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Necessity for research directed at stimulant type and treatment-onset age to access the impact of medication on drug abuse vulnerability in teenagers with ADHD

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Controversy continues regarding increased vulnerability for addiction to cocaine and other drugs of abuse in adulthood following the use of stimulant medications for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The results of recent research utilizing an animal model of ADHD strongly advocate for a closer look at this important issue in clinical populations, particularly where treatment is initiated in adolescence, and with certain ADHD medications.

The first meta-analysis examining the question of stimulant medication for ADHD and later substance use disorders (SUD) was conducted over a decade ago and concluded that stimulant medication in childhood is associated with a reduction in the risk for subsequent SUD during adolescence and young adulthood (Wilens et al., 2003). This stance regarding protective effects of stimulant medications has shifted over the years, with the most recent meta-analysis concluding that stimulant medication in childhood neither protects against nor increases the risk of later SUD beyond that associated with ADHD alone (Humphreys et al., 2013). A longitudinal 8-year follow-up of a large cohort of children in the Multimodal Treatment Study of ADHD (MTA) evaluated this same question and confirmed that stimulant medication in childhood does not protect against or increase SUD during

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Conflict of Interest

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adolescence (Molina et al., 2013). This is good news, but caution should be exercised in generalizing these findings beyond medication initiation in childhood.

A concern arises when ADHD treatment begins during adolescence. Some evidence that initiation of stimulant medication during adolescence may have different consequences for subsequent SUD than initiation in childhood is derived from research specifically analyzing age of treatment onset in ADHD patients. One study (Mannuzza et al., 2008) excluded participants with childhood conduct disorder (an uncontrolled variable in some earlier studies) and stratified children into age probands (8–12 vs. 6–7) for methylphenidate treatment initiation (treatment duration lasting 2–4 years). Lifetime rates of SUD (cocaine, amphetamines, marijuana, opiates) determined during late adolescence or young adulthood were significantly greater in the older ADHD proband (44%) compared to the younger ADHD proband (27%) and to non-ADHD comparison subjects (29%). The development of antisocial personality disorder also was positively associated with age at first methylphenidate exposure and mediated the relationship between age at first methylphenidate exposure and later SUD. In another study (Dalsgaard et al 2014), SUD risk in adulthood increased by a factor of 1.5 for every year older that childhood stimulant treatment began. Thus, initiation of stimulant medication (methylphenidate in particular) for ADHD during adolescence may have negative consequences with respect to later SUD.

There are several drawbacks to most clinical studies for understanding relationships between initiation of ADHD medication during adolescence and later SUD, such as inclusion of teens that began treatment in childhood and assessment of SUD while participants were still taking medication (e.g., Biederman et al 2008). Equally important, clinical studies tended to group ADHD drugs into a single medication variable and rarely evaluated the impact of individual medications on later SUD risk. Clearly, there is a critical gap in the clinical literature for analysis of SUD specifically in young adults that began treatment for ADHD as teenagers. To gain novel insights into this ongoing debate, we conducted a series of preclinical studies using Spontaneously Hypertensive Rats (SHR), the most widely studied animal model of ADHD (Russell, 2011).

We study SHR because this strain displays the same core behavioral characteristics as individuals with ADHD. Compared to controls, SHR are more hyperactive (Sagvolden et al., 1992), inattentive (Jentsch, 2005; De Bruin et al., 2003), and impulsive (Hand et al., 2009; Somkuwar et al., 2016). SHR also have impaired working memory (Nakamura-Palacios et al., 1996; De Bruin et al., 2003; Kantak et al., 2008) and show behavioral flexibility and habit learning deficits (Kantak et al., 2008; Wells et al., 2010; Harvey et al., 2013; Gauthier et al., 2014; Jordan et al., 2016). Importantly, the ADHD-like phenotype of SHR is unrelated to hypertension (e.g., Gattu et al., 1997; Kantak et al., 2008; Wells et al., 2010). SHR also have several neurobiological abnormalities as observed in ADHD, such as greater striatal DAT density (Roessner et al 2010; Silva et al 2014). Relative to other rat models of ADHD, SHR is the only rat model that mimics ADHD combined subtype (Russell 2011), which is the most common subtype in children and teens (Nikolas & Nigg 2013).

