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Research report

Attention-deficit hyperactivity disorder, its treatment with medication and the probability of developing a depressive disorder: A nationwide population-based study in Taiwan

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ABSTRACT

Objective: The purpose of this study is to determine the risk of developing depressive disorders by evaluating children with attention-deficit/hyperactivity disorder (ADHD) in comparison to controls that do not have ADHD, as well as to analyze whether the medications used to treat ADHD, methylphenidate (MPH) and atomoxetine (ATX), influence the risk of depression.
Methods: A group of patients newly diagnosed with ADHD ($n=71,080$) and age- and gender-matching controls ($n=71,080$) were chosen from Taiwan's National Health Insurance database during the period of January 2000 to December 2011. Both the patients and controls were monitored through December 31, 2011. We also explore the potential influence of the length of MPH and ATX treatment on developing depressive disorders.
Results: The ADHD patients showed a significantly increased probability of developing a depressive disorder when compared to the control group (ADHD: 5.3% vs. controls: 0.7%; aHR, 7.16, 99% CI: 6.28–8.16). Regarding treatment with MPH, a longer MPH use demonstrates significant protective effects against developing a depressive disorder (aOR, 0.91, 99%CI: 0.88–0.94). However, the duration of ATX treatment could not be significantly correlated with the probability of developing a depressive disorder.
Limitations: The database employed in this study lacks of comprehensive clinical information for the patients with ADHD. Potential moderating factors between ADHD and depression were not considered in-depth in this study.
Conclusions: The results of this study reveal that youths diagnosed with ADHD have a greater risk of developing depressive disorders. Long-term treatment with MPH correlated to the reduced probability of developing a depressive disorder among youths with ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neuropsychiatric disorder that affects about 7.2% of all children and adolescents (Thomas et al., 2015). Its general symptoms include inattention, hyperactivity, and impulsivity (Biederman and Faraone, 2005). ADHD has been shown to have a significantly negative influence ADHD sufferers' academic performance, family life and peer relationships, as well as increases the likelihood of difficult life events (Becker et al., 2012; Spencer et al., 2007). Children diagnosed as ADHD also have high comorbidity rates with other psychiatric disorders, including depression (Pliszka, 1998; Taurines et al., 2010). Depressive disorders present in a variety of forms that all involve a persistent feeling of sadness and loss of interest (Parker and Roy, 2001). Children with both ADHD and depression

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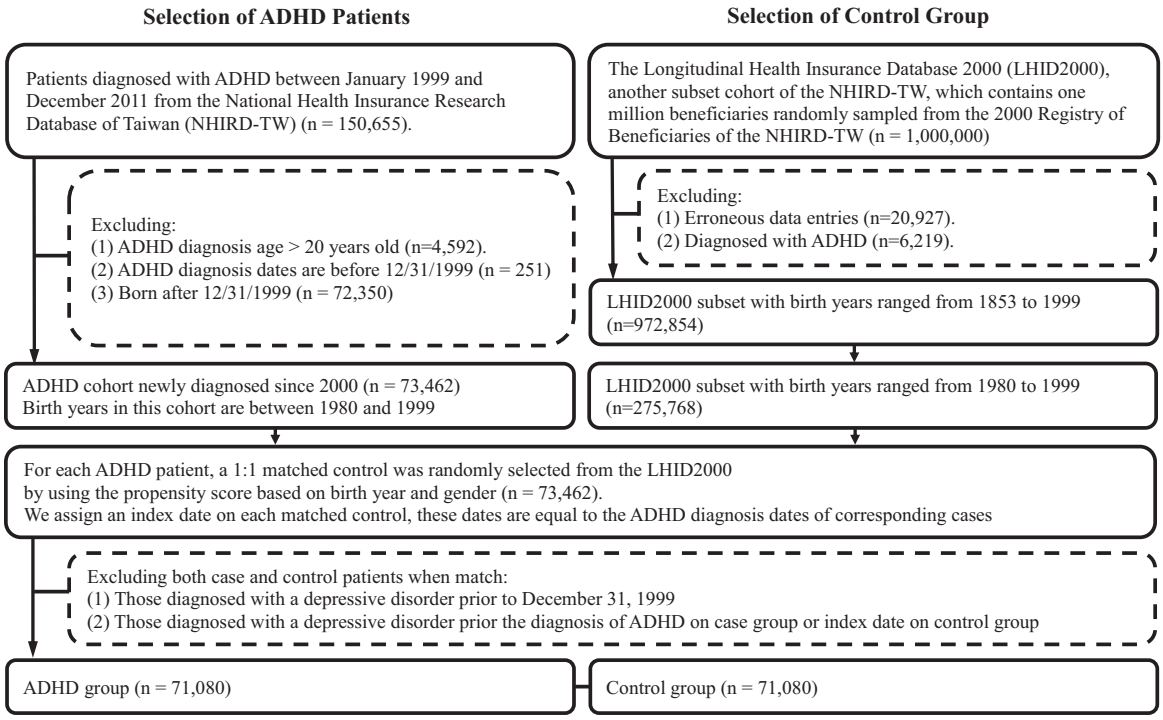

