

# Psychopharmacology

## First do no Harm: Promoting an Evidence-Based Approach to Atypical Antipsychotic use in Children and Adolescents

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### Abstract

**Objectives:** To review the evidence for efficacy and metabolic effects of atypical antipsychotics (AAPs), and to propose a metabolic monitoring protocol for AAP use in children and adolescents. **Methods:** A PubMed search was performed to obtain all studies related to efficacy, metabolic side-effects, and monitoring in those less than 18 years of age. **Results:** There are no approved indications for AAP use in children and adolescents in Canada. Based on US Food and Drug Administration approvals and a review of randomized controlled trials, we identified 7 indications for AAP use that target specific symptoms in youth including schizophrenia, bipolar I disorder, autism, pervasive developmental disorder, disruptive behaviour disorders (including conduct disorder and ADHD), developmental disabilities and Tourette Syndrome. A wide range of metabolic effects including weight gain, increased waist circumference, dysglycemia, dyslipidemia, hypertension, elevated hepatic transaminases and prolactin levels have been reported. We have developed a proposal for metabolic monitoring that includes anthropometric measurements and laboratory testing at baseline and appropriate intervals thereafter. **Conclusion:** There is an urgent need for national clinical practice guidelines that provide, not only appropriate treatment algorithms for AAP-use based on evidence, but also address metabolic monitoring and subsequent management of complications in this vulnerable population.

**Key words:** atypical antipsychotics, children, adolescents, efficacy, metabolic, monitoring

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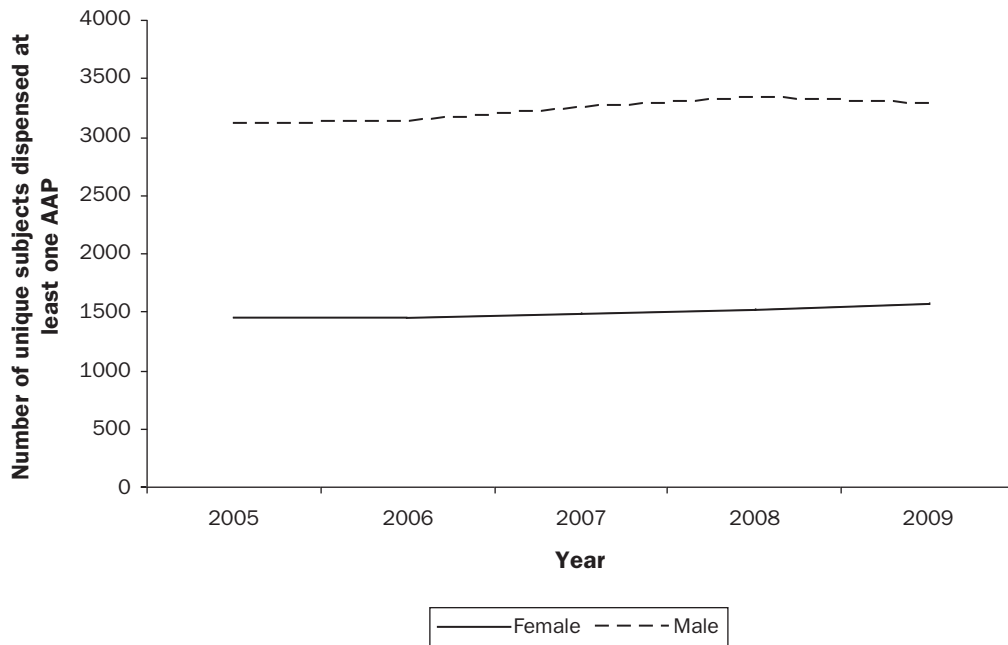
### Introduction

