JOURNAL
OF THE CANADIAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY / DE L'ACADÉMIE CANADIENNE DE PSYCHIATRIE DE L'ENFANT ET DE L'ADOLESCENT

CLINICAL CASE ROUNDS

Stimulant Withdrawal in a Child with Autism Spectrum Disorder and ADHD - A Case Report

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Abstract

Objective: To consider whether the concepts of tolerance and withdrawal to stimulant medications apply to a pre-adolescent female, affected by autism spectrum disorder (ASD) and treated for associated attention-deficit/hyperactivity disorder (ADHD). **Methods:** We describe the case history and review scientific English language literature pertaining to acute withdrawal effects associated with methylphenidate and amphetamine derivatives in children. **Results:** An 11-year-old female with ASD and ADHD referred to our clinic experienced vomiting, headaches, and light sensitivity following abrupt discontinuation of methylphenidate; she subsequently presented with migraines and marked malaise immediately after a dose reduction in lisdexamfetamine. Evidence supports the notion that ADHD symptoms in children with ASD can be effectively treated with methylphenidate; however, beneficial effects are less robust relative to children with a primary ADHD diagnosis. Children affected by ASD are also more susceptible to adverse effects. Literature on withdrawal from stimulants in children is limited to case studies; in contrast, in the adult population more information is available, especially in adults with substance abuse disorders. Adults experiencing stimulant withdrawal often experience depression, fatigue, changes in appetite, and insomnia or hypersomnia. **Conclusions:** We argue that tolerance to stimulants was conceivably developing in this young female, and consequently discontinuation of methylphenidate and dose reduction of lisdexamfetamine resulted in withdrawal symptoms. Children with ASD are more sensitive to stimulant medications and we wonder whether this extends to an increased sensitivity to developing tolerance to stimulant medication. Clinicians ought to be vigilant about the emergence of symptomology suggestive of withdrawal phenomena following stimulant discontinuation.

***Key Words*:** *ASD, ADHD, withdrawal, stimulant, amphetamine, methylphenidate*

Résumé

Objectif: Examiner si les concepts de tolérance et de sevrage des médicaments stimulants s'appliquent à une pré-adolescente souffrant d'un trouble du spectre de l'autisme (TSA) et traitée pour un trouble de déficit de l'attention avec hyperactivité (TDAH) associé. **Méthodes:** Nous décrivons les antécédents du cas et examinons la littérature scientifique en anglais relative aux effets de sevrage associés au méthylphénidate et aux dérivés d'amphétamine chez les enfants. **Résultats:** Une fillette de 11 ans souffrant de TSA et de TDAH envoyée à notre clinique éprouvait des vomissements, des maux de tête et une sensibilité à la lumière par suite d'une cessation abrupte de méthylphénidate; elle a ensuite présenté des migraines et un malaise marqué immédiatement après la réduction d'une dose de lisdexamfétamine. Les données probantes soutiennent la notion que les symptômes du TDAH chez les enfants souffrant du TSA peuvent être efficacement traités par méthylphénidate; cependant, les effets bénéfiques sont moins intenses chez les enfants dont le diagnostic primaire est le TDAH. Les enfants souffrant du TSA sont également plus susceptibles aux effets indésirables. La littérature sur le sevrage des stimulants chez les enfants se limite aux études de cas; par contre, il y a plus d'information dans la population adulte, spécialement chez les adultes souffrant de troubles d'abus de substances. Les adultes vivant un sevrage

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Submitted: July 24, 2017; Accepted: January 16, 2018

de stimulant présentent souvent dépression, fatigue, changements d'appétit, et insomnie ou hypersomnie. **Conclusions:** Nous alléguons que la tolérance aux stimulants se développait probablement chez cette jeune fille et que par conséquent, la cessation de méthylphénidate et la réduction de la dose de lisdexamfétamine ont entraîné des symptômes de sevrage. Les enfants souffrant de TSA sont plus sensibles aux médicaments stimulants et nous nous demandons si cela s'étend à une sensibilité accrue au développement d'une tolérance aux médicaments stimulants. Les cliniciens doivent être vigilants devant l'apparition d'une symptomatologie suggestive d'un phénomène de sevrage suivant la cessation d'un stimulant.

Mots clés: *TSA, TDAH, sevrage, stimulant, amphétamine, méthylphénidate*

Case Report

An 11-year-old female with a diagnosis of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and a learning disability (LD), being cared for by a community psychiatrist, was referred to our tertiary care center with concerns about marked irritability, excessive reactivity to frustration, prominent skin picking, persistent impairment due to inattention, and social difficulties. She was on a combination of lisdexamfetamine 50 mg/day, extended release guanfacine 3 mg/day, and fluoxetine 20 mg/day. Her parents did not believe this combination was effective. They also reported that the previous treatment, with an osmotic controlled release preparation of methylphenidate (Concerta ®) 36 mg, was not particularly effective either and upon abrupt discontinuation of the methylphenidate preparation the young female experienced a rather severe episode of vomiting, headaches and marked sensitivity to bright lights lasting several days.