Fig. 1. Flowchart showing the selection procedure of study subjects.

were discovered to be at a great risk for psychosocial impairments with negative results (Chronis-Tuscano et al., 2010).

An increasing amount of research has shown that ADHD and depression can often co-exist in a child (Daviss, 2008; Meinzer et al., 2014). However, the prevalence rates of depression among children diagnosed with ADHD differ greatly between studies due to methodological variety and heterogeneous samples. In recent years, cross-sectional studies have shown that the depression rates in youths with ADHD range from 9.3% to 40.7% (Biederman et al., 2008a; Di Trani et al., 2014; Hesson and Fowler, 2015; Roy et al., 2014; Yuce et al., 2013). Meanwhile, longitudinal studies have reported that developing depression in ADHD sufferers occurs at a rate of 5.4–8.9% (Chen et al., 2013; Jerrell et al., 2015; Klein et al., 2012; McIntyre et al., 2010). A meta-analytic review of such studies implies that obvious variability existed throughout studies researching the connection between ADHD and depression (Meinzer et al., 2014). Subgroup analyses of this review article showed an average positive association between ADHD and depression in the cross-sectional studies, but the longitudinal studies or those that used non-referred samples found a small, negative and/or unreliable association. Thus, debate regarding the relationship between ADHD during formative years and the subsequent diagnosis of depressive disorders has ensued.

Medication is the first treatment option for children with ADHD, with stimulants and non-stimulants being the two main categories approved for said treatment (Rabito-Alcon and Correas-Lauffer, 2014). Methylphenidate (MPH), a stimulant, works by increasing the levels of dopamine in the synaptic cleft (Wilens, 2008). A series of animal studies suggests that chronic exposure to MPH potentially induced depressive-like behaviors (Brookshire and Jones, 2012; Carlezon et al., 2003); a similar result has been seen in humans as well (Lakic, 2012). On the contrary, a number of longitudinal studies has provided evidence that MPH treatment may reduce the risk of subsequent depression in ADHD youths (Biederman et al., 2009; Daviss et al., 2008; Golubchik et al., 2013; Rasmussen et al., 2015). One study indicates that stimulant treatment for ADHD neither increases nor decreases the risk of depression (Staikova et al., 2010). On the other hand, Atomoxetine (ATX), a non-stimulant, is a selective norepinephrine reuptake inhibitor (Hammerness et al., 2009). One of ATX's supposed pharmacological properties is that it has anti-depressive effects (Cheng et al., 2007; Dell'Osso et al., 2011; Ding et al., 2014). However, Jerrell et al. (2015) reported that the likelihood of children diagnosed with ADHD developing depression was positively correlated with taking ATX. Ultimately, the effect of ADHD drug treatments regarding the emergence or improvement of depression has yet to be definitively determined, and none of the previous research has looked into the effect of the length of medication treatment on the risk of depression.

Therefore, the goal of this study is to clarify the relationship between ADHD, its drug treatments, and subsequent diagnoses of depressive disorders. This retrospective cohort study reviewed a nationwide population-based data set to analyze the probability of developing a subsequent depressive disorder by comparing children diagnosed with ADHD to controls without ADHD. Furthermore, this study determined whether the type of ADHD medication and the length of taking it influenced ADHD sufferers' risk of developing a subsequent depressive disorder.

2. Methods

2.1. Data source

This study has been approved by the institutional review board at Chang Gung Memorial Hospital. The database used in this study was that of ambulatory claims of Taiwan's National Health Insurance Research Database (NHIRD-TW). Implemented in 1995, Taiwan's National Health Insurance (NHI) program is a compulsory universal health insurance program, and the NHI Bureau became the sole payer of health care services. As of the end of 2008, 22.8 million people in Taiwan (more than 98% of the population) had been enrolled in the NHI program. The NHI Bureau has contracted 93% of all health care providers in Taiwan, and more than 96% of