



CLINICAL CASE ROUNDS

Psychopharmacology Challenge

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Editor's note: Welcome to the first ever "Psychopharmacology Challenge" an exciting new column format for the Journal of the Canadian Academy of Child and Adolescent Psychiatry. Three clinicians with expertise in pediatric psychopharmacology were asked to review the following patient vignette, and in 1000 words or less, describe the top three pharmacotherapy-related changes they would recommend for this patient, along with their clinical reasoning. Clinicians were asked to focus on psychopharmacology, but could also *briefly* indicate any suggested psychosocial intervention plans. For medication changes, clinicians were asked to include a recommended dosing titration plan [if applicable], and any additional testing they would order, including a recommended frequency of such testing. Clinicians were also asked to provide supporting literature citations for recommendations (where available, to a maximum 10 citations).

Psychopharmacology Challenge Case

AJ is a 9-year-old Caucasian male, who weighs 33.2 kg with a height of 128 cm (BMI 20.3 kg/m², 93rd percentile for age). AJ lives with his mother and 4-year-old brother, with weekend visits at his father's home. AJ is admitted to the inpatient child psychiatry unit for a scheduled elective 4-week assessment with historical diagnoses of autism spectrum disorder (ASD), mild intellectual disability (ID) and attention deficit/hyperactivity disorder –combined presentation (ADHD-CP). AJ is currently treated with risperidone 0.25 mg twice daily, which he has taken for the past two years to manage symptoms of irritability related to ASD. AJ also has been receiving quetiapine 25 mg at bedtime for treatment of insomnia for the past year.

The family's stated admission goals for AJ include reducing aggression, improved control of ADHD symptoms, and weight loss. During the intake meeting discussions with AJ's parents, the family reports they received some

parent-mediated training from a behavioural consultant targeting AJ's aggression with some small benefits and they are currently on a waitlist to receive another block of treatment in the future but are unsure when this will occur. AJ has been increasingly hitting his 4-year-old brother, and the school also reports an increasing number of aggressive incidents. His parents report AJ has gained approximately 10 kg of weight since starting risperidone two years ago. They also report that risperidone worked well at first, but initial benefits appear to have lessened in the last six months. Swanson, Nolan and Pelham, version 4 (SNAP-IV) ADHD rating forms received from his regular classroom teacher indicate scores of 2 or 3 ("quite a bit" or "very much" on 8 of 9 inattentive items, and 3 of 9 hyperactive/impulsive items).

Prior medication trials

- clonidine 0.025 mg twice daily for 2 weeks (trial discontinued due to sedation and lack of efficacy (parent report))
- dextroamphetamine immediate-release (IR) 5 mg BID (taken in morning and at noon) for 3 days (this trial pre-dates risperidone or clonidine treatment; parents report it was discontinued due to increased agitation)
- chlorpromazine 12.5 mg every 2 hours as needed for agitation, to a maximum of 50 mg in 24 hours (parents report chlorpromazine was useful, but was discontinued when AJ started on risperidone)

Despite treatment with risperidone for the past 2 years, no metabolic monitoring bloodwork has been completed, as recommended by the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guidelines (Pringsheim, Panagiotopoulos, Davidson, Ho & CAMESA guideline group, 2011). On admission, AJ is able to complete fasting blood work with the aid of topical EMLA cream and lorazepam 1 mg (a test lorazepam dose given the day before blood work did not lead to

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Table 1. Admission Fasting Laboratory Values