At the time of the initial consultation her interactions with the examiner were somewhat elusive; she acknowledged that eye contact with other persons is difficult and consequently preferred to gaze away. She was able to use language effectively to share thoughts, but she spoke at a fast rate and a flat tone in prosody was noted. Thoughts were connected and coherent, and no delusional content or perceptual abnormalities were noted. She reported discomfort with certain numbers but no clear obsessions or compulsions. Neither motor nor vocal tics were observed.

She presented with an elevated heart rate of 122 bpm, her blood pressure was 138/64 mmHg, and an ECG identified a sinus tachycardia with a QTc of 442 ms.

Given our concerns about her heart rate and blood pressure, as well as the suspicion that the lisdexamfetamine might be contributing to her irritability and skin picking, we recommended an immediate reduction of the lisdexamfetamine to 40 mg/day. We also advised that she continue guanfacine and fluoxetine at the stated doses.

Immediately after the dose of lisdexamfetamine was reduced to 40 mg/day, she began experiencing migraines and marked malaise. These symptoms lasted a few days; however, they were not as severe as those experienced with the discontinuation of methylphenidate. Also noted were a reduction of skin picking, better handling of frustrations, and less irritability. When lisdexamfetamine was further reduced to 30 mg/day, two days of migraines and general malaise were again experienced. Her irritability continued to improve and she was no longer picking at her skin. Within six months lisdexamfetamine was progressively tapered and discontinued. Minor episodes of withdrawal were experienced in association with each drug reduction.

A literature search was conducted in two databases (Medline and PsychINFO) in March 2017 with no restrictions on year of publication or publication type. An updated search was conducted in November 2017. A combination of MeSH-terms/index words and free text were used to search the databases. Search terms related to stimulants, ADHD, withdrawal and rebound. For example, the search in PsychINFO appears as follows: (exp Amphetamine OR exp Methylphenidate OR exp Central Nervous System Stimulants OR amphetamine* OR methylphenidate* OR stimulant*) AND (exp Attention Deficit Disorder OR exp Attention Deficit Disorder with Hyperactivity OR attention deficit hyperactivity disorder OR adhd) AND (exp Substance Withdrawal Syndrome OR withdrawal* OR rebound*). We also limited our search to English and studies done in children. A study was eligible for inclusion if it discussed withdrawal or rebound in the context of stimulant use in children with ADHD. We found seven studies that met inclusion criteria. Three of these were case reports and four were primary studies.

Vomiting, headaches and light sensitivity followed abrupt discontinuation of methylphenidate; migraines and marked malaise were experienced immediately after a dose reduction in lisdexamfetamine. We suggest these symptoms may be consistent with a stimulant withdrawal effect and wonder whether the presence of comorbid ASD may have augmented this young female's susceptibility to experiencing stimulant withdrawal. Long-acting stimulants, such as lisdexamfetamine and osmotic release methylphenidate are purportedly cleared in less than 24 hours. We do question whether this young female was experiencing withdrawal symptoms during the night and early morning hours and whether the prominent irritability experienced by her was, at least in part, a function of acute withdrawal. There was a

remarkable reduction of irritability following reduction and ultimate discontinuation of lisdexamfetamine.

A meta-analysis (Reichow, Volkmar, & Bloch, 2013) found that ADHD symptoms in children with pervasive developmental disorders can be effectively treated with methylphenidate; however, the effect size for this treatment is lower in this population compared to children with a primary ADHD diagnosis. Children affected by ASD are also more susceptible to adverse effects. A randomized control study (Research Units on Pediatric Psychopharmacology (RUPP) Autism Network, 2005), identified that 18% of children with PDD and ADHD symptoms discontinued methylphenidate treatment as a result of unwanted effects, with the most common reason being increased irritability. This is in contrast to the Mutimodal Treatment Study of Children with ADHD (MTA) by the The MTA Cooperative Group (1999) which found that over the course of 14-month treatment with ADHD medication (84% with methylphenidate or dextroamphetamine) the majority of children tolerated the medication well with 36% reporting no side effects and 50% reporting mild side effects. About 1% of participants were noted to discontinue because of side effects.

