THE DOPAMINE DILEMMA: Using Stimulants and Antipsychotics Concurrently

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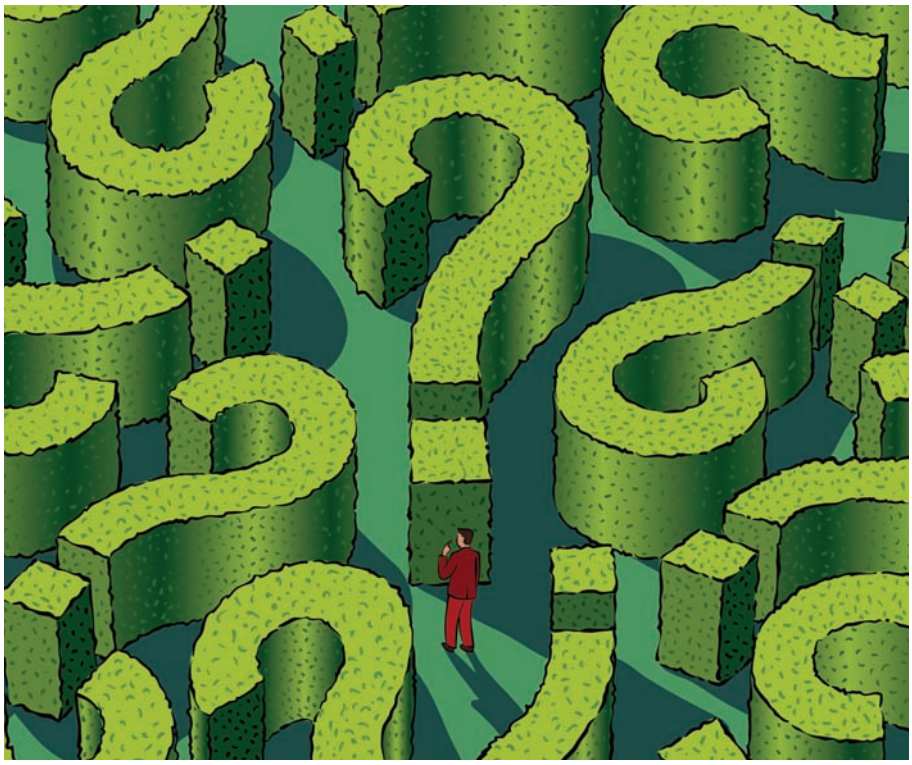
ABSTRACT

Stimulant and antipsychotic medications are commonly used together without concern, despite their potentially opposing mechanisms. An examination of dopamine pathways and receptors suggests that concerns regarding interactions between these two classes are justified and relevant. Efficacy of concurrent use is reviewed for several indications, with a focus on comorbid attention deficit hyperactivity disorder and aggression. The risk of adverse reactions is examined. Complex dopamine mechanisms are considered to explain the dilemma, and general treatment guidelines for stimulant-antipsychotic concurrent use are discussed.

INTRODUCTION TO THE DILEMMA

There has been a significant increase in the use of psychiatric medication in children over the last few decades, specifically dopamine agonists (stimulants) for attention deficit hyperactivity disorder (ADHD) and dopamine antagonists (antipsychotics) for psychotic, mood, and anxiety disorders. There was a fourfold increase in the use of stimulants in children from 1987 to



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1996.[1] The outpatient prescribing of antipsychotics for children in the United States increased almost fivefold between 1995 and 2002.[2] A 2006 review found that these trends remained stable.[3]

Polypsychopharmacology of stimulants and other psychiatric medications in children had a five-fold increase between just 1994 and 1998.[4] It has been estimated that more than half of children on stimulants have been prescribed a concurrent antipsychotic at some point in their treatment.[5]

Literature suggests that the increased use is related both to increased prevalence of various diagnoses in children, such as bipolar disorder and ADHD,[6] and also to increased off-label use,[7] particularly aggression.[2] Official guidelines from national and international psychiatric organizations support this use as being appropriate.[8,9]