Hematology	Chemistry	Metabolic
WBC 4.9x10 ⁹ (N=3.9-10.2x10 ⁹)	Sodium 143 mmol/L (N=135-145 mmol/L)	TChol 5.78 mmol/L (N=2.6-5.2 mmol/L)
Hgb 112 g/L (N=118-146 g/L)	Creatinine 54 mmol/L (N=20-61 mmol/L)	HDL 0.84 mmol/L (N=1-1.9 mmol/L)
MCV 77 fL (N=77-92 fL)	Urea 4.7 mmol/L (N=2.5-6.4 mmol/L)	LDL 1.59 mmol/L (N=1.3-3.4 mmol/L)
Neutrophils 2.7x10 ⁹ (N=1.7-5x10 ⁹)	ALT 89 U/L (N=10-35 U/L)	TG: 2.61 mmol/L (N=0.45-1.1 mmol/L)
Platelets 331x10 ⁹ (N=180-440x10 ⁹)	AST 76 U/L (N=15-40 U/L)	FBG: 5.6 mmol/L (N=3.9-5.9 mmol/L)
Ferritin 21 mg/L (N=13-66 mg/L)		Insulin: 227 pmol/L (N=13-127 pmol/L)
		Prolactin: 39 mg/L (N=3.7-17.9 mg/L)

Bolded values are outside of reference range
N: 'normal' reference range; WBC: White Blood Cell count; Hgb: Hemoglobin;
MCV: mean corpuscular volume; ALT: alanine aminotransferase; AST: aspartate
aminotransferase; TChol: Total Cholesterol; HDL: high-density lipoprotein;
LDL: low-density lipoprotein; TG: triglycerides; FBG: fasting glucose

behavioral disinhibition). AJ's admission fasting laboratory values are shown in Table 1.

Reference

Pringsheim, T., Panagiotopoulos, C., Davidson, J., Ho, J. & Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group. (2011). Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth. *Paediatrics & Child Health*, 16(9), 581-589. doi: 10.1093/pch/16.9.581.

Response #1

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This case illustrates the common dilemma of deciding which studies to rely on when applying evidence to clinical practice. AJ is a 9-year-old boy with three mental health conditions—autism spectrum disorder (ASD), mild intellectual disability (ID), and attention deficit/hyperactivity disorder (ADHD). Furthermore, the family is concerned about three outcomes—reducing aggression, improving

ADHD symptoms, and weight loss. One could very well imagine that for each of these conditions and outcomes, the evidence might point us in a different direction, leaving us in a quandary as to which studies are most applicable to the boy in front of us. Fortunately, however, this turns out to be a situation where studies conducted in different populations and examining different outcomes essentially come to the same conclusion regarding the medication of choice. That medication is a stimulant, specifically methylphenidate.

Based on a vast literature that includes the landmark Multimodal Treatment of ADHD study (MTA Group, 1999), clinical practice guidelines consistently identify stimulants as first-line medication in the management of uncomplicated ADHD (Canadian Agency for Drugs and Technologies in Health, 2016). Guidelines also recommend stimulants as first-line medication for the treatment of disruptive and aggressive behaviour that is associated with ADHD (Gorman et al., 2015). This recommendation reflects high-quality evidence showing a moderate-to-large effect size of stimulants for these outcomes, as well as their relatively minor side effect burden. In addition, secondary analyses of data from the MTA study found that stimulants improve irritability associated with ADHD (Fernández de la Cruz et al., 2015). In children and adolescents with ASD, limited evidence supports the use of methylphenidate as first-line pharmacotherapy for comorbid ADHD; however, the effect size is lower than in typically developing children with ADHD (Mahajan et al., 2012; Rodrigues et al. [in press]).

Similarly, limited evidence supports the use of methylphenidate first-line for ADHD in the context of ID, with a lower effect size than in children with ADHD and average intelligence (Arnold, 2013).

In addition to the substantial evidence supporting stimulant treatment for AJ, one must consider the serious side effects associated with second-generation antipsychotics, particularly weight gain and other metabolic effects (Cohen, Bonnot, Bodeau, Consoli & Laurent, 2012). Indeed, after two years of treatment with risperidone and one year with quetiapine, AJ has gained approximately 10 kg, his BMI of 20.3 kg/m² (93rd percentile) is in the “overweight” range (Centers for Disease Control and Prevention, 2018), and fasting blood work shows multiple metabolic abnormalities. In contrast, stimulants commonly cause appetite suppression and weight loss, and they are not associated with these metabolic abnormalities.