Second-generation or atypical antipsychotics (AAPs) have steadily replaced first-generation or typical antipsychotics since their introduction in the late 1980's. In parallel with rising adult prescription rates (Hermann et al., 2002; Mond, Morice, Owen, & Korten, 2003), there is a growing body of literature demonstrating that prescriptions of AAPs to children and adolescents have increased substantially over the last decade. In the United States (US), the number of office-based visits by youth that included an AAP prescription increased 6-fold from 201,000 in 1993 to 1,224,000 in 2002 (Olfson, Blanco, Liu, Moreno, & Laje, 2006). A more recent study (Domino & Swartz, 2008) reported that the average age of AAP users declined from 49 years of age to 43 years of age in the US, as a result of a shift in prescriptions from the elderly towards youth, who accounted for 15% of all AAP prescriptions in 2005, doubled from 7% in 1996. While similar national data are not available for Canada, prescriptions of AAPs for children under 14 years old increased 10-fold between 1997 and 2007 in British Columbia (Therapeutics initiative, 2009). Consistent with US data (Cooper et al., 2006; Olfson et al., 2006), BC Pharmacare data (Pharmacare, 2009) indicate

that prescriptions of AAPs are more common in boys than in girls (Figure 1a), with a substantial number of children under age 12 receiving these medications (Figure 1b). In a recent Canadian survey of child psychiatrists and developmental pediatricians (Doey, Handelman, Seabrook, & Steele, 2007), 12% of all AAP prescriptions were for children 8 years of age and under, which is of particular concern.

Reasons that may have contributed to the increased prescription rates of AAPs in youth include the following: increasing evidence that illnesses such as bipolar disorder (Geller, Tillman, & Bolhofner, 2007) and schizophrenia (Addington & Rapoport, 2009) may present in childhood; arguable overgeneralization of clinical trial data from efficacy trials in adults and sub-populations of children and youth; and, most importantly, a perception of an improved side-effect profile particularly with respect to extrapyramidal symptoms (EPS) including tardive dyskinesia (Correll, Leucht, & Kane, 2004; Kane, 2001) than the first-generation or typical antipsychotic medications. However, in adults, there has been a clear link between AAPs and metabolic adverse effects for some time. Many studies in adults confirm that AAPs can precipitate weight

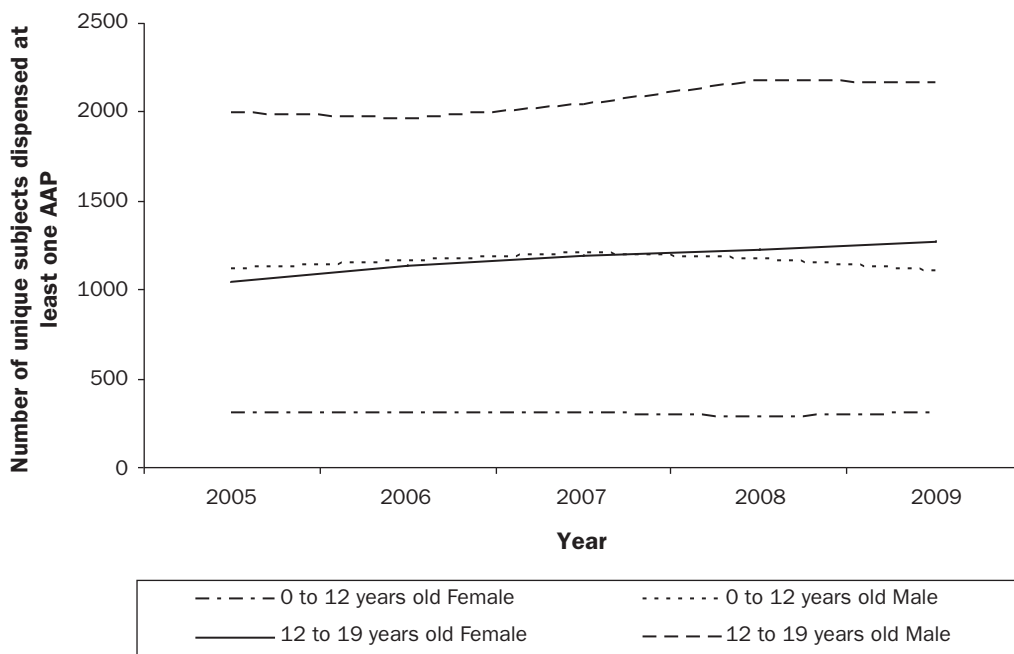
**Figure 1a. Sex distribution of atypical antipsychotic prescriptions in youth  $\leq 19$  years**



