# ADHD and Substance Misuse in Young people: From cutting edge research to the coal face reality of clinical practice

**Mirza, K.A.H.[1] Sudesh[2], R. and Mirza, S.[3]**

## Abstract

Children with ADHD are at high risk of developing substance misuse in adolescence and adulthood. The abuse potential of stimulant medication and the impact of medication treatment on long-term risk of substance misuse are areas of ongoing controversy. Existing literature indicates that treatment of ADHD with medication does not increase the risk of development of substance misuse in the treated individual. Stimulant medications can, however, be diverted or misused, either for subjective euphoric effects or for effects on performance. Integrated treatment of both substance misuse and ADHD should be provided. Strategies to minimize the risk for misuse or diversion of medications include use of extended-release formulations of currently used stimulant medications, new non-stimulant medications and novel pro-drugs. This article provides a brief overview of the extant literature and offers practical guidelines for the management of young people with ADHD and co-morbid substance misuse.

Keywords: substance misuse, substance dependence, substance abuse, co-morbidity, children, young people, abuse potential.

1. Consultant Psychiatrist and Hon. Senior Lecturer, Department of Child and Adolescent Psychiatry, BOX PO 85, Institute of Psychiatry and The Maudsley Hospital, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK

2. 4th year Medical student, King's College School of Medicine, Guy's Campus, King's College, London SE1 UL, UK

3. Professor of Forensic Medicine, Dr. Somerwell Memorial CSI Medical College Hospital, Kerala, India

Correspondence: kamirza@gmail.com or k.mirza@kcl.ac.uk

### Declaration of interests

K.A.H Mirza has served on the advisory boards of Janssen, Eli Lily and Shire pharmaceuticals and has received research and educational grants from Glaxo Smith Kline, and Shire pharmaceuticals. He has received honoraria for speaking at conferences organized by Janssen, Eli Lilly and Shire pharmaceuticals.

Roshin Sudesh and Sudeshni Mirza declare no competing interests.

## Introduction

Attention deficit hyperactivity disorder (ADHD) is a common, heterogeneous neuropsychiatric condition with significant levels of morbidity. ADHD can persist into adolescence and adulthood. Children with ADHD are at higher risk of developing substance misuse in adolescence and adulthood; the risk is higher if there is co-morbid conduct disorder and/or social adversity. Pharmacological treatment is a central component of intervention in children with ADHD and there is a robust body of evidence to attest the efficacy and safety of medications, at least in the short term (1). The global rise in ADHD diagnosis in children and the increasing rates of stimulant prescription over the previous two decades have led to a vigorous, often polemic, debate as to whether pharmacotherapy may in fact increase the risk of development of substance misuse. Critics of drug treatment point out that methylphenidate and other stimulants have strikingly a similar pharmacological profile to cocaine and

pharmacotherapy may increase the risk of development of substance misuse in young people (2,3). There have been reports of intranasal and intravenous abuse of methylphenidate and non-prescribed use of stimulants by university students in the USA (4 ) and diversion of methylphenidate into the illegal drug market in the UK (5,6). The aim of this review is to explore the complex relationship between ADHD and substance misuse and to provide clinical guidelines for treating children and young people

## Relationship between ADHD and substance misuse: causal pathways and Mechanisms

There are a number of complex pathways and mechanisms to describe the relationship between ADHD and substance misuse. Among drugs of abuse, specific risk from ADHD is most significantly associated with tobacco misuse. The risk of developing nicotine dependence may be mediated by self-medication, as nicotine appears to alleviate the symptoms of ADHD (7). Co-morbid conduct disorder was thought to be responsible for most of the risk with all other classes of drugs. More recent studies suggest that both ADHD and conduct disorder contribute to the risk of developing all drug and alcohol misuse, but conduct disorder poses the most significant risk (8).

### Does stimulant medication lead to substance misuse?

We aim to address this controversy by exploring the evidence from animal, clinical and pharmacological studies. A comprehensive review of animal studies concluded that there is insufficient evidence at present to suggest that exposure to stimulants would lead to long-term risk of addiction (9). It is difficult to extrapolate findings from animal studies to human beings for a variety of reasons.

