Does psychostimulant treatment in children with ADHD increase later risk of substance use disorder?

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Psychostimulants are the first choice medication in children with attention-deficit/hyperactivity disorder (ADHD). Despite the proven high efficacy of psychostimulants, at least in the short term, for ADHD core symptoms, concerns continue to be raised on their adverse effects, including putative increased risk of substance use disorders (SUDs). A recent multicentre, case–control, longitudinal, prospective, European study by Groenman and colleagues found that treatment with psychostimulants in children with ADHD lowered the risk of SUDs in adolescence. However, this finding is at odds with other recent evidence concluding that ADHD children with and without medication treatment history did not significantly differ on any subsequent SUDs rates. In the present paper, we discuss the study by Groenman and colleagues in view of its methodological strengths and limitations, and we suggest possible implications for day-to-day clinical practice.

Psychostimulants (including methylphenidate and amphetamines) are indicated by several guidelines (e.g., Pliszka, 2007; NICE, 2008) as first choice medication for children with attention-deficit/hyperactivity disorder (ADHD). Whereas a large body of randomised controlled trials supports the high efficacy of psychostimulants on ADHD core symptoms (at least in the short-term), concerns continue to be raised regarding their adverse effects, including possible increased risk of substance use disorders (SUDs) (Cortese *et al.* 2013).

To address the effects of psychostimulant treatment in childhood on later risk for SUDs, Groenman *et al.* (2013) analysed data from the International Multicenter ADHD Genetics study (IMAGE), a multi-site longitudinal, prospective study including probands with ADHD and healthy controls (HC). The authors assessed the relation between exposure to psychostimulants in childhood (age range: 5–17 years) and rates of SUDs (including nicotine dependence) at follow-up, on average 4.4 (±0.7) years after study entry. Baseline assessment included categorical measures of ADHD, oppositional defiant disorder (ODD) and conduct disorder (CD), as well as measures of ADHD symptoms severity. At follow-up, analysable

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data were available for 388 probands with ADHD and 211 HC. Among the participants with ADHD, 327 had been treated for at least 12 months with psychostimulants (ADHD-T) and 61 were either psychostimulants-naïve or had received a short or inconsistent treatment for <12 months (ADHD-NT). Follow-up assessment included indicators of SUDs/nicotine dependence, obtained combining self-rated and parent-reported measures, as well as data on medication history (current use, age at treatment initiation, age-adjusted duration use and cumulative dosage of psychostimulants) as per parents report and pharmacy records.

Results showed that ADHD-NT participants had a 2.6 times higher risk (hazard ratio (HR)) to develop any SUDs at follow-up compared to HC (95% confidence interval [CI]: 1.35–4.99) and two times higher risk in relation to ADHD-T participants (95% CI: 1.11–3.63); no statistically significant differences were found between ADHD-T and HC. However, both the ADHD-T and the ADHD-NT participants had an increased risk of developing nicotine dependence compared with HC (HR = 3.56, 95% CI: 1.28–9.88 and HR = 3.83, 95% CI: 1.11–13.28, respectively), whereas no differences were detected between ADHD-T and ADHD-NT participants for this outcome. These results remained substantially unchanged after adjusting for ODD, CD and ADHD severity at baseline. Among the possible moderators, earlier age at treatment initiation was associated with significantly lower risk of SUDs at follow-up; however, this effect diminished with age, and reversed around the age of 18.

The authors concluded that psychostimulant treatment in childhood has a protective effect on the risk of SUDs (except nicotine dependence) in adolescence. This finding is at odds with a recent meta-analysis of 15 longitudinal studies reporting that ADHD-T children did not differ from ADHD-NT on any subsequent SUD outcome (Humphreys *et al.* 2013).

However, before drawing any clinical conclusion, it is important to consider the methodological strengths and limitations of Groenman *et al.* study. This study has several remarkable strengths. The psychiatric assessment of ADHD and comorbid disorders was based on state-of-the-art tools and diagnostic algorithms. The authors controlled for the effect of comorbid disorders, such as ODD and CD, which have been shown to increase SUDs risk. They also explored possible moderators that have been overlooked in previous studies, such as age at treatment initiation, duration of treatment use and cumulative dosage. These variables were evaluated not only with parental reports, but also with pharmacy records, likely less prone to recall bias than retrospective information provided by parents.

Some limitations of the study should also be noted. As acknowledged by the authors, an important limitation is

related to the naturalistic design of the study. It is well known that in naturalistic studies, greater treatment intensity may paradoxically be associated with worse outcome, since individuals with more severe disorders tend to be treated with more intense treatment and may have worse outcome. In this regard, it is worth noting that the ADHD-NT group had fewer symptoms than the ADHD-T group, so that the study findings cannot be ascribed to the difference in symptoms severity between the two ADHD groups. However, other possible differences between the two groups might have introduced important bias. For example, information on some key family characteristics is not provided in the paper. Families who seek medication treatment for their youths might be more invested in their children's success and in parenting, which, in turn, is a protective factor for the risk of SUDs (Wilens *et al.* 2003). The uneven distribution of this confounding factor between ADHD-T and ADHD-NT would be reduced *a priori* using a randomised design (Cipriani & Geddes, 2009). However, given the well-established effectiveness of psychostimulants for ADHD core symptoms and the population of interest (children with mental illness), such design would be difficult to apply (Adams, 2013). It would anyway be recommended to control for this possible confounding factor *a poteriori*, during the statistical analyses. Another limitation of the study pertains to the duration of follow-up (about 4 years). In general, follow-up studies in adolescence have shown a greater protective effect of psychostimulants for risk of SUDs (average odd ratio, OR: 5.8) compared with those in adulthood, where the OR (average: 1.4), despite being still statistical significant, may be less relevant clinically (Wilens *et al.* 2003). Therefore, it is possible that psychostimulant use delays the occurrence of SUDs, rather than protecting from it. As such, follow-up studies in adulthood are more suited to address the relationship between psychostimulants and SUDs risk. A further limitation is related to the outcome. Groenman *et al.* (2013) used measures of SUDs either from parents or from adolescents and this may have introduced heterogeneity. Additionally, they considered categorical outcomes for SUDs. No information is provided on clinically relevant features such as frequency and amount of substance use. Finally, ADHD participants were considered as a homogenous group. Given the phenotypical heterogeneity of ADHD, analyses considering the moderating role of ADHD subtypes (i.e., inattentive and hyperactive/impulsive) and of related personality traits that have been shown to impact on SUDs risk (such as high levels of *sensation seeking*) would provide clinically meaningful information.

Therefore, further research addressing the limitations of the Groenman *et al.* study, building on its strengths, seems necessary to address the question:

'Does psychostimulant treatment in children with ADHD increase later risk of SUD?' An additional and perhaps more relevant question would be 'In which patients and to which extent do psychostimulants in childhood increase or decrease the risk for later SUD?' Addressing these questions with methodologically sound trials will provide meaningful information to support the clinician in daily practice.

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Conflict of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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