

Aggression in Attention-Deficit/Hyperactivity Disorder: When Do Psychotropics Backfire?

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Case: A healthy 9-year-old girl who is taking dexamethylphenidate extended-release (ER) (Focalin XR) 10 mg daily presents with residual attention-deficit/hyperactivity disorder (ADHD) symptoms and 1-2 episodes per month of aggressive tantrums. To treat the residual ADHD symptoms, dexamethylphenidate ER is increased to 15 mg daily. The family instantly notices an improvement in the girl's concentration, but also an increase in the severity, frequency, and duration of aggressive outbursts in the afternoon. These outbursts remit on weekends, when the medication is not administered. The possibility of stimulant rebound is considered, and a booster dose is added, resulting in worsening episodes of severe aggression throughout the evening. Guanfacine is added with little improvement. Dexamethylphenidate ER is tapered off successfully, and dextroamphetamine/amphetamine ER (Adderall XR) is started. Her ADHD symptoms improve, and her aggressive tantrums resolve.

The 2007 American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder states that “controlled trials of stimulants do not support the widespread belief that stimulant medications induce aggression.”^{1(p910)} Indeed, on the whole, aggression in young patients with ADHD tends to decline when they are treated with stimulants.^{1,2} Yet for a proportion of patients, aggression can worsen with pharmacotherapy for ADHD. Recognizing this phenomenon, the Parameter advises physicians to distinguish between aggression as a true adverse event and aggression as the result of stimulant medication wearing off, or “rebound phenomena.” If it is determined that the patient's aggression and/or emotional lability is clearly secondary to the ADHD medication, the Parameter recommends the medication be discontinued and a new medication begun.¹

Such a recommendation, while seemingly straightforward, belies the difficulty of determining the cause of new or worsening aggression in ADHD. Aggression, defined by Patel and Barzman as “age inappropriate verbal or physical acts that are reactive or impulsive in nature,”^{3(p408)} and by Saylor and Amann as “behavior with the immediate intent to cause harm – whether to self, others, objects, or property,”^{4(p19)} is difficult to evaluate

because of inconsistent usage of imprecise terms to describe the behavior. One parent might label a child's behavior “violent,” another parent witnessing the exact same behavior might call it “aggressive,” and another parent might label the behavior “hostile.” Because of our varied and imprecise usage of terms to describe similar behaviors, it is difficult to study and to address the already complex relationship between ADHD treatment and aggression. The inconsistent use of terminology can lead to unnecessary pharmacotherapy and an overall underreporting and underappreciation of aggression related to ADHD medications. In this article, we attempt to untangle the possible causes of aggression in the context of ADHD medication treatment, and offer suggestions for providers facing this challenge.

A Connection Between Aggression and ADHD Medications?

Given that there are medical causes of new-onset aggressive behaviors in children and adolescents, providers should always consider whether a primary medical condition could be causing the behavior change. Among such medical causes of aggression are hypothalamic hamartoma, gelastic seizures,⁵ limbic encephalitis,⁶ and other epileptic and neurological disorders involving the frontal and temporal lobes.⁷ Also, children and adolescents who are nonverbal and/or have communication

difficulties may be less able to express their feelings of pain, infection, or other concerns and, as a result, may demonstrate aggressive behaviors and irritability due to these physical symptoms.⁸

Aggression as Part of Rebound Phenomena

One possible cause of increased aggression in those treated with stimulants is rebound phenomena, also described as “transient behavioral deterioration,”⁹ which can occur when an ADHD stimulant medication wears off during the day. It can present as irritability, loss of patience, and worsening of core ADHD symptoms, such as increasing hyperactivity and impulsivity.^{1,10} But it does not mean that a medication is failing—rather, that its efficacy has worn off by the end of the day. According to the AACAP Practice Parameter on ADHD, clinicians need not seek out a new medication to treat aggression attributable to rebound phenomena. In order to determine if the phenomenon is present, the clinician can ask the patient’s caregiver to keep a diary, tracking the behavior throughout the day. Once it is determined that the behavior is secondary to rebound phenomena, prescribing an immediate release stimulant in the late afternoon may be helpful.

Aggression and Non-Stimulant Medications

To date, there is limited and conflicting literature regarding the relationship between non-stimulant medications and aggression as an adverse event. A retrospective review found that 51 out of 153 (33%) children with a mean age of 10.5 years exhibited “extreme irritability, aggression, mania, or hypomania induction” after receiving the non-stimulant atomoxetine.¹¹ However, the authors of the retrospective review did not indicate the statistical significance of their findings. A meta-analysis focusing specifically on the role of atomoxetine in aggression suggests that less than 2% of patients who took atomoxetine had events related to hostility or aggression.¹² These findings were not statistically significant when compared to the occurrence of aggression in patients taking placebo or methylphenidate. Finally, another meta-analysis of the safety of atomoxetine reported that there is no statistically significant increase

in the occurrence of aggression among youth who take atomoxetine.¹³ However, the authors of that meta-analysis note that concurrent use of an antipsychotic to manage the aggression may have masked the potential link between atomoxetine and aggression.¹³ In one study mentioned in the meta-analysis,¹³ 17% of children and adolescents carrying a diagnosis of ADHD were taking antipsychotic medications despite not having a Food and Drug Administration (FDA) indication for the antipsychotic.¹⁴