Drugs of abuse such as cocaine and stimulants act by increasing dopamine in the mesolimbic and mesocortical dopamine pathways (10). However, seminal studies by Nora Volkow and colleagues from the National Institute of Drug Abuse have shown that the route of administration and dosages of stimulants are the most important variables, determining the abuse potential (11). Thus methylphenidate, when taken orally in therapeutic doses and within a clinical context, appears to be associated with a much lower abuse potential than cocaine.

A meta-analysis of the prospective and retrospective clinical studies conducted before 2003 reported that those treated with stimulant medication were protected against the development of substance-related problems by a factor of two (Odds Ratio 1.9) (12). Three prospective studies since 2003 concurred with the above (13,14,15). Furthermore, 36 month follow-up of the Multimodal Treatment Trial (MTA) has suggested that medication does not contribute significantly to the risk for substance misuse in adolescence and behaviour therapy is associated with reduction of risk (16).

### Diversion of stimulants: "to get a high" or to enhance academic performance

Stimulant medications are controlled drugs and have the potential for misuse and diversion, either for subjective effects or for effects on performance. Methylphenidate can be misused intranasally by crushing the tablets and snorting the powder or intravenously by dissolving the powder in water for injection. More commonly, oral stimulants can be misused to enhance performance in sports or some kinds of cognitive tasks and examinations (17,18,4). Diversion of stimulants into the illegal drug market is rife in North America and there is early indication that the above phenomenon is not entirely uncommon in the UK (5,6).

## Summary and clinical implications

Children with ADHD are at high risk of developing substance misuse. Consequently, prevention of substance misuse should be a target for ADHD services. At least a substantial amount of the risk is mediated by conduct problems (or the social adversity leading to them). Reduction of conduct

problems could be helpful in reducing the risk of substance misuse and hence psychological and social measures should be included in the long-term treatment of ADHD. As stimulant medication does not appear to increase the risk of substance misuse, it is not contraindicated for that reason. It is, however, important to note that stimulants do have the potential to be misused, especially by people without ADHD.

## Guidelines for assessment and practical management

Young people presenting with substance misuse and ADHD pose significant challenges for assessment and treatment. Defining substance misuse in young people is not easy and developmentally sensitive classificatory systems are useful in everyday clinical practice (19). Pointers such as drug-misusing relatives, being in a drug-misusing peer group, the combination of absence of effect with ongoing requests for prescriptions and frequent mysterious "loss" of prescriptions, should alert clinicians to the risk of diversion and misuse of prescribed medication.

## Treatment

### a. General principles

Integrated, multimodal treatment of both substance misuse and ADHD has been found to be useful in clinical practice (20) and specific treatment for ADHD and substance misuse should, ideally, be provided under the same roof. Substance misuse, especially if it is chaotic, is often the first issue to be addressed before initiating ADHD treatment. Although abstinence is ideal prior to initiating medication treatment for ADHD, achieving complete or sustained abstinence may not be a realistic expectation.

### b. Specific treatment of ADHD: evidence base for medications

There is some empirical data to guide treatment. Although debate about the role of medication to treat ADHD continues, it appears that stimulant medication is indeed helpful, although it has been argued that it might add little or nothing to a well-delivered program of CBT (21). Medication does, however, appear to be safe and does not worsen substance misuse.

## Pharmacological strategies to reduce the abuse potential of medications

Long-acting or controlled-release formulations are less likely to be misused than short-acting agents (23). The lower risk for misuse of extended-release formulations of methylphenidate may also be related to the fact that active components cannot be rapidly extracted from the beaded or osmotic extended-release preparations of these stimulants (18). Atomoxetine, a selective norepinephrine reuptake inhibitor, has been reported to have little abuse potential, as evidenced by animal studies and small-scale studies in human volunteers (24). Other pharmacological strategies to reduce intranasal or intravenous abuse include use of a methylphenidate transdermal patch, (25) or a prodrug such as Lis-dexamfetamine Dimesylate (LDX). In its intact form, LDX is pharmacologically inactive. When taken orally, LDX is converted in the red blood cells by rate-limited enzymatic hydrolysis to L-lysine, a naturally occurring essential amino acid, and d-amphetamine. Neither of these is available in the United Kingdom yet.