gain (Tandon & Halbreich, 2003), hyperlipidemia (Meyer & Koro, 2004) and insulin resistance (Nasrallah & Newcomer, 2004; Wu et al., 2006), and that their use is associated with development of metabolic syndrome (Meyer, Koro, & L'Italien, 2005; Shirzadi & Ghaemi, 2006) and type 2 diabetes (Cohen, 2004; Henderson, 2002; Melkersson & Dahl, 2004; Newcomer, 2005).

There have been recent reports (Correll, 2009; Panagiotopoulos, Ronsley, & Davidson, 2009) of similar metabolic effects in children and adolescents. Of concern, there are data (Doey et al., 2007) indicating that a substantial percentage of physicians prescribe these medications for symptoms and diagnoses that have not been previously studied [e.g., poor frustration tolerance

**Figure 1b. Distribution of atypical antipsychotic prescriptions by age group and sex**



(75%), impulsivity (65%), obsessive-compulsive disorder (52%), insomnia (36%), post traumatic stress disorder (34%), depression (30%), and eating disorders (26%]. These observations, combined with the increase in AAP prescription rates, indicate that there is an urgent need to systematically review both the existing evidence for use of AAPs, and their metabolic effects.

Therefore, our objectives with regard to children and adolescents under 18 years of age (collectively referred to as youth) are to summarize the evidence for efficacy of AAPs, review the existing literature assessing the metabolic effects of AAPs, and propose a protocol for metabolic monitoring in youth prescribed AAPs.

## Methods

### *Efficacy*

A PubMed search was performed to obtain all efficacy studies using the following key words: children or adolescents or youth or pediatric; atypical or second generation antipsychotics; aripiprazole or clozapine or olanzapine or paliperidone or quetiapine or risperidone or ziprasidone; efficacy; safety; indications. Only randomized controlled trials (RCTs) with a primary outcome of efficacy of one or more AAP conducted in individuals under 18 years of age were included. Case reports, review articles and open label trials assessing indications for AAP efficacy were not included due to space limitations. Information about current US Food and Drug Administration (FDA) approvals for children was obtained from the FDA website (Food and Drug Administration, 2010). Information about current Health Canada approvals was obtained from the Health Canada website (Health Canada, 2009).

### *Metabolic effects*

A PubMed search was performed to obtain all studies assessing metabolic side effects using the following key words: children or adolescents or youth or pediatric; atypical or second generation antipsychotics; aripiprazole or clozapine or olanzapine or paliperidone or quetiapine or risperidone or ziprasidone; weight gain, obesity, dyslipidemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, diabetes, insulin resistance, hypertension or blood pressure, hepatic transaminases, metabolic side effects, monitoring. Given that rare side effects may not be identified from randomized clinical trials and that regulatory agencies have relied on case series of serious adverse events (Gitlin, Julie, Spurr, Lim, & Juarbe, 1998; Kohlroser, Mathai, Reichheld, Banner, & Bonkovsky, 2000; Malik, Prasad, Saboorian, Thiele, & Malet, 2000) as a basis for removing a drug from the market to protect patient safety, all studies with a primary or secondary outcome measure of the above metabolic side effects conducted in individuals under 18 years of age were included. Studies were also included for review if they contained guidelines for monitoring of metabolic side effects in AAP-treated youth or adults. Additional articles were

obtained from references and poster publications. Studies pertaining to cardiovascular disease (with the exception of hypertension/blood pressure), thyroid, parathyroid, or gonadal effects are beyond the scope of this review.

### *Classification*

Articles were classified into level of evidence categories based on the Centre for Evidence Based Medicine criteria (Cache Limited, 2010).