Given the evidence described above, as well as the limited benefits and considerable side effects that AJ has experienced with low doses of risperidone and quetiapine, my overall pharmacological strategy would be to discontinue the antipsychotics and address AJ’s ADHD, aggression, and irritability with a stimulant. Moreover, I would choose methylphenidate over amphetamine for the following four reasons: (1) more evidence exists in support of methylphenidate for treating ADHD in the context of ASD (Mahajan et al., 2012; Rodrigues et al. [in press]) and ID (Arnold, 2013); (2) methylphenidate is better tolerated, on average, than amphetamine in children and adolescents (Cortese et al., 2018), and children with ASD and ID may be particularly sensitive to medication side effects (Mahajan et al., 2012; Arnold, 2013); (3) AJ’s prior trial of dextroamphetamine immediate-release (IR) was discontinued because of increased agitation; and (4) AJ has never had a methylphenidate trial.

I will now describe my step-by-step approach to adjusting AJ’s medication, noting that I would decide on each step collaboratively with the family, and we might need to change course depending on AJ’s progress. For the first 2-3 days of the admission, I would recommend no medication changes. This would allow the team to observe AJ on his current regimen and assess the effect of the inpatient environment, including the use of evidence-based behavioural interventions, on his symptoms. My *first* pharmacological recommendation would then be to discontinue the quetiapine, while addressing AJ’s insomnia with measures to improve his sleep hygiene. After 2-3 days of continued observation, my *second* pharmacological recommendation would be to decrease the risperidone to 0.25 mg daily for 2-3 days, and then discontinue it. Thus, approximately one week into the admission, AJ would be off all medication. I would then recommend observing AJ without medication for 2-3 days. Provided that he still exhibits clinically impairing ADHD symptoms and aggressive behaviour, my

third pharmacological recommendation would be initiation and titration of a methylphenidate formulation.

The choice of methylphenidate formulation would depend on the family’s preference based on various factors, including: desired duration of action; level of concern about side effects (especially insomnia and appetite suppression); value placed on the convenience of a long-acting formulation vs. the control and flexibility afforded by methylphenidate IR; cost and insurance coverage; and AJ’s ability to swallow pills. Whichever methylphenidate formulation is chosen, I would start at a low dose and titrate up by small increments (e.g., if methylphenidate IR is used, I would start with 5 mg/dose and titrate by 2.5 mg increments). I would also assess response and side effects at each dose with rating scales.

In an outpatient setting I would increase the dose of methylphenidate approximately weekly, but given the inpatient setting’s stable environment and capacity for close monitoring, dose increases could be made every 3-4 days. This should allow completion of an adequate trial during the remainder of the 4-week admission. I would continue to titrate the methylphenidate dose until optimal response is achieved, unacceptable side effects develop (in which case I would reduce the dose or discontinue the medication), or the maximum dose is reached.

With respect to medical monitoring, I would order vital signs twice daily during the methylphenidate titration, with one set measured in the morning before AJ takes the medication, and the second set measured later in the day when he is on it. This is to monitor for tachycardia or hypertension, although increases in heart rate and blood pressure with stimulants are typically small and clinically insignificant. I would order blood work 2-3 weeks after admission, mainly to assess whether AJ’s liver enzymes are normalizing following discontinuation of the antipsychotics. I would also repeat the CBC to monitor AJ’s mild anemia, and check his TSH given that thyroid abnormalities have been associated with quetiapine (Pringsheim, Panagiotopoulos, Davidson, Ho & CAMESA guideline group, 2011), which was only recently discontinued. I would defer repeating the metabolic panel until a couple of months after discharge, as AJ’s metabolic abnormalities may take longer to normalize.