Another non-stimulant ADHD medication may be linked to aggression as an adverse event. According to an FDA safety review of 676,000 prescriptions (between September 2009 and 2010) for extended-release guanfacine (Intuniv), there were 45 total cases of serious non-fatal adverse events, including four cases of agitation, one case of irritability, and two cases of aggression (categorized as unlabeled adverse effects).¹⁵

Aggression and Methylphenidate-Based Stimulant Medications

Despite the AACAP Practice Parameter statement to the contrary, studies examining the efficacy and safety of methylphenidate-based stimulants raise concerns about aggression as a possible adverse event. Wilens *et al.* reported that hostility leading to early treatment discontinuation occurred in 0.5% of patients taking OROS methylphenidate (Concerta; $n = 2$); there was no placebo comparison as the individuals in this study had previously participated in an efficacy or pharmacokinetic study of OROS methylphenidate.¹⁶ Wigal *et al.*¹⁷ reported that, among patients treated with dextmethylphenidate, 3 patients out of a total of 44 exhibited emotional lability compared to 1 out of 42 on placebo. FDA safety reviews, which are observational and do not include a placebo comparison group, report aggressive behaviors as adverse events for the methylphenidate transdermal system (Daytrana; aggression, $n = 5$ out of 143 nonfatal serious adverse events reported to the FDA between 2006 and 2011),¹⁸ dextmethylphenidate hydrochloride (Focalin; aggression, agitation, irritability, $n = 4$ out of 164 nonfatal serious adverse events

reported to the FDA between 2005 and 2011),¹⁸ and methylphenidate hydrochloride (Quilivant XR; anger, $n = 1$ out of 11 serious nonfatal unlabeled adverse events reported to the FDA).¹⁹ In June 2005, the FDA released postmarketing reports that cautioned that methylphenidate (Concerta) and other methylphenidate-based medications could cause potential aggression or violent behavior.²⁰ In March 2006 and following a review of available clinical trial data, the FDA Pediatric Advisory Committee reported elevated rates, relative to placebo, of aggression events associated with methylphenidate hydrochloride (Daytrana, Ritalin LA) and atomoxetine (Strattera), but not with other ADHD medications.²¹

Aggression and Amphetamine-Based Stimulant Medications

FDA medication guides report hostility as an adverse event associated with amphetamine-based stimulant medications, as well as with methylphenidate-based stimulant medications.²² In a study by McGough *et al.*, hostility following the administration of extended-release mixed amphetamine salts (Adderall XR) was observed in 3 of 568 participants. Of note, the authors concluded that the hostility was unrelated to the medication.²³ In a pediatric case series reviewed by the FDA,²⁴ among 135 participants who received lisdexamfetamine (Vyvanse), 45 reported psychiatric adverse events. Of particular relevance to this discussion are the psychiatric adverse events categorized and listed as agitation ($n = 1$), irritability ($n = 1$), affect lability ($n = 2$), anger ($n = 9$), homicidal ideation/violence-related thinking ($n = 6$), and head-banging ($n = 1$).²⁴ Considering the aforementioned definition of aggression as behavior with immediate intent to cause harm,⁴ this review's classification of adverse effects highlights both (1) the manner in which numerous terms seem to capture various distinct and overlapping aspects of the broader phenomenon of aggression and (2) the possibility that the use of these and other related terms has made and may continue to make more difficult the detection of any true existing relationship between ADHD medications and aggression.

Summary of the Literature Regarding Aggression and ADHD Medications

Based on extant literature, the current consensus is that aggression is not a significant adverse event associated with psychopharmacological treatment of ADHD and that ADHD medications generally are well tolerated.² However, the existing literature does suggest that aggression is observed among youth receiving psychopharmacological treatment for ADHD. Furthermore, the authors of this article suspect that the literature does not adequately account for the possibilities that (1) observed aggression may reflect rebound phenomena (which, if unrecognized, would lead to an over-attribution of aggression to ADHD psychopharmacological treatment) and (2) the inconsistent use of varied terminology to describe adverse events may make more challenging the identification of a true relation between aggression and medications used in the treatment of ADHD (which would lead to an under-attribution of aggression to ADHD psychopharmacological treatment).

