[COMMENTARY]

The Dopamine Dilemma—Part II: Could Stimulants Cause Tolerance, Dependence, and Paradoxical Decompensation?

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ABSTRACT

In this commentary, the author calls to attention that stimulants are commonly prescribed to children for years without seeming regard to the lack of studies on efficacy and safety during long-term use. The author examines evidence for stimulants losing efficacy over time and provides multiple possible mechanisms. The potential for *paradoxical decompensation*, an iatrogenic worsening of symptoms over time, is considered and discussed. Recommendations for detecting and responding to possible stimulant tolerance and dependence are provided.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the most-studied and most-diagnosed psychiatric condition in children.[1] National guidelines report that the first-line treatment for ADHD is a stimulant medication,[2] and stimulants have been shown to have a short-term success rate as high as 68 to 80 percent.[2]

Prescriptions for stimulants have increased dramatically over the last two decades. There was a four-fold increase in the use of stimulants in children from 1987 to 1996,[3] and more recent examination showed that this increase remains stable.[4] More than half of pediatric outpatient appointments where a psychiatric medication is prescribed include a prescription for a stimulant.[5]

The high percentage of children being treated with stimulants suggests that most psychiatrists believe the benefits of stimulants outweigh the risk of any potential side effects. In fact, it is not uncommon for children to be prescribed stimulants continuously for a course of years. However, while the therapeutic effects of stimulants can be seen within minutes, concerns have been expressed that long-term studies on

the safety and efficacy of these medications are lacking,[7] especially in light of the fact that children may be more vulnerable than adults to psychiatric medication side effects.[6,10]

In this commentary, I will review the data available on the efficacy of long-term stimulant use. I will then discuss the possible mechanisms for loss of efficacy. I propose that an examination of stimulant tolerance and its potential ramifications is important and should be considered in clinical practice.

ADDICTION, TOLERANCE, AND DEPENDENCE

It is helpful to begin by defining the relevant terms. *Addiction* is a complicated biological and psychological phenomenon in which difficulty abstaining from substances leads to problems functioning within multiple life areas. *Tolerance* to a medication is present when the response to the same dose of a drug decreases with repeated use over time, such that larger doses of the medication become necessary to achieve the same level of response.[12]

Dependence on a medication is present when chronic use of a medication has caused the brain to adapt in such a way that the medication is now necessary in order to function at a level that was previously reachable without any medication. Furthermore, when the medication is removed, withdrawal symptoms appear, often leading to addiction.[13]

Generally, higher doses of medications and longer durations of use put patients at increased risk of developing dependence and tolerance. However, during periods of abstinence from the medication, these phenomena are reversible. Most psychopharmacological agents have the potential to cause at least some tolerance, dependence, and addiction, even medications considered safe for long-term use, such as antidepressants.[14]

Mechanisms of addiction vary, depending on the substance, but they share a common endpoint: feelings of reward and reinforcement due to dopamine (DA) release within the brain's "reward system."[15,16] The reward system is a product of the mesolimbic DA pathway, which connects the ventral tegmental area of the midbrain to the limbic system and involves the nucleus accumbens, amygdala, hippocampus, and medial prefrontal cortex.[17]

Complex DA Theory includes explanations of DA regulation at the level of the pre- and postsynaptic DA receptors. Both of these receptor types have been associated with important negative feedback mechanisms of DA regulation, particularly at D1 and D2.[24,28–32] When the brain becomes overstimulated by hyperdopaminergic states, it uses regulatory mechanisms as counter-acting defenses. More specifically, presynaptic DA receptors respond to hyperdopaminergic states by decreasing their rate of further DA release into the synapse.[29] Additionally, postsynaptic receptors respond by downregulating themselves, decreasing the binding of DA already in the synapse, desensitizing the brain to DA, and leading to tolerance and addiction.[24,30]

The most addicting substances known are heroine, cocaine, tobacco, barbituates, alcohol, benzodiazepines, amphetamine, cannabis, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamin (i.e., ecstacy), respectively.[18] While cocaine and amphetamine have direct effects on DA receptors, the remaining substances activate DA transmission indirectly, by way of secondary messengers.[13,15,16,19–24] For example, chronic nicotine use causes euphoria, relaxation, and eventual addiction as a result of binding to acetylcholine receptors, which indirectly causes DA release within the reward system.[16,24]

PARADOXICAL DECOMPENSATION

When a substance causes physical dependence, removal of the substance often leads to withdrawal symptoms. If a medication causes dependence over time, removal of the medication may unmask worsened symptoms. The phenomenon of long-term use of a medication causing a worsened baseline of the condition it was treating will be referred to as *paradoxical decompensation*.