## Results

### *Efficacy*

A total of 42 RCTs assessing efficacy of AAPs in children and adolescents were identified. Of these, 41 RCTs demonstrated a positive outcome, and one double-blind, placebo controlled RCT of quetiapine (DelBello et al., 2009) for symptoms of depression in adolescents 12-18 years of age with bipolar I disorder demonstrated no improvement.

While there are currently no Health Canada approved indications, there are several FDA approved indications for AAP use in children and adolescents. Table 1 summarizes the target symptoms, and mental health conditions, including the specific age ranges, for which there is either FDA approval or RCT evidence for use in this population.

### *Metabolic Effects*

A total of 24 studies were identified using our search criteria, and are presented in Table 2.

### *Absolute Weight Gain*

Compared to adults, AAPs have been found to produce significantly greater weight gain in children and do so within a very short time frame (Correll & Carlson, 2006; Fleischhaker et al., 2007; Penzner et al., 2009; Ratzoni et al., 2002). The magnitude of absolute weight gain varies between AAPs, with olanzapine producing the greatest weight gain (Correll et al., 2009; Fleischhaker et al., 2007; Fraguas et al., 2008; Patel, Kistler, James, & Crismon, 2004). Correll reported significant weight gain within 4 weeks of AAP initiation (average weight gain: olanzapine 4.52 kg; quetiapine 2.87 kg; risperidone 2.72 kg; aripiprazole 1.61 kg), that remained significantly higher than that seen in untreated youth after 12 weeks of treatment (olanzapine 8.5 kg; quetiapine 6.1 kg; risperidone 5.34 kg; aripiprazole 4.4 kg). Due to insufficient enrollment, the ziprasidone group was not analyzed. Extreme weight gain (defined as an increase of  $\geq 7\%$  from initial baseline weight) was observed in 84% of olanzapine-treated, 56% of quetiapine-treated, 64% of risperidone-treated and 58% of aripiprazole-treated patients (Correll et al., 2009; Ratzoni et al., 2002). Of note, one study (Fleischhaker et al., 2007) demonstrated that olanzapine and risperidone, but not clozapine, caused a disproportionately higher weight gain in children and adolescents compared to adults. There are limited long-term studies of AAPs in which weight gain is a primary or secondary

**Table 1. Evidence supporting atypical antipsychotic use for specific indications**

Antipsychotic	Indication	Target symptoms	Age range (years)	Evidence
Aripiprazole	Autism <sup>§</sup>	Irritability	6-17	Owen et al., 2009, Marcus et al., 2009.
	Bipolar I Disorder <sup>§</sup>	Manic or mixed episodes	8-17 (10-17) <sup>§</sup>	Findling et al., 2009, Tramontina et al., 2009.
	Schizophrenia <sup>§</sup>	Positive and negative symptoms	13-17	Findling et al., 2008.
Clozapine	Schizophrenia	Psychosis	8-18	Sporn et al., 2007.
Olanzapine	Bipolar I Disorder <sup>§</sup>	Manic or mixed episodes (acute and maintenance treatment)	13-17	Tohen et al., 2007
	PDD	Aggression	6-14	Hollander et al., 2006.
	Schizophrenia <sup>§</sup>	Positive and negative symptoms	13-17	Kryzhanovskaya et al., 2009.
Quetiapine	Schizophrenia <sup>§</sup>	Positive and negative symptoms	13-17	www.clinicaltrials.gov
	Bipolar I Disorder <sup>§</sup>	Manic episodes	12-18 (10-17) <sup>§</sup>	DelBello et al., 2006, Del Bello et al., 2002.
	Conduct disorder	Aggression	12-17	Connor et al., 2008.
Risperidone	Autism <sup>§</sup>	Irritability, Aggression, Communication, Hyperactivity, affect regulation	2-18 (5-16) <sup>§</sup>	Aman et al., 2008, Aman et al., 2005, McCracken et al., 2005, McCracken et al., 2002, McDougale et al., 2005, Miral et al., 2008, Nagaraj et al., 2006, Pandina et al., 2007, Shea et al., 2004.
	Bipolar I Disorder <sup>§</sup>	Manic or mixed episodes	10-17	www.clinicaltrials.gov, www.clinicaltrials.gov (Johnson et al., 2008), DelBello M et al., 2005, Wilson et al., 2009.
	Developmental Disabilities, Subaverage IQ	Aggression, SIB	6-18	Buitelaar et al., 2001, Zarcone et al., 2001.
	Disruptive Behaviour Disorders (including ADHD)	Conduct problems, Irritability, Hyperactivity, Aggression	4-14	Aman et al., 2009, Aman et al., 2002, Armenteros et al., 2007, Biederman et al., 2006, Correia Filho et al., 2005, Findling et al., 2004, Reyes et al., 2006, Snyder et al., 2002.
	Schizophrenia <sup>§</sup>	Positive and negative symptoms	13-17	Haas et al., 2009.
	Tourette Syndrome	Tics	7-17	Bruggeman et al., 2001, Gaffney et al., 2002, Gilbert et al., 2004, Scahill et al., 2003.
Ziprasidone	Bipolar I Disorder	Mania	10-17	DelBello et al., 2008.
	Tourette Syndrome	Tics	7-17	Salle et al., 2000.

