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Stimulants: use and abuse in the treatment of attention deficit hyperactivity disorder

Kevin CF Fone[1] and David J Nutt[2]

Attention deficit hyperactivity disorder (ADHD) is the most prevalent childhood developmental disorder and is also of unclear neurobiological aetiology. However, recent advances in molecular genetics and brain imaging implicate dopaminergic hypofunction in the frontal lobes and basal ganglia in ADHD. Psychostimulants (e.g. methylphenidate and amphetamine, which are potent inhibitors of the dopamine transporter) are the first choice medication for ADHD and have a good acute efficacy and safety profile when used for this disorder. Whether long-term psychostimulant administration to adolescents alters neural development and behaviour or increases the risk of substance abuse is less certain. The precise molecular mechanism of action of psychostimulants is beginning to be established. Furthermore, preclinical studies have begun to use lower clinically relevant doses and oral administration of psychostimulants to determine their long-term effect on development, behaviour and neurochemistry, which is an important public health issue associated with chronic medication of adolescents with ADHD.

Addresses
[1] Institute of Neuroscience, School of Biomedical Science, Queen's Medical Centre, University of Nottingham, Nottingham NG7 2UH, UK
[2] Psychopharmacology Research Unit, Dorothy Hodgkin Building, University of Bristol, Bristol BS8 1TD, UK

Corresponding authors: Fone, KCF (kevin.fone@nottingham.ac.uk); Nutt DJ (david.j.nutt@bristol.ac.uk)

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Abbreviations

ADHD	attention deficit hyperactivity disorder
CREB	cAMP response element binding protein
DA	dopamine
DAT	dopamine transporter
MRI	magnetic resonance imaging
NE	noradrenaline
NET	noradrenaline transporter
SERT	serotonin reuptake transporter
VMAT-2	vesicular monoamine transporter-2

Introduction

Attention deficit hyperactivity disorder (ADHD) is the most prevalent childhood developmental disorder that affects between 3% and 7% of school-age children. ADHD is a chronic condition that severely impairs function both at home and in school, and frequently persists into adulthood [1,2•,3]. Two separate classification systems are used internationally to diagnose ADHD (termed hyperkinetic disorder in some countries). In the Diagnostic and Statistical Manual of Mental Disease 4th Edition (DSMIV) [4], ADHD is characterised by persistent hyperactivity, impulsivity and inattention that are differentially expressed in three subtypes: primarily inattentive, primarily hyperactive/impulsive or combined in type. However, in the International Classification of Diseases 10th edition (ICD-10, extensively used in Europe [5]), all three behaviours must be present for the diagnosis of hyperkinetic disorder, which thus has no subtypes. In the UK and US, diagnosis is based on a structured clinical interview together with symptoms rated by parents and teachers in different settings (i.e. home, school and the community) [3] using diagnostic scales.

The aetiology of ADHD is unclear. However, estimates of heritability from twin studies range from 0.5 to 0.9 which, together with a fivefold increase in risk in first-degree relatives, strongly implicates a genetic component [6•]. Although the neurobiological basis of ADHD is unresolved, recent advances in molecular genetics and brain imaging have improved our understanding of ADHD, and increasing indirect evidence implicates dopaminergic hypofunction in the frontal lobes and basal ganglia [7]. Early structural magnetic resonance imaging (MRI) used to visualize anatomical changes demonstrated a smaller fronto-basal ganglia network [8] in ADHD, but these changes are not diagnostic. Functional MRI studies to detect brain region-specific changes in blood flow and metabolism resulting from neuronal activity show reduced striatal activation in both children [9] and adolescents [10] with ADHD during performance of tasks requiring response inhibition. Recent single positron emission tomography analysis using the dopamine (DA) transporter (DAT) ligands [^{123}I]altropane and [Tc-99min]TRODAT-1 to detect dopaminergic neuronal activity suggests that a marked increase in striatal DAT levels exists in patients with ADHD [11,12]. However, one group failed to replicate this finding in just nine adults with ADHD [13]. An increase in DAT levels would be predicted to result in greater clearance of DA from the synapse and hence a relative deficiency of this neurotransmitter. There is, however, considerable debate as to whether increased DAT levels reported in imaging studies causes a reduction in synaptic DA or whether elevated DA triggers the rise in DAT levels [1].