So where is the dilemma? According to mainstream psychiatry basic research and psychopharmacology, stimulant and antipsychotic medications have opposing mechanisms of action. Stimulants are thought to work by increasing dopamine (DA) levels between neurons, and antipsychotics work by blocking their effects at dopamine receptors. Concurrent stimulant-antipsychotic use has been rationalized by suggesting that they likely interact with different receptor subtypes and do so in different pathways of the brain.[10] In reality, while the main therapeutic sites of stimulants and antipsychotics are different, they both interact at the same receptors sub-types and do so in the same parts of the brain. Examination of DA pathways has revealed that stimulants have significant activation at both the limbic system and the cortex.[11] Antipsychotics have their strongest effects in the limbic system,[12] but they have also have effects on the cortex.[13,14]

Research on receptor subtypes has shown that the therapeutic effects of stimulants are strongest at D_1 receptors, but they also have significant action at D_2.[15,16] The therapeutic effects of antipsychotics come from D_2 antagonism,[17] but these medications are actually unselective antagonists, being able to bind to all five receptor types.[18] Going beyond theoretical implications, research has shown that stimulants and antipsychotics actually do block the effects of each other.[19,20]

This discrepancy between how dopamine medications are understood to work and how dopamine medications are used clinically has been underappreciated by psychiatrists and underrepresented in the literature. This discrepancy should be an impetus for critical thinking about the risks and benefits of prescribing stimulant and antipsychotic medications concurrently.

REVIEW OF EFFICACY, SAFETY, AND GUIDELINES REGARDING THEORETICAL INDICATIONS FOR CONCURRENT USE

ADHD without comorbidity. Stimulants are widely considered the first-line treatment recommendation for ADHD because of their high reported success rate.[21] However, atypical antipsychotics have been shown to treat ADHD symptoms.[22–25] Specifically, risperidone was shown to improve attention and hyperactivity,[26] and aripiprazole has been shown to improve cognitive functioning.[27] Not surprisingly, the methods and results of these studies have been criticized.[28]

While not commonly used clinically, and contrary to basic science research, clinical research has suggested that concurrent use of stimulants and antipsychotics may actually be more effective at treating ADHD than use of stimulants alone.[24,29]

ADHD with comorbid aggression. Determining whether pediatric aggression is a symptom of ADHD or an independent behavior problem is often difficult. A clinical practice article in the *New England Journal of Medicine* reported that aggression should not be considered a feature of ADHD.[21] On the other hand, the American Academy of Child and Adolescent Psychiatry (AACAP) reported that the majority of attention deficit disorders include symptoms of aggression and oppositional behavior.[30]

Several atypical antipsychotics, particularly risperidone, have been shown to be effective at treating aggression.[31,32] On the other hand, despite United States Food and Drug Administration (FDA) warnings that stimulants may worsen aggression, a body of research has suggested that, like antipsychotics, stimulants are also effective treatments for aggression, particularly in hyperactive children.[33–35]

In 2004, an international consensus of experts examined the appropriate treatment for ADHD in the setting of comorbid conduct disorder. They concluded that if aggression persisted after stimulants were prescribed, concurrent use of atypical antipsychotics would be indicated.[8]

In 2006, the AACAP recommendations based on the Texas Children's Medication Algorithm Project (CMAP) similarly reported that concurrent stimulant-antipsychotic use was appropriate to treat ADHD with comorbid aggression.[9] A follow-up letter to the editor criticized these recommendations, arguing that evidence was lacking for safety and efficacy, especially in light of their conflicting mechanisms of action.[36]

In 2007, when AACAP published its Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD, it warned that antipsychotics should not be used to treat aggression that is "clearly a side effect of the stimulant." Curiously, it failed to comment on a protocol for treating comorbid aggression in the setting of ADHD, despite the Academy's earlier stance that comorbid aggression was present more often than not.[30]

ADHD and depression. Epidemiologic studies suggest a high comorbidity between mood disorders and ADHD.[37] Antipsychotics and stimulants both have evidence supporting efficacy at treating depression.[38–42] Research needs to be

TABLE 1. Case reports of stimulant-antipsychotic syndrome (SAS)

MEDICATION CHANGE	MEDICATIONS INVOLVED	REACTION
Stimulant added to antipsychotic[36]	Methylphenidate, aripiprazole	Acute dystonia
Antipsychotic removed from stimulant[51]	Methylphenidate XL (Concerta), risperidone	Dyskinesia
Antipsychotic switched to stimulant[51]	Unclear	Dyskinesia
Stimulant removed from antipsychotic[51]	Unclear	Dyskinesia
Stimulant removed from antipsychotic[52]	Dextroamphetamine, perphenazine	Withdrawal dyskinesia, resolved after discontinuation of the antipsychotic
Stimulant removed from antipsychotic[53]	Methylphenidate, risperidone	Dystonic reaction, resolved after benztropine
Stimulant removed from antipsychotic[53]	Methylphenidate, risperidone	EPS, resolved after readministration of methylphenidate
Stimulant switched to antipsychotic[54]	Methylphenidate, risperidone	Severe adverse reactions in three children

done to examine the efficacy of stimulant-antipsychotic concurrent use in depression with and without comorbid ADHD.