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Response #2

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This complex and compelling case illustrates the complexity of non-pharmacological and pharmacological management for autism and intellectual disability. While attention deficit/hyperactivity disorder (ADHD) has established treatments that address the core symptoms, both autism and intellectual disability do not. Instead,

pharmacological treatment in autism is primarily directed at secondary symptoms, like irritability and aggression (IA), and sleep difficulties (Fung et al., 2016). Advice to both parents in the discussions around informed consent and psychoeducation would require this explicit discussion.

In populations with a complex overlap between diagnoses, comorbidities, and psychosocial issues (in this case, for example, the variance between father's home on the week-end and mother's home during the week), changes are best made one at a time. Preferably, a change is recommended, and observation for at least a week or two is made, and then new changes are gradually introduced. As the point of this exercise is to provide three pharmacological interventions, the order in which these could be done would be presented to parents and they could make the decision that works best for them.

Aggression, irritability, and weight gain: the pros and cons of antipsychotic use

It seems that AJ had some benefit from the initial start of risperidone. Unfortunately, increasing weight and prolactinemia have come into play. The doses of risperidone that have been shown to be most beneficial for IA in children with autism are between 1-2 mg/day (Lamberti et al., 2016). For AJ, I suspect we have hit a "dose-limiting side effect," in which it would not be feasible or acceptable to parents to increase the dose further (though, one could argue, perhaps the weight gain that was to occur has already occurred). Given that both aripiprazole and risperidone are efficacious for the treatment of IA in autism, and aripiprazole is associated with less prolactinemia and (in adults but not as much in children) less weight gain, I would recommend a tapering of risperidone downward by 0.125 mg per week for four weeks, while starting aripiprazole at 1 mg daily for one week, 2 mg daily for one week, followed by 5 mg daily for two weeks, then 10mg daily as a treatment dose.

Though the collection of bloodwork for metabolic monitoring can be challenging in children with autism and intellectual disabilities, it is essential in antipsychotic prescriptions, and every effort should be made. This should include: height, weight, waist circumference, blood pressure, and bloodwork: fasting plasma glucose, insulin, total cholesterol, LDL, HDL, triglycerides, and prolactin. Ideally, these values are monitored at baseline, three months, six months, and every six months thereafter (Pringsheim, Panagiotopoulos, Davidson, Ho & CAMESA guideline group, 2011).

It is also worth considering, given the weight gain, whether or not a trial first of no medication (simply removing the risperidone) is palatable to parents, to reduce weight gain and prolactinemia, but also to see if a residual effect of the risperidone is noticed. Families often experience many non-specific benefits from an inpatient evaluation, and energy could be focused on trying to treat ADHD or insomnia, as

below, while relying on non-pharmacological interventions for behavioural difficulties.

Off-label use of antipsychotics for sleep issues: a big no-no

For sleep management, there is significant concern in the current use of quetiapine. While many physicians use quetiapine off-label for sleep or anxiety, this is not evidence-based, potentially incurs more risk than benefit, and is specifically recommended against by the American Academy of Child & Adolescent Psychiatry (Findling, Drury, Jensen, Rapoport, & AACAP Committee on Quality Issues, 2011). My recommendation would be to stop using quetiapine (safely discontinued immediately at the current dose of 25 mg nightly), and to begin using melatonin, which has been specifically studied in people with autism and shown considerable benefit (Cortese, Wang, Angriman, Masi & Bruni, 2020).

ADHD specifically: to treat or not to treat

Currently, pharmacological treatment for AJ's ADHD is absent. There is considerable diagnostic overlap between ADHD symptoms and autism symptoms, but there was a rating scale done by teachers that was consistent with significant inattentive ADHD symptomatology. Inattention could be contributing to frustration and aggression, and it may be worth considering pharmacological treatment. However, I would consider ADHD treatment secondary to establishing the antipsychotic that is being used, for three reasons:

1. Many of the general symptoms of ADHD improve significantly with the use of an antipsychotic in autism (Lamberti et al., 2016).
2. It is likely that the increased aggression and irritability at home is of larger current concern.
3. Polypharmacy should be minimized whenever possible.

