

The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

## Managing ADHD and disruptive behaviour disorders with combination psychostimulant and antipsychotic treatment

A 9 year-old boy has a 4-year history of attention-deficit/hyperactivity disorder (ADHD), combined presentation and recent diagnoses of oppositional defiant disorder, severe and rule out conduct disorder, childhood-onset. He has a history of defiance and physical aggression toward his mother, with episodes escalating in severity. He was recently suspended from his school for assaulting the vice-principal, who told him to leave his classroom when it was discovered he had stolen an iPod from a peer. He was admitted to an inpatient child psychiatry unit for assessment and treatment. At the time of admission he was taking extended-release methylphenidate (Concerta, 27 mg daily in the morning).

The boy's aggression toward staff and peers on the unit continued during the first 3 weeks of his inpatient stay, and despite best efforts, he did not respond to behavioural interventions. Optimizing his extended-release methylphenidate dosage to 36 mg daily in the morning (just over 1 mg/kg/d) did not reduce his aggression. Following baseline measurements (fasting glucose, lipid panel, liver enzymes, serum prolactin, Abnormal Involuntary Movements Scale testing) and discussion with his parents about the potential benefits and risks of off-label use of second-generation antipsychotics in children, 0.5 mg of risperidone at bedtime was added to his medication regimen.

Combination psychostimulant and antipsychotic treatment appears to be increasing in frequency, with 1 Canadian population-based study reporting a nearly 3-fold increase in the rate of methylphenidate coprescription to children taking antipsychotics over a 10-year period (16% in 1999 to 45% in 2008).<sup>1</sup> Our group has also reported that 25% of children discharged on an antipsychotic from the Child and Adolescent Mental Health Inpatient Program at BC Children's Hospital were coprescribed a psychostimulant.<sup>2</sup> As monotherapy, both psychostimu-

lants and antipsychotics are supported by a reasonable amount of evidence for the treatment of ADHD and disruptive behaviour disorders. On first impression, the combination of a psychostimulant and antipsychotic, with their opposing effects on dopamine (DA) neurotransmission, (i.e., indirect agonist v. antagonist) seems contradictory and illogical. However, closer examination of their respective pharmacology can explain this apparent paradoxical therapeutic strategy, as they have differential effects on receptor subtypes and brain regions. Antipsychotics are antagonists at DA receptors in several circuits, but their primary activity is thought to be related to blockade of mesolimbic D2 receptors, whereas psychostimulants, such as methylphenidate and dextroamphetamine, are thought to exert their effects by increasing synaptic DA in the mesocortical system and downregulating the hyperactive nigrostriatal DA system via autoinhibition.<sup>3,4</sup> These agents may be exerting their therapeutic actions in different brain regions. However, it is likely that the nature of this synergistic interaction is much more complicated, as antipsychotics are not restricted to the mesolimbic region, nor are the effects of psychostimulants limited to the mesocortical and limbic-striatal systems.

A literature review revealed limited randomized controlled trial (RCT) data for combination psychostimulant and antipsychotic use.<sup>3</sup> Although several guidelines recommend combination therapy with psychostimulants and antipsychotics to treat comorbid aggression and ADHD, it is suggested only as a third-line option following sequential monotherapy trials of psychostimulants and behaviour interventions.<sup>3-7</sup> Despite the established efficacy of psychostimulant and antipsychotic monotherapy, the evidence for the efficacy of combination therapy is limited and not based on strong data.<sup>3</sup>

Although risperidone augmentation of psychostimulants has been most studied in RCTs,<sup>3</sup> rational use of another atypical antipsychotic may be warranted, depending on the clinical situation. However, clinicians must be aware that children and adolescents taking second-generation antipsychotics (particularly olanzapine)

appear to be at higher risk for metabolic adverse effects (weight gain, glucose and lipid abnormalities) than adults and require baseline and ongoing metabolic monitoring.<sup>8</sup> While it seems intuitive that the appetite-suppressant effects of psychostimulants may offset the appetite stimulation and weight gain often observed with second-generation antipsychotics, research reveals a high rate of metabolic abnormalities observed in children treated with combination therapy.<sup>9,10</sup>

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