ADHD and bipolar disorder. Atypical antipsychotics are a common and effective treatment for bipolar mania.[43,44] However, while stimulants treat hyperactivity associated with ADHD, there is concern that they would cause unsafe worsening of the hyperactivity seen during mania. Studies examining these concerns have shown conflicting results.[45–47]

ADHD and psychotic disorders. One in 400 children will experience psychosis with therapeutic doses of stimulant treatment,[48] and stimulants will produce psychotic symptoms in any patient at high enough doses.[49] Patients with comorbid psychotic conditions are especially likely to be affected.[49] Antipsychotics have been shown not to prevent stimulant-psychosis.[49]

STIMULANT-ANTIPSYCHOTIC SYNDROME (SAS)

Because stimulant and antipsychotic medications are known to cause tics and dystonia, respectively, risks of kinetic side effects with concurrent use must be considered. Empirical studies have minimized the need to be concerned about these risks.[5,50] However, several case studies have suggested a link between concurrent use and adverse kinetic reactions.[36–54]

The risk of creating extreme hyper- or hypodopaminergic states appears to be greatest when adjusting the dose of one class of medication in the setting of the other. For example, consider switching an antipsychotic with a stimulant without cross-tapering. Antipsychotic medications cause post-synaptic up-regulation of DA receptors over time.[51] Removing the antagonism on these hypersensitive DA receptors while simultaneously increasing synaptic DA levels by an indirect agonist could cause an extreme hyperdopaminergic state. See Table 1.

BASIC AND COMPLEX DOPAMINE MODELS

Despite theoretical concerns of the counteracting nature of stimulants and antipsychotics, large studies, as well as clinical practice, minimize the potential for risks with their concurrent use. If we are not going to change our practice, can we escape the dilemma by changing our theory?

A basic view of dopamine in relation to psychiatric disorders and their treatment would focus on DA levels being too high or too low in particular parts of the brain. However, there is sufficient basic science research on pre- and post-synaptic feedback and mechanisms of DA regulation to consider clinical explanations based out of a more complex DA model.

During periods of inactivation, neurons release DA presynaptically into the synapse at a steady rate, and the synapse maintains DA at a certain tonic level. Stimuli that trigger nerve impulses cause larger amounts of DA to be released through phasic dopamine bursts. These bursts are thought to be the main activating force at postsynaptic receptors and to cause the brain's consciousness to direct focus and attention on the stimuli.[55]

By negative feedback mechanisms at presynaptic auto-receptors, a low tonic dopamine level during neuron inactivation results in larger burst responses during activation, and vice versa.[56]

This inverse relationship has been implicated in ADHD. One hypothesis is that these children suffer from low

tonic levels of DA, and the feedback system causes hyper-bursts. This leads to a brain that is hypersensitive to stimuli and a child that is inattentive and impulsive.[57,58] In other words, it is a problem of too little and too much DA. By this model, stimulants would work to decrease the burst responses indirectly by increasing the tonic DA levels.

While Basic Dopamine Model views ADHD and schizophrenia as being problems on opposite sides of the DA spectrum, Complex Dopamine Model has been used to suggest that schizophrenia could be a result of the same problem of low tonic DA levels, leading to increased burst responses (Figure 1).[59]

Complex DA Model also suggests that, while stimulants and antipsychotics appear to have opposite mechanisms of action, they both result in increased tonic DA levels and decreased burst responses. In fact, the main difference between the two classes may be that while stimulants cause postsynaptic down-regulation over time, antipsychotics cause up-regulation.[60–62] Interestingly, these opposite problems may cancel each other out if both medications are given concurrently, decreasing risks of tolerance to both.[60] If there is a synergistic effect, the total amount of medication needed may be less, reducing risks of other side effects.[60]