An advantage to another stimulant trial (methylphenidate extended-release, for example) would be the "side effect" (in this case, perhaps a benefit) of appetite suppression, but it is also quite common in children with autism to respond to stimulants with worsening behaviours, irritability, and insomnia (DeFillippis & Wagner, 2016). Some studies have shown a benefit, so this would be a "back pocket" option to use once the primary psychopharmacological intervention has been established.

Overall recommendations

Ultimately, the information about medications, their risks, benefits, and alternatives needs to be discussed with the parents for their ability to give informed consent or dissent.

Each medication comes with potential side effects and benefits, and one area of concern may be addressed while the other deteriorates with each intervention. Close follow-up following guidance on metabolic and side effect monitoring, and active engagement with caregivers would be of enormous benefit.

To answer the question of the "challenge," my overall recommendations to AJ's family would be:

1. Switch risperidone to aripiprazole and try to attain an established treatment dose
2. Remove quetiapine and use melatonin as a safer sleep aid.
3. Consider methylphenidate extended-release to target ADHD symptoms ongoing.

As per usual, I would set up regular follow-up and provide my e-mail address, as families of children with complex needs require ongoing support and care.

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Response #3

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In this case, preliminary information about AJ's behaviours that challenge and adverse effects related to medications are presented. To better tailor recommendations to his needs, one should explore individual patient, family and environmental factors contributing to AJ's presentation (McGuire et al., 2016). Characterization of the nature, severity, timing, frequency and duration of AJ's behaviour, setting, antecedents, and consequences is essential. Psychosocial stressors including family dynamics and coping, abuse or neglect, peer relationships and bullying, and educational supports should be considered. Co-existing medical, neurologic and psychiatric conditions, level of functional communication and sensory needs may also contribute to his behaviour. The safety of AJ, his sibling and caregivers should be considered as it may prompt more aggressive pharmacologic management. In combination with the history, a physical examination, interview with the child, and direct observation of AJ's behaviour supported by individuals experienced in functional behavioural analysis (i.e. board certified behaviour analyst) will clarify his presentation. This information will help to identify target behaviours which hopefully align with the family's goals and which will direct both non-pharmacologic and pharmacologic intervention (Ameis et al., 2018).

As reducing aggression is one of the family's goals, further history and observation may reveal the nature of his aggression, which could include irritability, impulsivity, anxiety or behavioural causes. Contributing factors warranting non-pharmacologic treatments should be considered prior to initiating medications. Should irritability or severe aggression resulting in significant functional or safety concerns (i.e. harm towards others, self-injurious behaviours and property destruction) be identified, atypical antipsychotics including risperidone and aripiprazole are considered first-line treatments as they have the strongest evidence for reduction of Aberrant Behaviour Checklist Irritability Subscale Scores (McGuire et al., 2016; Ameis et al., 2018). If impulsivity or anxiety are the main contributors to aggression, pharmacologic options targeting these symptoms

should be considered before atypical antipsychotics (Ameis et al., 2018). A limitation in the use of atypical antipsychotics is the risk of metabolic and extrapyramidal adverse effects (Pringsheim, Panagiotopoulos, Davidson, Ho & CAMESA guideline group, 2011).