ADHD is known to be comorbid with SUD. Meta-analysis of patients with non-medicated ADHD show 2–3 times greater use of cocaine, other stimulants, tobacco, and marijuana

during adolescence and adulthood compared to controls without ADHD (Lee et al., 2011). Studies showing similar results in SHR strengthen the predictive power of this rat model of ADHD. The SHR self-administer more cocaine (Harvey et al., 2011; Somkuwar et al., 2013; Jordan et al., 2014; Jordan et al., 2016) and other stimulants (Meyer et al., 2010; Marusich et al., 2011; dela Pena et al., 2011) compared to Wistar-Kyoto (WKY) and Wistar (WIS) controls. Nicotine self-administration and cannabinoid-induced conditioned place preference also are greater in SHR than WKY or WIS (Pandolfo et al., 2009; Chen et al., 2012). These findings show that SHR are a reliable animal model not only of ADHD, but also of comorbid ADHD and SUD.

We investigated adolescent treatment (from postnatal day 28 to 55) with stimulant and non-stimulant ADHD medications. Low, clinically relevant doses (based on plasma drug levels and other factors) were used (1.5 mg/kg p.o. methylphenidate, 0.3 mg/kg i.p. atomoxetine, and 0.5 mg/kg i.p. d-amphetamine) to determine changes in cocaine abuse vulnerability during adulthood (from postnatal day 77 to ~150) after medications were discontinued. In all tests, male rats were used and the inbred SHR were compared to inbred WKY (controlling for the genetic homogeneity of the SHR) and outbred WIS (representing the genetic heterogeneity of the general population). To assess cocaine abuse vulnerability in adulthood, various schedules of drug delivery were used to determine the speed to acquire cocaine self-administration (fixed ratio 1 schedule), the efficacy of cocaine reinforcement across a range of cocaine doses (fixed ratio 1 schedule), the motivating influence of cocaine reinforcement across a range of cocaine doses (progressive ratio schedule), and the strength of cocaine seeking/cocaine-cue reactivity under drug maintenance, extinction, and cue-reinstatement test conditions (second-order schedule). In addition, locomotor hyperactivity and sensitization induced by cocaine as well as inherent impulsive action were measured as possible factors contributing to elevated cocaine abuse in SHR.

Across studies, SHR exhibited greater cocaine abuse vulnerability than control strains. Cocaine self-administration was acquired faster in SHR than WKY and WIS, and cocaine was a more efficacious reinforcer and had a greater motivating influence in SHR than WKY and WIS (Harvey et al., 2011; Somkuwar et al., 2013; Jordan et al., submitted). In addition, SHR were more reactive to cocaine-paired cues and took longer to extinguish cocaine-seeking responses than WKY and WIS (Jordan et al., 2014; Jordan et al., 2016). Moreover, SHR had heightened locomotor activity, cocaine sensitization, and impulsive action compared to WKY and WIS (Somkuwar et al., 2016).

Adolescent methylphenidate further enhanced cocaine abuse vulnerability in SHR during adulthood by producing an even faster speed of acquisition, a greater upward shift in the cocaine dose-response curve, a greater increase in progressive ratio breakpoints, and a greater increase in cocaine intake under the second-order schedule relative to vehicle treatment (Harvey et al., 2011; Jordan et al., 2014; Baskin et al 2015). Impulsive action, a symptom of antisocial personality disorder in people, also was further enhanced in adult SHR after discontinuing adolescent methylphenidate treatment (Somkuwar et al., 2016). This latter outcome may reflect an endophenotype contributing to the further enhancement of cocaine abuse (Phillips & Di Ciano, 1996). Adolescent methylphenidate did not alter any

measure of cocaine abuse in WKY and WIS during adulthood, except for a slower speed of acquisition in WIS (Harvey et al., 2011).

In contrast to methylphenidate, treatment with atomoxetine, a non-stimulant medication, during adolescence did not further increase any measure of cocaine abuse in SHR during adulthood (Somkuwar et al., 2013). Although extinction of cocaine-seeking responses took longer, cue-induced reinstatement of cocaine-seeking responses was reduced in adult SHR by adolescent atomoxetine across the seven test sessions (Jordan et al., 2014). Adolescent atomoxetine did not alter any measure of cocaine abuse in WKY and WIS during adulthood, except for a faster speed of acquisition in WKY (Somkuwar et al., 2013).