In summary, the choice of a medication is dependent on the personal and family history of substance misuse, in particular the potential risk of misuse and diversion. In young people with non-chaotic substance abuse/dependence, and in the absence of significant family history of substance misuse, long-acting preparations of stimulant medication may be the preferred option, in view of its superior efficacy. However, if there is personal or family history of stimulant misuse and the substance misuse is chaotic, atomoxetine or other non-stimulants should be considered as the drugs of choice.

## Conclusions

Substance misuse in adolescence is a major public health problem with substantial levels of morbidity and mortality. ADHD is a significant risk factor for the development of substance misuse through a number of complex causal pathways. Medication for children with ADHD is unlikely to increase the long-term risk of substance misuse. Given the consistent findings of misuse of stimulants (either illicit use or for enhancing performance), General Practitioners, CAMHS clinicians, youth offending officers, substance misuse workers, teachers and other professionals should be made aware of the scope of the problem. Extended-release stimulants, non-stimulants or pro-drugs may be less likely to be misused or diverted. Identification and optimal treatment of ADHD in children and adolescents may, hopefully, result in lower rates of substance misuse and diversion of stimulants but research will be needed to establish whether interventions are effective.

## GP Comment

### What have I learned from this paper?

1. As a group, people with ADHD are more at risk for substance misuse than the general population.

2. Treatment of ADHD should include psychological and social measures to prevent development of conduct disorder and substance misuse.

3. Despite previous concerns, treating ADHD almost certainly does not increase the risk for substance misuse.

4. Careful consideration needs to be given to the management of the ADHD patient with risk factors for substance misuse, such as a personal or family history of substance misuse.

5. Illicit diversion of medication used to treat ADHD can be minimised by using controlled-release/ extended-release stimulants or by using non-stimulant drugs such as atomoxetine.

6. As a GP who used to run an ADHD clinic and who now offers a substance misuse clinic I was certainly interested by this paper. I was previously unaware of the link between ADHD and smoking but will undoubtedly share this information with patients in the future. I had prior understanding that pharmacological treatment of ADHD reduces risk of subsequent substance misuse and it was interesting to note that the risk actually relates more to the associated condition of conduct disorder. As a GP this paper will be useful for providing knowledge based reassurance to parents that stimulant medications are an appropriate therapy and counter-intuitively do protect them from the risk of substance misuse. It seems that perhaps GPs could be alert to the more conduct disordered children amongst those who suffer ADHD and seek to ensure that these children do not simply receive a repeat prescription for methylphenidate but are enrolled onto therapeutic programmes. Diversion is an important consideration and I would need to have greater understanding of the different extended release preparations as it seems that some exist that would resist the option of simply being crushed to allow misuse. It is disappointing that the more novel preparations are not yet available in the UK. Finally there should perhaps be more onus on those of us running substance misuse clinics to have a lower threshold for suspecting ADHD amongst our adult clients but this would then have implications for the commissioning of services which I understand are currently very limited.

**Dr Marcus Thomas, GP, Bedfordshire.**

## References


1. NICE (2006) Methylphenidate, Atomoxetine and dexamphetamine for the treatment of Attention deficit hyperactivity disorder in children and adolescents. Technology Appraisal 98. London: NICE. Available at: www.nice.org.uk/TA98.

2. Robbins T.W (2002) ADHD and Addiction, Nature Medicine, 8(1) 24-25.

3. Breggin P.R and Baughman P.A (2001): Questioning the treatment for ADHD, Science, 291, 595.

4. Barrett, S.P.,Darredeau, C., Lana E Bordy, C. E., Robert, O.,(2005). Characteristics of Methylphenidate Misuse in a University Student Sample, Canadian Journal of Psychiatry 50: 457–461.

5. Woolfall K (2006) Substance use among young people in Wirral, Merseyside. Liverpool, Liverpool John Moores University.

6. Geraghty, O (2008) An Exploration of the Black Market Availability and Costs of Licensed Medicines in the North West. Liverpool, Liverpool John Moores University School of Pharmacy and Chemistry ( MPharm dissertation).

7. Levin, F.R. Evans, S.M. McDowell D.M. and. Kleber, H.D (1998), Methylphenidate treatment for cocaine abusers with adult attention-deficit/hyperactivity disorder: a pilot study, J. Clin. Psychiatry 59, 300–305.

