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Attention-deficit hyperactivity disorder, its pharmacotherapy, and the risk of developing bipolar disorder: A nationwide population-based study in Taiwan

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ABSTRACT

In this study, we aimed to evaluate the relationship between attention-deficit/hyperactivity disorder (ADHD) during childhood and subsequent diagnoses of bipolar disorder (BD), as well as to determine whether the pharmacotherapy for ADHD (methylphenidate and atomoxetine) influence the risks of developing BD. A nationwide cohort of patients newly diagnosed with ADHD (n = 144,920) and age- and gender-matching controls (n = 144,920) were found in Taiwan's National Health Insurance database from January 2000 to December 2011. Both patients and controls were observed until December 31, 2011. To determine the effect that the duration of methylphenidate and atomoxetine exposure had on BD, the difference in the risk of developing BD was compared among non-users, short-term users (≤365 days), and long-term users (>365 days). In comparison to the control group, the ADHD group showed a significantly increased risk of developing BD (ADHD: 2.1% vs. controls: 0.4%; aHR: 7.85, 95% CI: 7.09–8.70), and had a younger mean age at the time of first diagnosis (ADHD: 12.0 years vs. controls: 18.8 years). Compared to ADHD patients that had never taken methylphenidate, patients with long-term use of methylphenidate were less likely to be diagnosed with BD (aOR: 0.72, 95% CI: 0.65–0.80). However, the duration of exposure to atomoxetine did not have a significant relationship to a BD diagnosis. The results suggested that a previous diagnosis of ADHD was a powerful indicator of BD, particularly juvenile-onset BD. Nevertheless, the exact mechanisms of the relationships among ADHD, its pharmacotherapy, and BD require further clarification in the future.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD), a common neurodevelopmental disorder that appears in childhood, includes such symptoms as inattention, hyperactivity, and impulsivity (Feldman and Reiff, 2014). Furthermore, mood swings are an often cited characteristic of ADHD (Martel, 2009) and one of the possible psychiatric comorbidities that present in many ADHD patients (Taurines et al., 2010). Bipolar disorder (BD) displays mood swings that range from depressive lows to manic highs. Although traditionally considered an adult-onset mental disorder (Merikangas et al., 2011), recent evidence has shown that about 2% of youth under the age of 18 have BD (Frias et al., 2014a). A number of features of ADHD overlap with those of BD, including excessive talking,

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distraction, impulsivity, and irritability (Asherson et al., 2014; Baroni et al., 2009; Kim and Miklowitz, 2002; Kleinman et al., 2015). However, unlike ADHD, which is chronic, symptoms of BD appear in an episodic pattern. We are not certain of how clinicians determine ADHD and BP diagnoses, so some overlap between them is possible. Because ADHD and BD may have comparable neurocognitive profiles and risk genes (Frias et al., 2014b; Lotan et al., 2014), related research has increasingly emphasized the co-occurrence of these two psychiatric disorders (Galanter and Leibenluft, 2008; Kent and Craddock, 2003; Masi et al., 2006b; Pataki and Carlson, 2013; Skirrow et al., 2012; Wingo and Ghaemi, 2007).

Convincing retrospective studies have indicated a high prevalence of ADHD comorbidity among the BD population, ranging from 4% to 94% (Andersen et al., 2013; Asherson et al., 2014; Frias et al., 2014a). Although the comorbidity rates differed greatly amongst studies, researchers generally agree that BD is related to a preceding ADHD diagnosis (Asherson et al., 2014). However, retrospective studies are susceptible to recall bias compared to prospective studies. Duffy (2012) reviewed qualitative prospective studies focused on the relationship between ADHD and BD by evaluating high-risk children and suggested that childhood ADHD was an unreliable indicator of the development of BD in adulthood. However, a 10-year follow-up study showed that ADHD youths were at high risk for a wide range of adverse psychiatric conditions, including BD (Biederman et al., 2006). Furthermore, a number of recent studies used large sample sizes of claims datasets to show that children and adolescents with ADHD, especially those that also had comorbid disruptive behavior disorders, were at an elevated risk of developing BD later in life (Chen et al., 2015, 2013; Jerrell et al., 2014). Debate has ensued regarding whether ADHD during childhood was associated with a subsequent diagnosis of BD. An ADHD diagnosis may be indicative a very early onset of bipolar disorder (Faraone et al., 1997a, 1997b). Patients with ADHD even before being diagnosed with BD often experienced manic or mixed index episodes (Masi et al., 2012).