Although both methylphenidate and d-amphetamine are medications from the stimulant class that increase extracellular concentrations of dopamine and norepinephrine, our behavioral findings showed that adolescent d-amphetamine, unlike methylphenidate, did not further increase cocaine abuse vulnerability in adult SHR and was preventative of cocaine abuse vulnerability in adult WIS relative to vehicle treatment. In adult SHR, adolescent d-amphetamine reduced some aspects of cocaine abuse by decreasing cocaine intake at acquisition and decreasing cue-induced reinstatement of cocaine-seeking responses during the first of seven test sessions (Jordan et al., 2016; Jordan et al., submitted). In adult WIS, adolescent d-amphetamine slowed the speed of acquisition, decreased cocaine intake at acquisition, produced a downward shift in the cocaine dose-response curve, and decreased progressive ratio breakpoints (Jordan et al., submitted). Adolescent d-amphetamine did not alter any measure of cocaine abuse in WKY, except for a faster speed of acquisition (Jordan et al., submitted). The dissimilar effects of adolescent d-amphetamine and methylphenidate on cocaine abuse vulnerability in adult SHR may relate to differences in the primary mechanisms of action of these medications, leading to distinctive long-term neural consequences for transporter function, particularly in SHR. Whereas methylphenidate is a dopamine transporter (DAT) and norepinephrine transporter (NET) inhibitor that reduces neurotransmitter uptake at DAT and NET, d-amphetamine is a DAT and NET substrate that reverses neurotransmitter transport at DAT and NET (Robertson et al., 2009; Zahniser & Sorkin, 2009). In comparison, atomoxetine is a selective NET inhibitor (Bymaster et al., 2002).

Given the high translational relevance of the SHR model of ADHD, these preclinical findings suggest that by precluding a further increase in cocaine abuse vulnerability, atomoxetine and d-amphetamine may be safer alternatives to methylphenidate for treating teens newly diagnosed or newly medicated for ADHD. Currently, ~20% of teens with ADHD in the United States receive a first time diagnosis of ADHD between ages 11–17, representing an estimated 700,000 people (National Survey of Children's Health Database, 2011/2012) and making this an understudied public health concern. In our opinion, the preclinical findings in SHR advocate for sufficiently powered prospective and retrospective clinical investigations of teens newly diagnosed or newly medicated for ADHD and for whom the impact of medications on subsequent SUD is determined in young adulthood after medication is discontinued. Our preclinical findings strongly support the view that the grouping of stimulant and other ADHD drugs into a single medication variable should be abandoned in all future clinical studies and that proper diagnosis is critical. It is important to

determine whether initiation of methylphenidate treatment for ADHD during adolescence is uniquely associated with harmful long-term consequences for SUD risk, as found in SHR but not in WKY or WIS self-administering cocaine. Furthermore, the interactions between ADHD medications and other drugs of abuse bear scrutiny in preclinical and clinical investigations, as ADHD is comorbid with the use of a range of drugs in addition to cocaine (Lee et al., 2011). Evaluation of sex differences also is crucial. If armed with evidenced-based guidelines, physicians and parents can make informed and personalized medical decisions regarding the best choice and time course of ADHD medication for their children and teenagers.