Understanding New-Onset Aggression in the Context of Psychopharmacological Treatment of ADHD

To determine whether new-onset aggression in the context of psychopharmacological treatment for ADHD is the result of rebound phenomena or a direct medication adverse event, it is important for clinicians to obtain a detailed history and to carefully establish a timeline. Table 1 offers possible questions a clinician can ask to elucidate a potential relation between the medication and the observed behaviors. Questioning when the patient first began demonstrating the aggressive episodes helps clarify whether the aggressive behavior predated the start of medication or whether the onset of the aggressive behaviors coincides either with the initiation of medication treatment or any dose increases. The temporal relation between the aggressive episodes and the time of administration of a medication dose and, relatedly, between the aggressive episodes and the time of effect onset (based on phar-

Table 1. Possible Questions to Ask About New-Onset Aggression After Psychopharmacological Treatment

■ When did these aggressive episodes start?
■ How do these episodes relate temporally to the time of medication dosing? <ul style="list-style-type: none">■ When is the medication given?■ When do the episodes of aggression occur? Soon after the medication is given? Throughout the day? When the medicine is wearing off? After the medicine has worn off?
■ Are triggers evident prior to the episodes of aggression?
■ Do these episodes occur in multiple settings or contexts, or do they occur consistently and almost exclusively in specific settings or contexts?
■ Are there any other medications (including non-psychotropics, like antihistamines or steroids) that could be contributing directly or through interactions?
■ Are there any non-medication issues potentially at play (either medical or psychosocial)?

macokinetics) may also be important. If the aggression occurs almost exclusively after a medication is administered and/or during the time when the medication is expected to be active, the aggression may represent an adverse event. If, based on a medication’s pharmacokinetics, the aggression happens at a time of day when the effects of the medication are likely wearing off, the aggression may reflect rebound phenomena. If, based on pharmacokinetics, the aggression occurs during periods during which the medication is no longer active (the effects having worn off), the aggression may reflect baseline symptomatology for which treatment was initiated. In the case of aggression related to either rebound phenomena or the absence of medication effect, the aggression may seem particularly prominent given its presence relative to its prior absence during periods of active medication effect.

The environmental settings and/or contexts in which aggressive episodes occur also may help clarify if the aggression is a medication-related adverse event, reflective of rebound phenomena, or neither. For example, if the episodes occur almost exclusively in a specific setting or context and that setting/context does not coincide with the period of time during which the effects of the medication are wearing off, the behavior is less likely to be an adverse event or a sign of rebound phenomena and is more likely reflective of the specific setting/context itself.

A thorough assessment of new-onset aggression, including the examination of the timeline and circum-

stances around the behaviors, will increase the likelihood of identifying accurately contributors to the aggression. Doing so will help the clinician distinguish between aggression related to medication adverse effects, rebound phenomena, baseline symptomatology, and/or treatment-resistant symptomatology and, as a result, will also help the clinician avoid potentially ineffective, unnecessary, or even harmful interventions, such as polypharmacological treatment.

Conclusion

The literature exploring the relation between aggression and ADHD is marked by imprecision in how aggression is described and accounted for, and offers inconsistent conclusions regarding any relation between aggression and ADHD medications. As such, for these authors, the question of whether ADHD medications lead to an increased likelihood of aggressive behaviors presently remains unanswered. More research is needed to fully explore the relation between the two. In the meantime, we suggest that clinicians consider whether aggression occurring in the context of psychopharmacological treatment of ADHD reflects adverse medication events. We also suggest that if, based on a comprehensive history and established timeline, the suspicion of medication-related aggression is high, clinicians consider switching to a different medication to treat ADHD. As in the case vignette at the outset of this article, the timeline was assessed carefully and then the medication, dexamethylphenidate ER, was removed. The aggressive

behaviors remitted, and the patient responded positively to a different ADHD medication.

Take Home Summary

- It remains unclear whether both classes of stimulant medications as well as non-stimulant medications used in the treatment of ADHD may cause aggression as an adverse event.
- Before switching to or adding on an additional medication, the onset of aggressive behaviors, their temporal relationship to medication administration, and the settings/contexts in which these behaviors occur should be carefully evaluated to determine any potential contributing role of the medication to the aggression.

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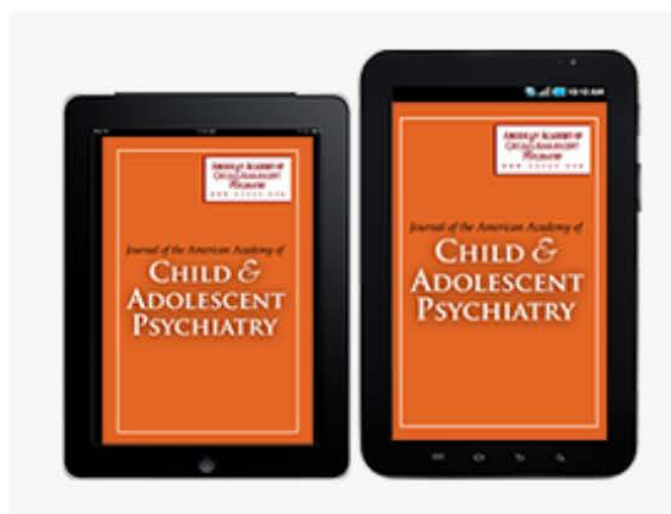
Disclosure: Drs. Charoensook and Cooper report no biomedical financial interests or potential conflicts of interest.

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