§ - FDA Approved Indication

outcome measure. However, an RCT (Arango et al., 2009) comparing olanzapine and quetiapine in adolescent patients with a first psychotic episode, reported the mean incremental weight gain to be 15.5 kg and 5.4 kg respectively during the 6 month study. Although it has been argued that youth may be more vulnerable to AAP-induced weight gain than adults, recent work (Correll et al., 2009) challenges this hypothesis by suggesting that the greater weight gain in youth is related to less frequent AAP exposure compared with most adult samples.

#### *Body mass index (BMI)*

Because childhood and adolescence involves continuing increases in height and weight as part of normal growth, body mass index (BMI: weight (kg)/height (m)<sup>2</sup>) normalized for age and sex (BMI z-score) provides a more accurate method with which to assess the appropriateness of absolute weight gain in the context of linear growth. For children, overweight is defined as a BMI ≥85th percentile and obese as ≥95th percentile for age and sex (Center for Disease Control and Prevention, 2007) (corre-

**Table 2. Summary of studies assessing metabolic effects of antipsychotics as a primary outcome**

Type of Study (Level of evidence)	AP	Length of study (weeks)	Study sample (N, %male, mean age [years])	Metabolic Outcomes	Reference
Randomized controlled trial (1a)	R	8	N=101, 81% 8.8	prolactin	Anderson, et al., 2007.
Prospective open label (1b)	A, O, Q, R	12	N=272, 57%; 13.9	weight, weight%, BMI, zBMI, fat mass, waist circumference, lipids, triglycerides, glucose, insulin	Correll, et al., 2009.
Prospective open label (1b)	A, C, O, Q, R, Z	12	N=153; 77.8%; 11.3	body composition parameters, lipids, glucose, insulin, metabolic syndrome	Penzner, et al., 2009.
Prospective open label (1b)	R	4	N=120, 76% 8.56	alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase, alkaline phosphatase	Erdogan, et al., 2008.
Open label or double blind (1b)	C, H, O	68	N=57, 60% C: 14.2, H: 13.8, O: 14.5	prolactin	Alfaro, et al., 2002.
Cross sectional open label (2b)	Q, R	N/A	N=194, 77% 11.6	zBMI, BMI, waist circumference, glucose, insulin, lipids, metabolic syndrome	Weiss, et al., 2009.
Naturalistic longitudinal (2b)	O, Q, R	24	N=66, 66.6% 15.2	zBMI, lipids, glucose, thyroid stimulating hormone	Fraguas, et al., 2008.
Prospective open label (2b)	C, O, R	6	N=45, 69% C: 17.4, O: 15.7, R: 15.2	weight, BMI, zBMI	Fleischhaker, et al., 2007.
Prospective open label (2b)	R	24	N=63, 78% 8.6	weight, leptin	Martin, et al., 2004.
Prospective open label (2b)	H, O, R	12	N=50, 62% H: 17.3, O: 17.0, R: 17.1	weight, BMI	Ratzoni, et al., 2002.
Prospective open label (2b)	R	10	N=25, 88% 4.10	prolactin	Masi, et al., 2001.
Prospective open label (2b)	C, H, O	6	N=35, 63% 14.1	prolactin	Wudarsky, et al., 1999.
Retrospective chart review (2b)	C, O, Q, R	N/A	N=432, 62% treated: 13.7, control: 13.9	zBMI, glucose, lipids, blood pressure, metabolic syndrome	Panagiotopoulos, et al., 2009.