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References

- Baskin BM, Dwoskin LP, Kantak KM. Methylphenidate treatment beyond adolescence maintains increased cocaine self-administration in the spontaneously hypertensive rat model of attention deficit/hyperactivity disorder. *Pharmacol Biochem Behav.* 2015; 131:51–56.
- Biederman J, Monuteaux MC, Spencer T, Wilens TE, Macpherson HA, Faraone SV. Stimulant therapy and risk for subsequent substance use disorders in male adults with ADHD: a naturalistic controlled 10-year follow-up study. *Am J Psychiatry.* 2008; 165:597–603. [PubMed: 18316421]
- Bymaster FP, Katner JS, Nelson DL, Hemrick-Luecke SK, Threlkeld PG, Heiligenstein JH, Morin SM, Gehlert DR, Perry KW. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology.* 2002; 27:699–711. [PubMed: 12431845]
- Chen H, Hiler KA, Tolley EA, Matta SG, Sharp BM. Genetic factors control nicotine self-administration in isogenic adolescent rat strains. *PLoS One.* 2012; 7:e44234. [PubMed: 22937166]
- Dalsgaard S, Mortensen PB, Frydenberg M, Thomsen PH. ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood - a naturalistic long-term follow-up study. *Addict Behav.* 2014; 39:325–328. [PubMed: 24090624]
- De Bruin NM, Kiliaan AJ, De Wilde MC, Broersen LM. Combined uridine and choline administration improves cognitive deficits in spontaneously hypertensive rats. *Neurobiol Learn Mem.* 2003; 80:63–79. [PubMed: 12737935]
- dela Pena IC, Ahn HS, Choi JY, Shin CY, Ryu JH, Cheong JH. Methylphenidate self-administration and conditioned place preference in an animal model of attention-deficit hyperactivity disorder: the spontaneously hypertensive rat. *Behav Pharmacol.* 2011; 22:31–39. [PubMed: 21160423]
- Gattu M, Terry AV Jr, Pauly JR, Buccafusco JJ. Cognitive impairment in spontaneously hypertensive rats: role of central nicotinic receptors. Part II. *Brain Res.* 1997; 771:104–114. [PubMed: 9383013]
- Gauthier JM, Tassin DH, Dwoskin LP, Kantak KM. Effects of dopamine D1 receptor blockade in the prefrontal cortex or lateral dorsal striatum on frontostriatal function in Wistar and Spontaneously Hypertensive Rats. *Behav Brain Res.* 2014; 268:229–238. [PubMed: 24755309]
- Hand DJ, Fox AT, Reilly MP. Differential effects of d-amphetamine on impulsive choice in spontaneously hypertensive and Wistar-Kyoto rats. *Behav Pharmacol.* 2009; 20:549–553. [PubMed: 19654504]
- Harvey RC, Jordan CJ, Tassin DH, Moody KR, Dwoskin LP, Kantak KM. Performance on a strategy set shifting task during adolescence in a genetic model of attention deficit/hyperactivity disorder: methylphenidate vs. atomoxetine treatments. *Behav Brain Res.* 2013; 244:38–47. [PubMed: 23376704]
- Harvey RC, Sen S, Deaciuc A, Dwoskin LP, Kantak KM. Methylphenidate treatment in adolescent rats with an attention deficit/hyperactivity disorder phenotype: cocaine addiction vulnerability and

- dopamine transporter function. *Neuropsychopharmacology*. 2011; 36:837–847. [PubMed: 21150910]
- Humphreys KL, Eng T, Lee SS. Stimulant medication and substance use outcomes: a meta-analysis. *JAMA Psychiatry*. 2013; 70:740–749. [PubMed: 23754458]
- Jentsch JD. Impaired visuospatial divided attention in the spontaneously hypertensive rat. *Behav Brain Res*. 2005; 157:323–330.
- Jordan CJ, Dwoskin LP, Kantak KM. Adolescent d-amphetamine treatment in a rodent model of attention-deficit/hyperactivity disorder: Impact on cocaine abuse vulnerability in adulthood. Submitted.
- Jordan CJ, Harvey RC, Baskin BB, Dwoskin LP, Kantak KM. Cocaine-seeking behavior in a genetic model of attention-deficit/hyperactivity disorder following adolescent methylphenidate or atomoxetine treatments. *Drug Alcohol Depend*. 2014; 140:25–32. [PubMed: 24811203]
- Jordan CJ, Taylor DM, Dwoskin LP, Kantak KM. Adolescent d-amphetamine treatment in a rodent model of ADHD: Pro-cognitive effects in adolescence without an impact on cocaine cue reactivity in adulthood. *Behav Brain Res*. 2016; 297:165–179. [PubMed: 26467602]
- Kantak KM, Singh T, Kerstetter KA, Dembro KA, Mutebi MM, Harvey RC, Deschepper CF, Dwoskin LP. Advancing the spontaneous hypertensive rat model of attention deficit/hyperactivity disorder. *Behav Neurosci*. 2008; 122:340–357.
- Lee SS, Humphreys KL, Flory K, Liu R, Glass K. Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: a meta-analytic review. *Clin Psychol Rev*. 2011; 31:328–341. [PubMed: 21382538]
- Mannuzza S, Klein RG, Truong NL, Moulton JL 3rd, Roizen ER, Howell KH, Castellanos FX. Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. *Am J Psychiatry*. 2008; 165:604–609. [PubMed: 18381904]
- Marusich JA, McCuddy WT, Beckmann JS, Gipson CD, Bardo MT. Strain differences in self-administration of methylphenidate and sucrose pellets in a rat model of attention-deficit hyperactivity disorder. *Behav Pharmacol*. 2011; 22:794–804. [PubMed: 22015805]
- Meyer AC, Rahman S, Charnigo RJ, Dwoskin LP, Crabbe JC, Bardo MT. Genetics of novelty seeking, amphetamine self-administration and reinstatement using inbred rats. *Genes Brain Behav*. 2010; 9:790–798. [PubMed: 20618445]
- Molina BS, Hinshaw SP, Eugene Arnold L, Swanson JM, Pelham WE, Hechtman L, Hoza B, Epstein JN, Wigal T, Abikoff HB, Greenhill LL, Jensen PS, Wells KC, Vitiello B, Gibbons RD, Howard A, Houck PR, Hur K, Lu B, Marcus S. Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. *J Am Acad Child Adolesc Psychiatry*. 2013; 52:250–263. [PubMed: 23452682]
- Nakamura-Palacios EM, Caldas CK, Fiorini A, Chagas KD, Chagas KN, Vasquez EC. Deficits of spatial learning and working memory in spontaneously hypertensive rats. *Behav Brain Res*. 1996; 74:217–227. [PubMed: 8851933]
- National Survey of Children’s Health Database 2011/2012. Available at <http://www.nschdata.org/browse/survey/results?q=2390&r=1&g=451>.
- Nikolas MA, Nigg JT. Neuropsychological performance and attention-deficit hyperactivity disorder subtypes and symptom dimensions. *Neuropsychology*. 2013; 27:107–120. [PubMed: 23148496]
- Pandolfo P, Vendruscolo LF, Sordi R, Takahashi RN. Cannabinoid-induced conditioned place preference in the spontaneously hypertensive rat-an animal model of attention deficit hyperactivity disorder. *Psychopharmacology (Berl)*. 2009; 205:319–326. [PubMed: 19407992]
- Phillips AG, Di Ciano P. Behavioral sensitization is induced by intravenous self-administration of cocaine by rats. *Psychopharmacology (Berl)*. 1996; 124:279–281. [PubMed: 8740051]
- Robertson SD, Matthies HJ, Galli A. A closer look at amphetamine-induced reverse transport and trafficking of the dopamine and norepinephrine transporters. *Mol Neurobiol*. 2009; 39:73–80. [PubMed: 19199083]
- Roessner V, Sagvolden T, DasBanerjee T, Middleton FA, Faraone SV, Walaas SI, Becker A, Rothenberger A, Bock N. Methylphenidate normalizes elevated dopamine transporter densities in an animal model of the attention-deficit/hyperactivity disorder combined type, but not to the same