Clear examples of paradoxical decompensation are difficult to find in the literature, but they exist, often with their own terminology. Restless legs syndrome (RLS) has been linked with ADHD, and is treated with similar medications (e.g., dopamine agonists).[46] While these medications treat RLS symptoms initially, within a matter of days, they cause a worsening of symptoms in up to 82 percent of patients, referred to as *augmentation*. This is reflected by higher intensity of symptoms and by symptoms starting earlier in the evening.[47]

Benzodiazepines are highly effective at rapidly reducing anxiety.[48,49] However, similar to stimulant use, it is common for patients using benzodiazepines to require an increased dose or use of multiple agents when the medication was initially effective but then lost efficacy over time.[50–52]

The same phenomenon has been recognized with long-term use of antidepressants and has been referred to as the *oppositional model of tolerance*. There is evidence that long-term use of antidepressants can result in more depressive episodes and worse outcomes over time. This oppositional model suggests that chronic use of antidepressants "recruit processes that oppose the initial acute effect of a drug," and when the drug is removed, "these processes may operate unopposed, at least for some time and increase vulnerability to relapse."[14]

Recognition of paradoxical decompensation caused by caffeine is particularly relevant to stimulant use, because of the shared ability to increase alertness and motivation. People who regularly use caffeine, an adenosine antagonist, adapt to the frequent presence of it by up-regulating the number of adenosine receptors. This mechanism of tolerance and dependence seen with coffee has been referred to as *tolerance adaptation*.[53]

STIMULANTS AND ADDICTION: BASIC SCIENCE

While most substances that lead to addiction increase DA release by indirect pathways, stimulants act directly on presynaptic DA receptors themselves, leading to release of DA in storage vesicles. The two types of prescribed stimulants, methylphenidate and amphetamine, have slightly different mechanisms of action. Methylphenidate inhibits the reuptake of dopamine.[37,38] Amphetamine has the additional function of entering the presynaptic neuron and forcing additional vesicular DA into the synapse. Stimulants are thought to have their therapeutic effects mostly through D1, but they have been shown to also have significant action at D2.[38,39]

In theory, by manipulating DA directly, stimulants should be especially conducive to activating DA regulatory mechanisms (e.g., reduction of presynaptic release and postsynaptic receptor downregulation). DA receptor changes have been found to correlate both with observed and reported signs of tolerance to both DA agonists (e.g., stimulants) and antagonists (e.g., antipsychotics) as a result changes in D2 receptor density.[31,32] For example, "supersensitive" DA receptors have been demonstrated with chronic antipsychotic use[31] and correlate with observed medication tolerance.[32] One study showed that repeating the same dose of stimulant, immediately after therapeutic effects were lost, produced only half the efficacy of the initial dose.[44] This suggests that tolerance to stimulants occurs at some degree even within several hours.

Additionally, the pre- and postsynaptic DA regulatory mechanisms associated with stimulants lead not only to tolerance of the stimulants, but to the brain's endogenous DA, as well.[28–30] Since low dopamine is theorized to be the cause of ADHD, decreasing the brain's sensitivity to DA is the opposite of what patients with ADHD need, and could theoretically lead to paradoxical decompensation of the ADHD symptoms (Figures 1 and 2).

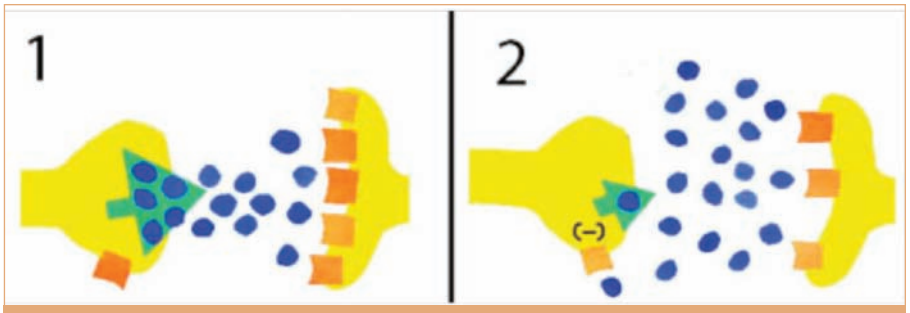

FIGURE 1. Stimulants and complex dopamine theory. Box 1 represents the short-term effects of a stimulant: an increased amount of DA in the synapse;Box 2 represents the long-term effects of a stimulant on the DA synapse. Over time, high levels of synaptic DA initiate negative feedback mechanisms: post-synaptic receptors down-regulate and pre-synaptic DA release is decreased.

