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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

Kathleen M. Kantak[1] and **Linda P. Dwoskin**[2]

[1]Department of Psychological and Brain Sciences, Boston University, Boston, Massachusetts 02215, USA

[2]Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, Kentucky 40536, USA

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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

Corresponding Author: Dr. Kathleen M. Kantak, Department of Psychological and Brain Sciences, Boston University, 64 Cummington Mall, Boston, MA 02215, Phone: (617) 353-9201, Fax: (617) 353-2894, kkantak@bu.edu.

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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