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Methylphenidate doses in Attention Deficit/Hyperactivity Disorder and comorbid substance use disorders

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Abstract
Patients with Attention Deficit/Hyperactivity Disorder (ADHD) and comorbid Substance Use Disorders (SUD) are increasingly being treated with central stimulant medication despite limited evidence for its effectiveness. Lack of longitudinal follow-up studies of dosing and adverse effects has resulted in conflicting treatment guidelines. This study aims to explore whether individuals with ADHD and comorbid SUD are treated with higher stimulant doses than individuals with ADHD only, and whether doses increase over time as a sign of tolerance, a core symptom of addiction.

Information on methylphenidate doses for 14 314 Swedish adults, including 4870 individuals with comorbid SUD was obtained through linkages of Swedish national registers between 2006 and 2009. Differences in doses between patients with and without SUD were estimated using logistic regression while a linear regression model calculated time trends in mean doses.

Individuals with SUD were prescribed higher methylphenidate doses than those without (OR_{day365}; 2.12, 95% CI 1.81–2.47: OR_{day730} 2.65, 95% CI 2.13–3.30). Patients with SUD were, two years after initiating stimulant treatment, prescribed approximately 40% higher doses compared to individuals with ADHD only.

The results may suggest a need for increased doses in this population to achieve optimal ADHD symptom control. A tendency towards increasing doses during the first years of treatment, more pronounced in individuals with comorbid SUD, may reflect a reluctance to prescribe adequate

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doses due to lack of clinical guidelines. Mean doses stabilized after about two years in both groups, which does not lend support to continuously increasing tolerance over time.

1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental disorder (Wilens and Spencer, 2010), and individuals with ADHD are at increased risk for Substance Use Disorders (SUD) (van Emmerik-van Oortmerssen et al., 2012). Despite a substantial overlap and signs of common pathophysiological mechanisms (Frodl, 2010) little is known about how patients with ADHD and comorbid SUD can be safely and effectively treated (Cunill et al., 2015).

It is well established that pharmacological treatment of ADHD using stimulant medication improves ADHD core symptoms (Faraone and Buitelaar, 2010, Faraone and Glatt, 2010). Methylphenidate is the most commonly used stimulant medication (NICE guidelines 2008, Kooij et al., 2010) with an expected treatment response observed in about 80% of the patients (Pliszka, 2007). Serious adverse effects are rarely associated with stimulant medication use (Santosh et al., 2011). However, stimulant medications are controlled substances (Controlled Substance Act, FDA, 2016) that increase dopamine levels in brain areas involved in development of addiction and thus can be recreationally abused (Wilens et al., 2008). Whereas stimulant treatment among patients with ADHD has increased in recent years (McCarthy et al., 2012), few studies have addressed treatment efficacy in individuals with comorbid SUD (Cunill et al., 2015). Consistent with clinical observations that individuals with SUD may need substantially higher stimulant doses than those with ADHD only, two recent randomized controlled trials showed significant improvements in ADHD symptoms and SUD outcomes using higher stimulant doses than earlier studies (Konstenius et al., 2014, Levin et al., 2015). Although tolerance is a core symptom of addiction and may underlie a need for higher initial stimulant doses in patients with SUD, continuously increasing doses during maintenance pharmacotherapy should raise concerns as that may reflect a worsening of the SUD. Societal and clinical concerns or inappropriate beliefs about the safety of stimulant treatment in individuals with coexisting SUD (Cassidy et al., 2015, Faraone and Glatt, 2010, Kaye and Darke, 2012), lack of longitudinal follow-up studies of dosing and adverse effects, such as harmful use and dependence, and a fear that stimulant treatment might put susceptible individuals at risk for future SUD, relapse or worsening of ongoing SUD is mirrored in conflicting treatment guidelines (Bolea-Alamanac et al., 2014, Cunill et al., 2015, NICE 2008).

Observational studies allow for large sample sizes to relatively small economical costs and can provide longitudinal information on changes in prescribed methylphenidate doses over time. In this population-based cohort study of all 14 314 adults with one or more prescriptions of methylphenidate between 2006 and 2009 in Sweden, we aimed to explore potential differences in prescribed stimulant doses between individuals with and without comorbid SUD, and whether doses increase over time as a proxy for medication tolerance.

2. Experimental procedures

2.1. Sample

The study was approved by the Research Ethics committee at Karolinska Institutet, Stockholm, Sweden, protocol no. 2009/5:10, 2009/939-31/5. We obtained data from a record linkage of four population-based registries in Sweden; personal identification numbers enabled accurate linkage. The *Swedish Prescribed Drug Register* includes information on drug identity using Anatomical Therapeutic Chemical (ATC) codes and dates of all prescribed drugs filled at Swedish pharmacies since July 2005. Each unique prescription has a specific dose text describing the quantity and dosage filled out by the prescribing physician. The *National Patient Register* provides data on in-patient psychiatric care since 1973 and outpatient care since 2001, categorized according to diagnostic coding in the eighth, ninth and tenth revision of the International Classification of Diseases (ICD-8, ICD-9 and ICD-10). To account for death and migration all data was linked to the *Cause of Death Register* and the *Migration Register*.

2.2. Measures

2.2.1. Diagnostic categories

A total of 14 314 individuals, aged 18–59, with an initial prescription of methylphenidate (ATC code for methylphenidate N06BA04 in the Prescribed Drug register), including 4870 with a diagnosis of SUD, were included in the main analysis. The National Patient Register and the Prescribed Drug Register were used to identify patients diagnosed with alcohol and/or drug use disorders in accordance with the ICD diagnostic guidelines and/or a prescription including an ATC code for drugs used exclusively in the treatment of SUD. Alcohol use disorder was defined using ICD codes from the National Patient Register (ICD-8: 291 and 303, ICD-9: 291, 303 and 305A and ICD-10: F10.0-F10.9) and ATC codes for prescriptions of medications used in the treatment of alcoholism (N07BB03 (acamprosate), N07BB04 (naltrexone) and N07BB01 (disulfiram)) from the Prescribed Drug Register. Psychoactive drug abuse was measured by ICD codes from the National Patient Register (ICD-8: 304, ICD-9: 292, 304 and 305X and ICD-10: F11.0-F16.9 and F18.0-F19.9) and ATC codes from the Prescribed Drug Register for prescriptions of medications used in the treatment of drug abuse (N02AE01 (buprenorphine), N07BC51 (buprenorphine+naltrexone) and N07BC02 (methadone)). An individual was classified as having SUD or not when included in the study (at the time of the initial prescription of methylphenidate). In addition, the National Patient Register

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