8. Elkins, I.J., McGue. M, Iacono, W.G ( 2007) Prospective Effects of Attention-Deficit/Hyperactivity Disorder, Conduct Disorder, and Sex on Adolescent Substance Use and Abuse Arch Gen Psychiatry. 64(10):1145-1152.

9. Kollins SH, MacDonald EK, and Rush CR (2001): Assessing the abuse potential of methyl phenidate in nonhuman and human subjects: a review, Pharmacology, Biochemistry, and Behaviour, 68, pp 611-627.

10. Robbins T.W, Everitt B.J. Drug addiction: bad habits add up. Nature. 1999;398:567–570.

11. Volkow, N.D., Ding, Y.S., Fowler, J.S., Wang, G.J., Logan, J., Gatley, J.S., Dewey, S., Ashby, C., Liebermann, J., Hitzemann, R., et al., (1995), Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in the human brain, Arch Gen Psychiatry Jun; 52(6): 456-63.

12. Wilens, T.E., Faraone, S.V., Biederman, J., Gunawardene, S., (2003) Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Paediatrics, 111(1): 179-185.

13. Mannuzza. S., Klein, R.G., Truong, N.L., Moultan, J.L., 3rd, Roizen, E.R., Howell, E.R., Castellanos, F.X., 2008. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. American journal of psychiatry, 165(5): 604-609.

14. Biederman, J., Monuteaux, M.C., Spencer, T., Wilens, T.E., Macpherson, H.A., Faraone, S.V., 2008. Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. American journal of psychiatry, 165(5): 597-603.

15. Wilens TE, Martelon M, Joshi G, Bateman C, Fried R, Petty C, Biederman J ( 2011): Does ADHD predict substance-use disorders? A 10-year follow-up study of young adults with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry 50(6):543-553.

16. Molina, B. S. G., Flory, K., Hinshaw, S. P., et al. (2007) Delinquent behaviour and emerging substance use in MTA at 36 months: prevalence, course, and treatment effects. Journal of the American Academy of Child and Adolescent Psychiatry,46, 1–11.

17. Wilens TE, Gignac M, Swezey A, Monuteaux MC, Biederman J (2006);. Characteristics of adolescents and young adults with ADHD who divert or misuse their prescribed medications. Journal of American Academy of Child and Adolescent Psychiatry. 45: 408–414.

18. Wilens, T. E., Adler, L. A., Adams, J., et al. (2008) Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. Journal of the American Academy of Child and Adolescent Psychiatry, 47, 21–31.

19. Mirza KAH and Mirza S. (2008) Adolescent substance misuse. In: Bruce H and Skuse. D (eds), Psychiatry. London: Elsevier, for the Medicine Publishing Group, pp. 357–62.

20. Mirza KAH and Buckstein O. (2010): Assessment and treatment of young people with ADHD, disruptive behaviour disorder and co-morbid substance use disorder. In: Kaminer Y and Winters K (eds), Clinical Manual of Adolescent Substance Abuse Treatment. Washington, DC: American Psychiatric Publishing,; pp. 283–305.

21. Riggs P.D, Winhusen, T, Davies R. D et al (2011) Randomized Controlled Trial of Osmotic-Release Methylphenidate (OROS-MPH) for Attention Deficit Hyperactivity Disorder in Adolescents with Substance Use Disorders. Journal of American academy of child and adolescent psychiatry, Vol.50, 9 903-914.

22. Thurstone,C, Riggs, P.D, Salomonsen-Sautel, S., and Mikulich-Gilbertson,S.K (2010) Randomized, controlled trial of Atomoxetine for ADHD in adolescents with substance use disorder, Journal of American Academy of Child and Adolescent Psychiatry, 2010 June; 49(6): 573–582.

23. Wilens, T. E., (2007). The nature of the relationship between attention-deficit/hyperactivity disorder and substance use, Journal of clinical psychiatry, 68 supplement, 11: 4-8.

24. Heil SH, Holmes HW, Bickel WK, et al: ( 2002) Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users. Drug and alcohol dependence 67, 149-156.

25. Findling RL, Bukstein OG, Melmed RD, et al. (2008) A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. J Clin Psychiatry.;69(1):149–159.