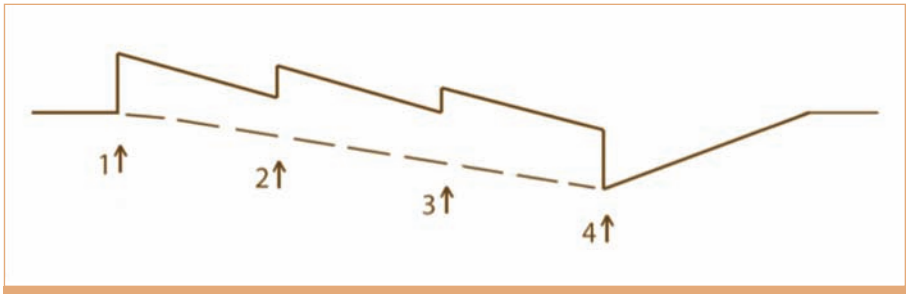

FIGURE 2. Paradoxical decompensation in a medicated patient. Solid line: symptom improvement over time (including effects of medication); Dotted line: underlying condition (symptom improvement if medication was not present at any given moment); 1=medication started, 2=dose increased, 3=dose increased again, 4=medication discontinued

CLINICAL EXAMINATION OF ADHD, STIMULANTS, AND TOLERANCE

Though stimulants and cocaine share a similar mechanism, a longer half-life has been suggested as the reason that stimulant medications, when used appropriately, are less likely to cause addiction.[25] Abuse of stimulants is widespread, particularly abuse of stimulants with a short time of onset. Studies have shown stimulant abuse to be as prevalent as 8 to 14 percent in certain populations, and the most common reasons for stimulant abuse include increasing concentration/alertness and getting "high." Amphetamine, the stimulant closest to cocaine, is chosen three times more often than methylphenidate. Not surprisingly, snorting stimulants, which increases the speed that the chemical reaches the brain, is a popular route of abuse.[26,27]

Stimulants' ability to cause tolerance is controversial, but the need for dose increases over time has been recognized in the literature by the American Academy of Child and Adolescent Psychiatry (AACAP). Their treatment guidelines state that "most" children will "require dose adjustment upward as treatment progresses."[55] Additionally, the Multimodal Treatment Study of Children with ADHD (MTA), the largest ADHD treatment study in existence, found that stimulants may have less efficacy over time. Their data supported the short-term efficacy of stimulants in ADHD, but recent follow-up after several years showed that patients taking stimulant medications had the same level of symptoms as those who had never been medicated.[11]

These findings do not necessarily suggest the presence of tolerance.

The participants may have also been nonadherent, dosed inadequately, or misdiagnosed to begin with. However, when a correctly diagnosed and dosed child's ADHD symptoms respond to a stimulant for several weeks or months and then relapse, what is the most likely cause? Why might stimulants lose efficacy, requiring higher doses over time?

The four main proposed mechanisms for tolerance include the following:

1. **Changes in pharmacokinetics.** It has been shown that larger children have less exposure to the same dose of stimulant medications than smaller children.[66] This suggests that if a child grows and his stimulant dose is kept the same, it may lose efficacy.
2. **Progression of disorder.** The underlying illness may have worsened naturally and a higher dose of stimulant is required.[43] While the usual trend is for symptoms to stay the same or improve over time,[45] it is possible for a child to have a naturally worsening course.
3. **Environmental changes.** A child could be placed in a new environment with more attention demands, unmasking hidden symptoms and requiring a higher dose of stimulant.
4. **Paradoxical decompensation.** An alternative explanation is that the medication itself has worsened the ADHD[28,31,32] because tolerance and dependence have caused paradoxical decompensation (Figure 1). If this is the case, an increase in the dose may help temporarily but lead to worsened decompensation in the long term. There also may be a psychological component. Children who take stimulants for several years may develop less natural coping mechanisms while medicated than children who were not treated.[54]

Because long-term studies are lacking and the efficacy of stimulants over time is not known, it is unclear which of these mechanisms is most likely to cause loss of efficacy. The first three mechanisms warrant dose increases, while the fourth mechanism does not. Despite United States Food and Drug Administration (FDA) warnings about risks of tolerance and dependence with long-term stimulant use, practice trends suggest that psychiatrists are not concerned about the possibility of paradoxical decompensation.[3–6] In fact, AACAP practice parameters state that stimulant treatment should be continued, "as long as symptoms remain present."[55]

Is the general lack of concern about paradoxical decompensation justified? While the basic science research I describe is suggestive of the potential for this phenomenon, clinical research aimed specifically at examining the likelihood of stimulant tolerance is sparse. There has never been a study designed specifically to examine whether or not stimulants have the potential to worsen ADHD symptoms over time. One review of 166 patients found that 60 percent of children developed dose-dependent tolerance to stimulants.[43] However, because of the lack of other research in this area, the verdict is still out.

