Stimulant Medications: How to Minimize Their Reinforcing Effects?

It is believed that methylphenidate and amphetamine, the most frequently used pharmacological treatments for ADHD, exert their therapeutic effects in part by their ability to increase extracellular dopamine in the striatum and cortical brain regions (1). Both increase dopamine by their actions on dopamine transporters: methylphenidate by blocking them (2) and amphetamine by releasing dopamine from the terminal using the dopamine transporter as the carrier (3). The ability of methylphenidate and amphetamine to increase dopamine is also associated with their reinforcing effects, and this is likely to be one of the main mechanisms underlying their abuse; other reasons for abuse are to improve performance or to lose weight. Note that the ability to increase dopamine in the nucleus accumbens (ventral part of the striatum involved with reward circuitry) is believed to be a common pharmacological effect underlying the reinforcing effects of drugs of abuse (4). However, the patterns of stimulant-induced increases in dopamine that are associated with therapeutic effects differ from those accounting for reinforcing effects. Whereas steady state and stable dopamine increases are associated with the therapeutic effects of stimulant medications, abrupt and fast dopamine increases are associated with their reinforcing effects (5). This is likely to reflect the two processes that regulate dopamine extracellular levels and signaling in the brain: tonic dopamine cell firing (which maintains baseline steady state dopamine levels and sets the overall responsiveness of the dopamine system) and phasic dopamine cell firing (which leads to fast dopamine changes that highlight the saliency of stimuli) (6). Whether a stimulant drug induces a fast versus a slow increase in dopamine will be dependent on the rate at which the stimulant enters the brain and reaches the dopamine transporter. Because the rate of entry into the brain is affected by the dose (larger doses will lead to higher concentrations per unit of time) and the route of administration (fastest rate of brain delivery: smoking, followed by injection, then snorting, then oral ingestion), these are variables that modify the reinforcing effects of stimulant medications. Thus, higher doses are more reinforcing than lower doses and the faster the rate of delivery, the greater the reinforcing effects of stimulant medications. Indeed, when stimulant medications are abused for their reinforcing effects they are frequently snorted or injected, and when given orally at therapeutically recommended doses they have minimal or no reinforcing effects (5).

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On the basis of these findings from basic research over the past decade, preparations of methylphenidate or amphetamine that lead to slow rates of brain uptake as well as those that cannot be snorted or injected are predicted to have less abuse liability. The paper by Spencer and colleagues in this issue of the Journal provides evidence that even for oral formulations of stimulant medications, delivery by systems that lead to slower rates of release will be less reinforcing than delivery that leads to faster rates of release. In their study, they compared the brain pharmacokinetics and the reinforcing effects of methylphenidate when delivered by an immediate-release oral formulation to the effects when delivered by a controlled osmotic-release formulation. They used positron emission tomography (PET) and the dopamine transporter radioligand [^{11}C]altropane

to measure dopamine transporter blockade by methylphenidate at different times after its administration when delivered as immediate-release versus when delivered as osmotic-release methylphenidate. They found that doses of immediate-release methylphenidate (40 mg) and osmotic-release methylphenidate (90 mg) led to equivalent peak levels of dopamine transporter blockade (immediate release: 72%; osmotic release: 68%) but at different times after administration of the doses. The peak dopamine transporter blockade was achieved significantly faster (after 1.7 hours) with the immediate-release formulation than with osmotic-release methylphenidate (5 hours). Also, the levels of dopamine transporter blockade during the first 2 hours were significantly higher and thus achieved faster for immediate-release methylphenidate than for the osmotic-release formulation. The peak level of dopamine transporter blockade achieved with 40 mg of immediate-release methylphenidate was associated with mild but still significant reinforcing effects (according to subjects' self-reports of drug liking), but the same peak level achieved with 90 mg of osmotic-release methylphenidate was devoid of any reinforcing effects. These findings corroborate that the relevant variable for the reinforcing effects of stimulant drugs is the rate at which dopamine increases (change in dopamine concentration per time unit) rather than dopamine level per se. Thus, delivery systems that lead to very slow rates of dopamine transporter blockade and slow rates of dopamine increases are likely to have less abuse liability than delivery systems that lead to faster dopamine changes.

Dr. Spencer and colleagues also found that the duration of dopamine transporter blockade was longer with the 90-mg dose of osmotic-release methylphenidate than with the 40-mg dose of immediate-release methylphenidate, so that at a constant time after dosing (e.g., 7 hours) the level of dopamine transporter blockade for osmotic-release methylphenidate was considerably higher (65% versus 40% for immediate-release methylphenidate). If the rate of dopamine change is positively associated with the reinforcing effects of methylphenidate, its slow clearance from and its long occupancy of dopamine transporter will limit the rate at which it can be administered before producing dopamine transporter saturation. Also, because the rate at which rodents self-administer stimulant drugs is associated with the downward slope of dopamine after prior increases in the nucleus accumbens (7), this predicts that delivery systems that maintain steady state plasma levels for longer time periods are less likely to be abused than delivery systems that lead to more abrupt changes.

The relatively high rates of stimulant abuse highlight the urgent need to develop strategies that minimize stimulants' potential reinforcing effects and prevent their abuse. Prevalence rates for the abuse of stimulant medications in the general population are not negligible. In 2005, the prevalence rates among 12th graders for amphetamine and methylphenidate abuse in the past year were 8.6% and 4.4%, respectively (8). The data from Spencer and collaborators provide an example of how imaging technologies can now be utilized to predict the likelihood for a drug to have reinforcing effects by being able to directly monitor the temporal course of their effects in dopamine targets in the human brain. Since most prescriptions for methylphenidate are now for controlled-release formulations, and much less immediate-release methylphenidate is produced and thus available, monitoring over time should reveal a decrease in methylphenidate abuse.

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