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Commentary

Long-Term Safety of Stimulant Use for ADHD: Findings from Nonhuman Primates

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Stimulant medications (methylphenidate (MPH) and amphetamine (AMP)) have been used for the treatment of ADHD for >50 years. At the time of their approval, the regulatory processes were much less stringent with respect to safety information than those of today. Currently, around 4 million children are treated with stimulants each day in the USA (Zuvekas and Vitiello, 2012), which has led to valid concerns over their possible developmental effects, particularly as children and adolescents are being treated with stimulant medications at the time of profound neural, hormonal, and physical changes and usually over relatively long time periods—several years. A chief concern has been the potential adverse effects of stimulant medications to the developing brain, specifically as they relate to dopamine (DA) brain function and the risk for substance use disorder (Volkow and Swanson, 2008). This is because stimulant medications increase DA in the nucleus accumbens, which is the pharmacological effect that underlies drug reward and that with repeated use triggers the neuroadaptations in dopaminergic and glutamatergic signaling associated with addiction (Kalivas and Volkow, 2005). Indeed, MPH and AMP are abused and can result in addiction (Volkow and Swanson, 2003). Another clinical concern has been the potential adverse effects of stimulant medications on physical growth (Swanson *et al*, 2007). However, resolution of these critical clinical issues about stimulant medications has been difficult to address directly in humans because of ethical and practical considerations.

Preclinical studies have aimed to resolve this issue, and over the past 10 years several studies have assessed the effects of chronic exposure to stimulants during early development (corresponding to childhood and adolescence) in the sensitivity to drug rewards and to its effects on brain DA signaling. The findings have been inconclusive, with some studies showing enhanced sensitivity to drug rewards and changes in DA signaling whereas others reporting no changes or decreased drug responses (Volkow and Insel, 2003). The reasons for discrepancies are many, and include among others the time at which medications are initiated as well as the doses and route of administration used (Volkow and Insel, 2003). On the other hand, there have been no reported preclinical studies on the effects of stimulant medications on physical growth.

In the current issue, two studies provide important data on the safety of chronic stimulant use by examining their effects in young non-human primates, which share greater similarity to humans than the rodent model and incorporate important methodological advances (such as how the drugs were administered and titrated to achieve clinically relevant drug concentrations in plasma). Gill *et al* (2012) administered extended-release MPH or placebo for 12 months to adolescent male monkeys and measured synaptic DA markers in the brain (DA transporters and D2/D3 receptors), vulnerability to cocaine abuse (self-administration paradigm after a 3–5 month washout period), and physical growth and showed no significant effects of MPH on any of these measures.

Similar findings were reported by Soto *et al* (2012) when peri-adolescent male monkeys were treated with either MPH, AMP, or placebo for 18 months and failed to show effects of stimulant treatment on synaptic DA markers in brain (transporters and D2/D3 receptors; they also failed to see changes in AMP-induced DA increases) as well as in physical growth, both when tested shortly after drug discontinuation and 6 months later. Additionally, they did not observe any major effects on cognitive (ie, reaction times, cognitive control) or motor behaviors (spontaneous locomotor activity) after chronic treatment following immediate or prolonged discontinuation.

Therefore, the results of both articles suggest that chronic MPH or AMP started in peri-adolescence/adolescence at clinically relevant doses do not significantly alter DA system development nor do they affect physical growth in non-human primates. They also suggest that they do not sensitize the brain to drug rewards (Gill *et al*, 2012) nor that they negatively affect cognitive or motor behaviors after discontinuation (Soto *et al*, 2012).

A limitation from these studies is that they are done in healthy animals and the long lasting effects from chronic treatment with stimulant medications may differ in

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individuals with ADHD. However, the findings, at least as they relate to substance use disorders, are consistent with those from long-term follow-up studies that showed no long-term effects—positive (ie, decreasing risk for substance use) or negative (increasing risk for substance use)—of clinical treatment with stimulant medication (Volkow and Swanson, 2008).

These two studies support the safety of stimulant usage for ADHD in children and adolescents and are a state-of-the-art example of translational research from animal to human studies that address an important public health issue (ie, the exposure of a large percentage of children and adolescents to a medication that is assumed but not proven to have long-term side effects).

DISCLOSURE

The author declares no conflict interest.

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