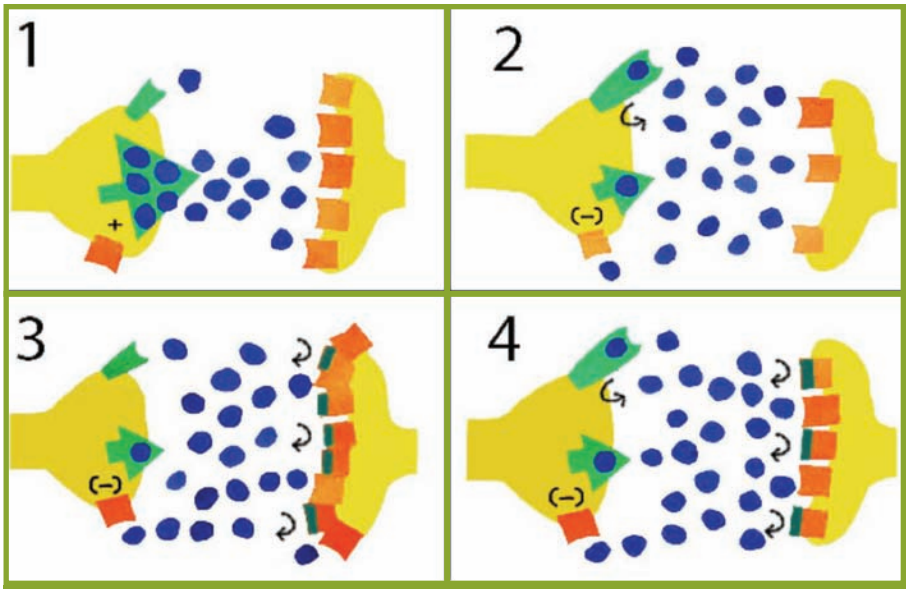

FIGURE 1. Complex Dopamine Theory

Box 1: Low tonic DA state -> large DA bursts (a possible mechanism of ADHD)

Box 2: Stimulant use -> increased tonic DA levels through presynaptic action -> decreased burst size and postsynaptic downregulation

Box 3: Antipsychotic use -> increased tonic DA levels through postsynaptic action -> decreased burst size and postsynaptic up-regulation

Box 4: Concurrent stimulant and antipsychotic use -> increased tonic DA levels through both pre- and postsynaptic action -> decreased burst size but no net postsynaptic up- or down-regulation.

KEY: DA: dopamine; ADHD: attention deficit hyperactivity disorder

CONCLUSION

Basic Dopamine Theory suggests that stimulants and antipsychotics have activity at most DA receptor-subtypes and in most DA pathways. Basic science confirms this. Complex Dopamine Theory suggests possible new insights into mechanisms of action, but further research is needed. Studies on clinical risks and benefits of concurrent use appear promising but often show conflicting data, and significant kinetic side effects have been described. Most physicians are not concerned, but it can be dangerous to ignore potential receptor interactions. Physicians considering the concurrent use of stimulants and antipsychotics should appreciate the following guiding points:

1. Concurrent use of stimulants and antipsychotics should be accompanied with hesitation and caution because of both theoretical and empirical concerns.
2. When using a stimulant and a comorbid disorder indicates an antipsychotic, or vice versa, a trial with a non-DA-medication should be initiated first.
3. Treating side effects of a stimulant with an antipsychotic, or vice versa, may mask symptoms temporarily while worsening the underlying chemical imbalance over the long term.
4. If using stimulants and antipsychotics concurrently, special caution should be made to taper either class of medication slowly when the other class is being used or when switching from one class to another.
5. Stimulant-antipsychotic syndrome should be suspected when adverse reactions are seen in the setting of concurrent use, especially following a medication change.
6. When using stimulants and antipsychotics concurrently, all side effects should be viewed as the product of the interactions of both medications together at their respective doses.
7. Complex Dopamine Theory suggests that concurrent stimulant-antipsychotic use at low doses may decrease the risk of tolerance and side effects.
8. Most clinical research on concurrent stimulant-antipsychotic use has been done to assess safety and efficacy despite potential interactions. Studies assessing benefits from their interactions are lacking.
9. Guidelines for absolute or relative dosing of concurrent stimulant-antipsychotic regimens cannot

currently be formulated because of lack of data.

10. Despite the appropriateness of conservatism with concurrent use, clinical data from aggressive prescribers will be educational.

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