Retrospective chart review (2b)	R	151	N=99, 88% normal BMI:11.9, high BMI:11.3	weight, BMI, zBMI, blood pressure, waist circumference, lipids, glucose, insulin	Calarge, et al., 2009.
Retrospective cohort design (2b)	A, O, Q, R, Z	N/A	N=4140, 68% 10.4	BMI, type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease, cerebrovascular/orthostatic hypotension adverse events	McIntyre, et al., 2008.
Retrospective chart review (2b)	A, C, O, Q, R, Z	4	N=95, 57% 14	BMI, lipids	Patel, et al., 2007.
Cross sectional study (2b)	O, Q, R	1-127	N=126, 61.9% 15.62	glucose, lipids, BMI, prolactin, thyroid stimulating hormone, glycosylated hemoglobin A1c, blood pressure	Laita, et al., 2007.
Retrospective chart review (2b)	O, Q	45	N=103, 48% O: 14.2, Q: 14.4	weight, BMI	Patel, et al., 2004.
Retrospective chart review (2b)	R	34	N=22, 86% 12.8	weight, triglycerides, total cholesterol	Martin, et al., 2002.
Retrospective chart review (2b)	R	24	N=37, 76% 12.5	weight, BMI, tanner staging, zweight	Martin, et al., 2000.
Retrospective chart review (2b)	R	106	N=38, 84% 10.6	aspartate aminotransferase, alanine aminotransferase, total bilirubin, weight	Szigethy, et al., 1999.
Case series (3a)	R	N/A	N=3, 66% cases aged 15, 17, 18	prolactin	Madhusoodanan, et al., 2006.
Letter to editor (3b)	R	N/A	N=12, 58% 13.5	diabetes mellitus	Koller, et al., 2004.
Letter to editor (3b)	O, C	N/A	20, 55% cases age range: 13-18	hyperglycemia	Koller, et al., 2001.

**Legend: A:** Aripiprazole; **AP:** Antipsychotic; **C:** Clozapine; **H:** Haloperidol; **N/A:** not available; **O:** Olanzapine; **Q:** Quetiapine; **R:** Risperidone; **Z:** Ziprasidone  
**Lipids:** total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol  
**R:** Risperidone; **Z:** Ziprasidone; **zBMI:** body mass index standardized for age and sex; **weight:** weight standardized for age and sex

sponding to BMI z-scores of 1.04 and 1.64, respectively). An absolute increase in BMI z-score of  $\geq 0.5$  has been proposed as significant because this degree of growth-adjusted weight gain was found to increase the risk for metabolic syndrome by more than 50% (Correll & Carlson, 2006; Weiss et al., 2004). Within 12 weeks of treatment, Correll reported (Correll et al., 2009) an increase in BMI z-score of  $> 0.5$  in 62% of olanzapine-treated, 36% of quetiapine-treated, 47% of risperidone-treated, and 22% of aripiprazole-treated youth. Overall, 17% of these patients had become overweight or obese. In the short-stay, child and adolescent psychiatric emergency (CAPE) unit at BC Children's Hospital (BCCH), cross-sectional prevalence rates of obesity/overweight were more than double in AAP-treated youth (57%) compared with AAP-naïve youth (23%) (Panagiotopoulos et al., 2009). This finding is consistent with Patel (Patel et al., 2007), who reported an overall prevalence of 68% obesity/overweight in their inpatient sample which was 2.2 times greater than a sample from the general population (31%).