Treatment with medications is often the first-choice for dealing with ADHD (Rabito-Alcon and Correas-Lauffer, 2014). Several case reports suggest that one common medication, methylphenidate, can induce manic-like symptoms when used to treat ADHD patients (Kraemer et al., 2010; Lahti et al., 2009; Wingo and Ghaemi, 2008). Furthermore, collected data have found that mania and hypomania or mood dysregulation can occur in 4% of ADHD patients undergoing treatment with atomoxetine (Henderson and Hartman, 2004). A recent longitudinal study indicated that long-term treatment with methylphenidate or atomoxetine significantly related to mania in patients with ADHD (Jerrell et al., 2014). However, other studies found contradictory results, reporting that treatment with methylphenidate was a protective factor against BD in children with ADHD (Tillman and Geller, 2006); children with ADHD and comorbid manic symptoms have responded well to psychostimulants without compounding their probability of developing BD (Galanter et al., 2003). Furthermore, some research has indicated that atomoxetine is a safe and effective treatment for ADHD for adjunctive therapies in children with BD as a comorbidity (Hah and Chang, 2005). Consequently, whether pharmacotherapy treatment for ADHD affects the emergence or improvement of BD symptoms remains debatable.

According to the aforementioned information, this study aims to determine the relationship between ADHD, its pharmaceutical treatments, and a subsequent diagnosis of BD. This study employs a nationwide population-based data set to assess the risk of developing BD by paralleling children with ADHD to controls without ADHD. Furthermore, this study analyzed whether the duration of undergoing ADHD pharmacotherapy influenced the risk of BD.

2. Methods

2.1. Data source

The institutional review board at Chang Gung Memorial Hospital approved this study. Its data were obtained from the ambulatory claims database of the National Health Insurance Research Database of Taiwan (NHIRD-TW). The National Health Insurance (NHI) program was started in Taiwan in 1995 as a required universal health insurance program. By implementing this program, the NHI Bureau became the only payer of healthcare services in the country. By the end of 2008, 22.8 million people in Taiwan (more than 98% of the population) had enrolled in the NHI program. The NHI Bureau has established contracts with 93% of all the healthcare providers in Taiwan, and more than 96% of insured people have used healthcare services at least once through such a hospital or clinic since 1995.

2.2. Choosing the ADHD patients and controls

Fig. 1 represents the process used to select the study population. Patients diagnosed with ADHD between January 1, 1999 and December 31, 2011were recruited from the NHIRD-TW (N = 146,063). ADHD was identified by using at least two NHI claims records in any diagnosis codes within a visit, which were indicated by the presence of International Classification of Diseases, 9th revision, Clinical Modifications (ICD-9-CM) codes of 314.X. According to the NHIRD-TW data set, 68.7%, 11.4% and 19.9% of ADHD patients were diagnosed by psychiatrists, pediatricians, and doctors in other specialties, respectively. This study excluded patients if they had any of the following conditions: (a) patients who had been diagnosed with ADHD before December 31, 1999 ($n = 251$) to ensure that the ADHD was a new diagnosis and (b) patients whose BD diagnoses were made before December 31, 1999 or preceded their ADHD diagnoses ($n = 892$). Once ineligible data were excluded, our data set consisted of 144,920 patients in the ADHD group. We defined the index date as the date that the ADHD diagnosis was first made, and the patients' NHIRD-TW medical records were followed up through December 31, 2011 or until they were diagnosed with BD.

Because of our limited budget, we only purchased a dataset of the study group (patients with ADHD) from the entire NHIRD-TW, which consists of 22.8 million people in Taiwan. We aimed to choose an age- and gender-matched control group from another subset cohort of the NHIRD-TW, the Longitudinal Health Insurance Database 2000 (LHID2000), which consists of 1 million beneficiaries randomly sampled from the 2000 NHIRD-TW Registry of Beneficiaries. The LHID2000 has records of all medical procedures and prescriptions during the period from January 1, 1996 to December 31, 2011. The age and gender distributions of the people in the LHID2000 sample do not differ significantly from those of Taiwan's general population (National Health Research Institutes, 2015). We excluded any subjects that had a diagnosis of ADHD between January 1, 1996 and December 31, 2011 or a BD diagnosis prior to December 31, 1999. A matching control for each ADHD patient was randomly selected from the LHID2000 using the propensity score matching technique (the ratio of ADHD patients to controls was 1:1). A multivariable logistic regression model with the covariates of age and gender was used to estimate the propensity score. January 1, 2000 was established as the date of initial observation. The control subjects were followed from this date until they left the LHID2000 (i.e., terminating NHI, emigration to another country, or death), developed BD, or the study period ended (December 31, 2011).