences of traffic injuries between the bipolar and non-bipolar matched cohorts were illustrated and compared using Kaplan-Meier curves with a log-rank test. The association between BD and subsequent risk of road injuries for time- fixed variables (sex, urbanization, income, CCI) were estimated using Cox proportional hazard regression analyses. Time- varying variables, (age, lithium, antipsychotics, anticonvulsants, antidepressants, BZD, NBSH, anticholinergics, antihistamines, and corticosteroids use), were analyzed by time-dependent Cox model in univariate and multivariate regression models to compare whether these drugs would modify the risk of road injuries in patients with BD. SAS software version 9.4 (SAS Institute Inc., Carey, NC) was used to conduct all statistical analyses. The level of significance was set at 0.05 for two-tailed tests.