Literature on withdrawal from stimulants in children is limited to case studies. One case study (Brown, Borden, Spunt, & Medenis, 1985) reported that a child experienced symptoms of depression for a few days following discontinuation of the older psychostimulant drug, pemoline, and demonstrated improvement of the symptoms shortly after a stimulant was reinitiated. Another case study (Rosenfeld, 1978) reported that a child experienced symptoms of transient psychosis for one week following eight days of methylphenidate discontinuation.

Literature on withdrawal is more extensive in the adult population, especially in adults with substance abuse disorders. Adults experiencing stimulant withdrawal often experience depression, fatigue, changes in appetite, and insomnia or hypersomnia [reviewed by Harro (2015)]. However, it is unclear whether literature on stimulant withdrawal in adults with substance abuse disorders can be generalized to children with ADHD taking prescribed stimulant medication. Individuals are more likely to abuse amphetamines than methylphenidates because of its higher reinforcing efficacy (Kollins, 2003), and to abuse short acting stimulants than long acting stimulants because of their faster rate of onset (Kollins, Rush, Pazzaglia, & Ali, 1998). Individuals are also more likely to abuse IV stimulants than oral stimulants (Kollins, 2003). As stimulant type, formulation, and route of administration influences the risk of abuse, it is possible that it also influences withdrawal.

Stimulant "rebound" has been reported in studies in children and adolescents (Carlson & Kelly, 2003; Cox et al., 2008; Johnston, Pelham, Hoza, & Sturges, 1998; Lopez et al., 2017). One case report also describes how stimulant rebound can potentially mimic a pediatric bipolar disorder (Sarampote, Efron, Robb, Pearl, & Stein, 2002). The "rebound" effect is generally considered to include a worsening of behaviour, beyond the child's baseline, when the stimulant medication wears off. For children on longer-acting formulations this occurs in the evening. Reported "rebound" phenomenon include tearfulness and irritability (Carlson & Kelly, 2003), suggesting a possible relation to stimulant withdrawal. This phenomenon continues to cause debate in medical literature as it is unclear if this behaviour constitutes a true escalation of behavior or a return to a stimulant-free baseline (Pliszka, 2007).

The concept of tolerance to stimulant medication among children treated for ADHD is another important source of discussion and debate. Tolerance is generally defined as the need for an increasing dose of medication over time in order to maintain the same level of response to the medication (Turton & Lingford-Hughes, 2016). Acute tolerance to stimulant medication has been supported in a study by Swanson et al. (1999). The authors compared the efficacy of a constant methylphenidate delivery pattern with an ascending methylphenidate delivery pattern in children with ADHD and found that in the constant drug delivery pattern, 40% of the drug efficacy was lost in the afternoon, thus suggesting that acute tolerance had developed. Chronic tolerance to stimulant medication has also been supported in long-term studies by Wilens et al. (2005) and Safer and Allen (1989) which showed that in a proportion of children, there is lack of clinical response to stimulants over time suggesting the possibility of tolerance having developed.

We argue that tolerance to methylphenidate and lisdexamfetamine was conceivably developing in this young female. Consequently, abrupt discontinuation of methylphenidate, and to a lesser extent dose reduction of lisdexamfetamine, resulted in withdrawal symptoms. Of note the dose reduction of lisdexamfetamine was quite small, especially when considering that lisdexamfetamine is a prodrug that is converted into its active metabolite d-amphetamine (Boellner, Stark, Krishnan, & Zhang, 2010). Cognisant of the presence of a neurodevelopmental disorder, the possibility that her response was idiosyncratic and not necessarily reflective of tolerance or withdrawal merits consideration.

It is of great interest that children with ASD are more sensitive to stimulant medications, and we wonder whether this extends to an increased sensitivity to developing tolerance to stimulant medication. Acute tolerance has been hypothesized to develop secondary to neuroadaptations at the level of the dopamine transporter (Swanson et al., 1999; Volkow et al., 1995). Studies in human subjects with ADHD have also shown that long-term use of methylphenidate results in upregulation of dopamine transporters in the striatum (Wang et al., 2013) and a decrease in dopamine release in the striatum (Volkow et al., 2012), suggesting a possible mechanism for the development of chronic tolerance. There is preliminary evidence for alterations in dopaminergic

systems in individuals with autism (Nakamura et al., 2010) and it is plausible that such alterations influence response and possible tolerance to stimulants. Future research is clearly needed to determine whether drug tolerance and withdrawal develops in children on stimulant medication, and whether susceptibility to tolerance and withdrawal differs in children with atypical neurodevelopmental trajectories. In the interim, clinicians ought to be vigilant about emergence of symptomology suggestive of withdrawal phenomena following stimulant discontinuation.

Acknowledgements / Conflicts of Interest

The authors have no financial relationships to disclose.

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