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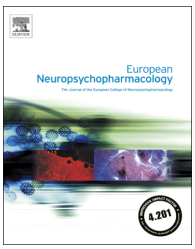

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Substance use disorders in association with attention-deficit/hyperactivity disorder, co-morbid mental disorders, and medication in a nationwide sample

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Abstract
Background: The association of substance use disorders (SUD) with attention-deficit disorder (ADHD), co-morbid mental disorders, and medication has only been studied in isolation and in rather small samples.
Procedure: Data were based on four Danish national registers covering a total of 20,742 patients with ADHD, their dispensed medications, co-morbid mental disorders, and associated SUD between 1994 and 2010. The analyses considered the risk of various medications (methylphenidate only, antidepressants only, antipsychotic only, mixed medication) in comparison to a control group of non-medicated patients with ADHD, various co-morbid disorders, duration of medication, age at diagnosis, year of birth, and sex for developing SUD.
Results: The observation period of the cohort ranged between 2.25 and 66.21 years and the prevalence for SUD was 9.51%. The SUD rates were significantly higher prior to, compared to following the onset of medication in the methylphenidate and the mixed medication subgroup, whereas they were significantly higher following onset of medication in the antidepressants and the antipsychotics subgroups. However, the SUD rates were significantly higher in all drug conditions except for methylphenidate after onset of medication compared to the non-medicated subgroup. Risk factors obtained by regression analysis did not include methylphenidate but did include antidepressants, antipsychotics, and mixed medications, in combination with co-morbid mood,

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anxiety, personality, and conduct disorders, and older age at diagnosis. Longer duration of medication and female sex were protective factors.
Conclusions: This representative study based on a large nationwide psychiatric sample provides solid evidence into the patterns of SUD in patients with ADHD based on medication use and co-morbidities.

1. Introduction

Based on 27 studies including 4142–4175 ADHD probands and 6835–6880 non-ADHD controls available for analysis (depending on the specific substance outcome analyzed), a recent meta-analysis of the prospective association of childhood attention-deficit hyperactivity disorder (ADHD) and substance use and abuse/dependence concluded that children with ADHD were significantly more likely to develop disorders of abuse/dependence for nicotine, alcohol, marijuana, cocaine, and other substances (i.e., unspecified). This increased risk was robust to demographic and methodological differences that varied across the studies (Lee et al., 2011). Another meta-analysis published in the same year was based on only 13 studies and concluded that childhood ADHD was associated with alcohol use disorder by young adulthood, and with nicotine use by middle adolescence (Charach et al., 2011).

In this association of ADHD and substance use disorders (SUD), various co-morbidities serve as mediating factors. In particular, children with ADHD and comorbid disruptive behaviour disorders (DBD), i.e., conduct disorders (CD) and oppositional defiant disorders (ODD) are at risk of developing SUD. Based on rigorous criteria, the large meta-analysis mentioned above identified 10 longitudinal studies, suggesting that comorbid ADHD+ODD/CD children may demonstrate significantly greater substance problems than children with ADHD only and controls (when included) (Lee et al., 2011). Furthermore, symptoms of depression are also commonly related to ADHD symptoms (Skirrow et al., 2009) and may be another important mediating factor.

The concern that using stimulant medication to treat ADHD in young people can increase the risk of developing later substance abuse, has been raised repeatedly. Another recent meta-analysis of 15 studies published between January 1980 and February 2012 based on 2565 participants found that treatment of ADHD with stimulants neither protected nor increased the risk of later SUD (Humphreys, et al., 2013). The same finding was also obtained in the most recent report from the Multimodal Treatment of ADHD (MTA) study by adolescence (Molina et al., 2013).

A major limitation of all existing studies addressing either the association of ADHD and SUD or the potential role that stimulant medication might play in this association, is their lack of representativeness. This is due in part to the existing community studies not representing all age groups in their samples. It is also due to the fact that as samples from clinical cohort studies largely consist of patients from specialized ADHD care and research centres with potential referral and selection biases, its is questionable whether they are representative of ADHD patients at large. The role of medications other than stimulants is almost never considered in analyses, and most studies do not analyse the role of co-morbid disorders and medication simultaneously.

The present study based on a nationwide psychiatric cohort of ADHD patients of all ages diagnosed and treated in Denmark tried to overcome the limitations of previous studies. We were aiming to investigate the risk of various medications in comparison to a control group of non-medicated patients with ADHD, and furthermore risk factors including various co-morbid disorders, duration of medication, age at onset of medication, and year of birth for developing SUD.

2. Procedure

2.1. Data sources

The study was approved by the Danish Data Protection Agency, National Board of Health and Statistics Denmark. In Denmark, at birth each individual is assigned a unique identification number (CPR) which makes it possible to identify the individual across various registers. Patients in this study had to be included in the IDA database (Integrated Database for Labour Market Research) in order to extract birth year and gender information.

Danish psychiatric central register (*DPCR*) was used for identification of all patients diagnosed with ADHD in the period between 1994 and 2010 according to ICD-10 criteria for Hyperkinetic Disorders (HD) (F90) including F90.0 (disturbance of activity and attention which is largely equivalent to ADHD combined type according to DSM-IV criteria), F90.1 (hyperkinetic conduct disorder which needs a dual diagnosis in DSM-IV), F90.8 (other hyperkinetic disorder), and F90.9 (hyperkinetic disorder – unspecified). The definition of ADHD and Hyperkinetic Disorder differ slightly, with the latter being less inclusive than the former. However, because all Hyperkinetic Disorders fulfil criteria of ADHD we have chosen to retain the common nomenclature and use the abbreviation ADHD for our sample in this paper.

To identify any SUD and co-morbid disorder prior to the onset of the study period, data from the period preceding 1994 were included into the analyses. In this period, Denmark still used the ICD-8 classification including alcoholism and drug dependence. In the following, we refer to these combined codes also as SUD (ICD-8: 303, 304; ICD-10: F1). In addition, the following major co-morbid mental disorders were considered for the analyses: mood disorders (296, 300.4; F3), anxiety disorders (300.0-300.3; F40, 41, 93.0-2, 93.8), personality disorders (301; F60-61.1), conduct disorders (308.1; F90.1, 91.1, 92) and autism spectrum disorder (308.0; F84).

Prescription database (*PD*): This register contains information on all individually prescribed and dispensed medications, except during hospitalizations. ADHD drugs in this register are defined according to the World Health Organization (WHO) Anatomic Therapeutic Chemical classification system.