While AJ remains on risperidone for irritability and quetiapine for insomnia, the benefit of remaining on two atypical antipsychotics is unclear and this may in fact contribute to his adverse effects. An initial consideration would be to wean AJ off quetiapine and to consider other measures to address his sleep, which are discussed below. While AJ's initial response to risperidone was positive, his diminishing response, weight gain, and metabolic adverse effects (though not clear if they are attributable to medication alone due to lack of baseline bloodwork) are concerning. If AJ and his family are motivated to implement dietary and lifestyle measures (possibly including a referral to a paediatric weight management clinic), one could increase AJ's risperidone dose (0.5 mg per day every two weeks, to a maximum total daily dose of 3 mg per day while monitoring his weight, blood pressure, and bloodwork parameters as per the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guidelines every three months (Pringsheim et al., 2011; Ameis, Corbett-Dick, Cole & Correll, 2013; Lexicomp Online, 2020). Behavioural logs to track AJ's aggression at baseline and with changes in his risperidone dose should be kept to ensure that medication changes are supported by behavioural data. Should AJ experience worsening adverse effects or show no response, one could switch to aripiprazole whilst continuing monitoring as per CAMESA guidelines (Pringsheim et al., 2011). Alternatives include initiating an alpha-agonist such as clonidine (McGuire et al., 2016) or N-acetylcysteine which has emerging evidence in treating irritability based on one randomized controlled trial (Antonio et al., 2012). Metformin could be added to his regimen to decrease weight gain if AJ responds positively to an atypical antipsychotic but weight remains a concern (Anagnostou et al., 2016).

Another target behaviour identified is ADHD. Though AJ presents with predominantly inattentive ADHD symptoms at school, it would be important to ascertain whether these symptoms are present in at least one other setting, to screen the child and family for cardiac risk factors, and to ensure that behavioural and educational supports are in place before initiating pharmacologic management (Mahajan et al., 2012). First line treatment for ADHD would include stimulants (i.e. methylphenidate and dextroamphetamine) (Mahajan et al., 2012). AJ may have failed a trial of dextroamphetamine in the past as children with ASD and ADHD tend to have less response and more adverse effects (e.g. emotional outbursts, appetite suppression, sleep disturbance) with stimulants (Mahajan et al., 2012). AJ could consider a trial of intermediate-acting methylphenidate (e.g., methylphenidate 12 hour multi-layer release [Biphentin(R), MPH-MLR12]

– starting dose 10 mg, maximum daily dose of 2 mg/kg; or methylphenidate osmotic-release [Concerta(R), MPH-OROS] – starting dose 18 mg, maximum daily dose of 2 mg/kg) starting at a low dose and titrating the dose at one-week intervals to the lowest effective dose (Feldman, Charach & Belanger, 2018). Monitoring should include documentation of blood pressure and heart rate and completion of symptom monitoring questionnaires. Should AJ experience adverse effects, one should gauge the severity of the adverse effect (e.g. appetite suppression versus significant weight loss) and degree of symptom improvement, before either reducing the dose of the medication or discontinuing it completely. Should AJ experience significant adverse effects or not respond to stimulants, then second-line options would include alpha-agonists or atomoxetine, with additional considerations including increased length of time to response to medications and warning against abrupt discontinuation of the medication (Mahajan et al., 2012). AJ's previous experience with clonidine should not be considered a full trial given the short duration of use and the known risk of sedation that improves within a few weeks of starting the medication.

While sleep was not raised as a goal, AJ's insomnia should be explored through careful history and observation to elicit the presence of primary sleep disorders (e.g. obstructive sleep apnea), co-existing medical conditions, and poor sleep hygiene (Buckley et al., 2020). Non-pharmacologic interventions such as sleep hygiene and cognitive-behavioural therapy based strategies should be employed before initiating pharmacologic treatments (Buckley et al., 2020). Melatonin is the first-line pharmacologic treatment recommended in children with ASD like AJ to address sleep onset and maintenance (Buckley et al., 2020).

While medications may help to stabilize a child's behaviour, they are not a replacement for the need for behavioural (e.g. applied behavioural analysis), educational (e.g. educational assistant, individual education plan, assistive technology), or psychosocial interventions (e.g. respite, family therapy). Behavioural interventions to address the functions of AJ's behaviour should be initiated while AJ remains an inpatient and strategies should be shared with AJ's caregivers to ensure that they are appropriately trained and consistent in implementing these strategies at home. AJ would benefit from having these supports in place prior to returning home to ensure a successful transition back to the community.

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