No single gene abnormality reliably predicts ADHD but consistent association occurs between polymorphisms in a 40 base pair variable tandem nucleotide repeat in the 3′-untranslated region of the human *DAT1* gene and the DA D4 receptor 7 repeat allele [6•]. Furthermore, psychomotor stimulants such as methylphenidate (Ritalin) and dexamphetamine (Adderall), which are potent DAT inhibitors, are first-line medication for non-comorbid ADHD. Positron emission tomography imaging with a DA D2 receptor radioligand, [^{12}C]raclopride, shows that oral administration of therapeutic doses of methylphenidate increases synaptic DA levels sufficiently to displace striatal D2 receptor occupancy in the human brain [14] and causes greater striatal DA release during more highly motivated tasks [15•], consistent with the role of DA in attention.

The psychostimulants methylphenidate and amphetamine are the drugs of choice for ADHD, providing clinical benefit against the three core symptoms in 70–80% of patients in all age groups [3,16]. Development of slow-release preparations has addressed the problematic short half-life (2–5 h) of original preparations. However, occasional marked side effects (including loss of appetite, insomnia and, less commonly, motor tics) and rebound symptoms following rapid drug withdrawal makes the development of alternative medication desirable. The psychostimulant pemoline is no longer recommended as a treatment because of hepatic toxicity. The α_2-adrenoceptor agonist clonidine is used, particularly in ADHD with comorbid conditions, but is associated with more severe side effects, such as sedation. Tricyclic antidepressants are considered as second-choice drugs for ADHD but are less effective than psychostimulants and less frequently used because of potential cardiotoxicity [3,16,17]. The antidepressant buproprion has few adverse effects but is mainly prescribed for comorbid ADHD and depression [17].

Although the acute effects of methylphenidate on human and animal behaviour are well established, fewer reports have documented longer-term effects or benefits. Furthermore, the consequence of repeated psychostimulant administration to adolescent animals or humans on brain development is poorly understood. Given the progressive increase in the prescription of psychostimulants for ADHD, there is an urgent need to better understand their potential long-term adverse effects and molecular mechanisms of action, which are herein reviewed.

Psychostimulant treatment — use and abuse

Diagnosis of ADHD in young children is difficult because the characteristic behaviours are common daily events in this age group, and there is no specific clinical feature or any confirmatory biological marker. There is considerable debate among psychiatrists as to whether many cases of ADHD go untreated. In a sample of 1422 adolescents in North Carolina, one-quarter of those confirmed to have ADHD according to DSMIII criteria were not receiving drug therapy and more than half receiving stimulants failed to meet the diagnostic criteria [18], suggesting a considerable mismatch between symptoms and medication. However, the revised criteria for ADHD and hyperkinetic disorder in DSMIV and ICD-10 classification systems, respectively, require a pervasive impairment in psychological development (occurring in two or more life settings), which has improved diagnostic consistency [19].

Almost 200 randomized controlled clinical trials have confirmed the efficacy and safety of the range of psychostimulants used to treat ADHD. However, a major concern of repeated use of psychostimulants is whether this increases the risk of individuals turning to substance abuse in later life. The oral, rather than the intravenous, route of administration of methylphenidate limits abuse potential owing to the lower bioavailability and increased (first-pass) metabolism. In addition, the slower brain entry seen with oral preparations reduces the onset of DAT blockade and the rate of elevation of extracellular DA measured by microdialysis in rats [20]. In addition, the newer longer-acting formulations of methylphenidate (e.g. Concerta and Ritalin LA) are designed to give slower regulated release during the day, further attenuating acute effects. With intravenous administration in rats, dogs and primates, methylphenidate maintains high rates of self-administration comparable with amphetamine and cocaine, and methylphenidate can substitute for intraperitoneal or subcutaneous cocaine in rat drug discrimination studies [21]. However, with oral methylphenidate administration, most human studies show no preference in double-blind tablet choice procedures over placebo or no drug, and much lower subjective ratings of drug effect are seen than with amphetamine [21]. This is consistent with the low levels of drug abuse reported in ADHD patients on psychostimulants [17]. Indeed, one recent meta-analysis found that untreated ADHD adolescents were at a twofold higher risk of developing drug abuse [22••] than were those on medication, suggesting that previous exposure to methylphenidate may reduce the subsequent risk of abuse of stimulant drugs. This might be explained by an improved school performance leading to less exclusion, less criminal activity and greater feelings of self-worth. It is also possible that the presence of methylphenidate in the brain reduces the effects of illicit stimulants or other drugs. The diversion of prescribed psychostimulants to adolescents not suffering from ADHD is another area of concern, but there is little quantitative information on this topic [21]. One area of current concern is that the methylphenidate capsule might be opened and the contents taken intra-nasally ('snorted') to get a 'rush' as a consequence of faster brain entry.