extent in one of the attention-deficit/hyperactivity disorder inattentive type. *Neurosci.* 2010; 167:183–1191.

- Russell VA. Overview of animal models of attention deficit hyperactivity disorder (ADHD). *Curr Protoc Neurosci.* 2011; Chapter 9(Unit9):35. [PubMed: 21207367]
- Sagvolden T, Metzger MA, Schiorbeck HK, Rugland AL, Spinnangr I, Sagvolden G. The spontaneously hypertensive rat (SHR) as an animal model of childhood hyperactivity (ADHD): changed reactivity to reinforcers and to psychomotor stimulants. *Behav Neural Biol.* 1992; 58:103–112. [PubMed: 1360797]
- Silva N, Szobot CM, Shih MC, Hoexter MQ, Anselmi CE, Pechansky F, Bressan RA, Rohde LA. Searching for a neurobiological basis for self-medication theory in ADHD comorbid with substance use disorders: an in vivo study of dopamine transporters using (99m)Tc-TRODAT-1 SPECT. *Clin Nucl Med.* 2014; 39:e129–e134. [PubMed: 23856832]
- Somkuwar * SS, Jordan * CJ, Kantak KM, Dwoskin LP. Adolescent atomoxetine treatment in a rodent model of ADHD: effects on cocaine self-administration and dopamine transporters in frontostriatal regions. *Neuropsychopharmacology.* 2013; 38:2588–2597. * co-first authors. [PubMed: 23822950]
- Somkuwar SS, Kantak KM, Bardo MT, Dwoskin LP. Adolescent methylphenidate treatment differentially alters adult impulsivity and hyperactivity in the Spontaneously Hypertensive Rat model of ADHD. *Pharmacol Biochem Behav.* 2016; 141:66–77. [PubMed: 26657171]
- Wells AM, Janes AC, Liu X, Deschepper CF, Kaufman MJ, Kantak KM. Medial temporal lobe functioning and structure in the spontaneously hypertensive rat: comparison with Wistar-Kyoto normotensive and Wistar-Kyoto hypertensive strains. *Hippocampus.* 2010; 20:787–797. [PubMed: 19623608]
- Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics.* 2003; 111:179–185. [PubMed: 12509574]
- Zahniser NR, Sorkin A. Trafficking of dopamine transporters in psychostimulant actions. *Semin Cell Dev Biol.* 2009; 20:411–417. [PubMed: 19560046]