RECOGNIZING AND REACTING TO STIMULANT TOLERANCE AND PARADOXICAL DECOMPENSATION

While it is unclear whether paradoxical decompensation is a frequent phenomenon with stimulant use, at the very least, it should be recognized as a possibility that may be seen with some children.

If stimulants were to cause long-term worsening of underlying ADHD symptoms, and complete symptom relief was continuously sought after, this could lead to a paradoxical decompensation cycle (i.e., progressive symptom worsening over time and the appearance of higher and higher dosages being needed to reach the same level of benefit).

The potential long-term cost of chasing symptom relief by way of multiple increases in dose size or frequency warrants further study. If paradoxical decompensation is present, it may be appropriate to view the symptom relief received by stimulants as a "borrowed benefit." Much like borrowing money from a bank, these symptoms must be paid back in the future. The payback upon stimulant discontinuation may be a subacute syndrome, during which the patient will function "attention-wise" below their baseline (due to downregulated postsynaptic DA receptors and decreased presynaptic DA release).[28–30] This subclinical withdrawal would decrease over time, but may be present, to some degree, until the receptors are completely reversed back to their baseline set-point.

If stimulant dependence exists with a patient, it may be difficult to recognize because, even though the medication may appear to have "pooped out," removing it may cause symptoms to worsen further. This need for higher doses of stimulants would mask the possibility of stimulants causing dependence because stimulants are not classically considered to be addictive medications.

If paradoxical decompensation with stimulants is suspected, the appropriate corrective action would be a period of abstinence from the medication. These temporary detoxifications have has often been referred to as *drug holidays*. These breaks from treatment serve to "partially reverse the physiological adaptive effects that result from chronic pharmacological stimulation," and they result in resensitizing neurons."[59] These changes should help to both decrease the underlying ADHD symptoms over time and make stimulant medications more effective again if used in the future, essentially by reversing tolerance, dependence, and paradoxical decompensation.

Studies have shown that weekend drug holidays reduce stimulant side effects without causing significant symptom increases, likely because the medications were reduced during the days when less focus was required.[60] However, the exact duration and dosage of the preceding treatment needed for a drug holiday to be effective is unclear and needs further

research. Because paradoxical decompensation is minimized in the literature, stimulant drug holidays are not included in ADHD treatment guidelines.

Eliciting adherence with stimulant drug holidays may be difficult. A parent who frequently seeks increases in their child's stimulant dose over time because they cannot tolerate any ADHD symptoms may be resistant to discontinue the medication for even a short period. This scenario may represent a form of addiction-by-proxy.

When drug holidays are found to be ineffective at reducing dependence and paradoxical decompensation, complete abstinence of the medication should be considered. Withdrawal effects from stimulant discontinuation do occur, but they are usually not serious and can be minimized by gradually tapering the dose.[61] Close psychological support for both the child and the parent are important at this time.

Nonstimulant medications, such as atomoxetine, clonidine, buproprion, modafinil, guanfacine extended release, and tricyclic antidepressants may be appropriate treatments following stimulant discontinuation.[62,63] Nonpharmacological approaches, including parent training, social skills training, and assessment for appropriate educational placement, are also likely to provide significant benefit.[64]

CONCLUSION

Complex dopamine theory and clinical studies suggest that stimulant medications may have the potential to cause tolerance and dependence over time but the data are unclear. Only time will tell what the "stimulant generation" will teach us about ADHD treatment patterns over the recent decades.

Thoughtful physicians should appreciate the following guiding points:

1. Stimulants act to directly increase dopamine activity in the brain, sharing a similar mechanism of action with many addictive drugs of abuse.
2. Theory and evidence suggest the possibility that even "'appropriate" use of stimulants may lead to tolerance and dependence, but to what degree, if any, these phenomena should be considered real concerns is unclear.
3. A child's pattern of requiring multiple stimulant dose increases over weeks, months, and years may suggest that he or she has been developing tolerance and dependence, but this is only one of multiple possible explanations.
4. Using stimulants for short durations or with consistent drug holidays might decrease the risk of these phenomena.
5. If drug holidays are shown to be ineffective at preventing escalating symptom intensity and the need to make frequent dose increases, the patient may need to be gradually tapered off the stimulant with close psychological support.

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