#### *Waist Circumference*

Waist circumference has been used as a surrogate measure of central adiposity, and has been shown to be a strong predictor of other components of the metabolic syndrome (Bitsori, Linardakis, Tabakaki, & Kafatos, 2009; Zimmet et al., 2007). There is a growing body of evidence that AAPs can result in a rapid increase in waist circumference. In the CAPE unit at BCCH, 49% of AAP-treated youth had a waist circumference  $\geq 90^{\text{th}}$  percentile compared to only 18% of AAP-naïve youth (Panagiotopoulos, Davidson, Weiss, 2009). In a subset of children ( $n=27$ ) treated with both risperidone and a psychostimulant for ADHD, and enrolled in a protocol for metabolic monitoring at BCCH, increased waist circumference was documented in 68% (Weiss et al., 2009). Correll (Correll et al., 2009) reported significant mean increases in waist circumference after 12 weeks of therapy with olanzapine (8.6 cm), aripiprazole (5.4 cm), quetiapine (5.3 cm), and risperidone (5.1 cm) compared to untreated controls. Similar to increases in body weight, increases in waist circumference were noted within 4 weeks of treatment.

#### *Glucose and Insulin*

In the US FDA MedWatch Drug Surveillance System, there are several case series (Koller, Malozowski, & Doraiswamy, 2001; Koller, Cross, & Schneider, 2004; Koller, Weber, Doraiswamy, & Schneider, 2004) reporting the occurrence of diabetes and diabetic ketoacidosis in children and adolescents following treatment with clozapine, olanzapine, risperidone and quetiapine. Although most of these cases occurred within 6 months of drug initiation, some occurred as late as 12-24 months of therapy. Of 46 cases of quetiapine-related diabetes (Koller, Weber et al., 2004), 11 deaths were reported

(age range 12-47 years). Significant elevations in fasting glucose (without overt diabetes symptoms) have been shown to occur following 12 weeks of olanzapine treatment (Correll et al., 2009; Sikich et al., 2008). The cross-sectional prevalence of impaired fasting glucose and/or type 2 diabetes from the CAPE unit at BCCH was 21.5% in AAP-treated youth, almost three times that seen in AAP-naïve youth (7.5%) (Panagiotopoulos et al., 2009), likely due to a longer duration of AAP treatment. While the exact pathophysiology of AAP-induced diabetes/hyperglycemia remains unclear, there is evidence (Calarge, Acion, Kuperman, Tansey, & Schlechte, 2009; Correll et al., 2009; Weiss et al., 2009) that AAPs promote insulin resistance with compensatory fasting hyperinsulinemia. Although rapid weight gain and central adiposity likely contribute to insulin resistance, emerging evidence from animal models (Chintoh et al., 2008; Savoy et al., 2008) suggest that AAPs may also exert direct effects on beta-cell function.

#### *Lipids*

Significant increases in total cholesterol have been documented following olanzapine and quetiapine treatment (Fraguas et al., 2008; Sikich et al., 2008), in triglycerides following olanzapine, quetiapine and risperidone treatment, and in LDL-cholesterol following aripiprazole and olanzapine treatment (Correll et al., 2009). Using administrative datasets, McIntyre and Jerrell (McIntyre & Jerrell, 2008) previously reported that the odds of incident dyslipidemia are higher for those exposed to multiple antipsychotics (OR 5.26; 95% confidence interval (CI): 1.64-16.82). The risk of patients with preexisting obesity and hypertension developing type 2 diabetes or dyslipidemia was 4.5 times higher following antipsychotic exposure than those without these pre-existing conditions. One study (Martin et al., 2004), found that almost 25% of the variance in triglyceride levels could be explained by weight gain alone, and another study (Patel et al., 2007) reported that BMI z-scores were positively associated with total cholesterol, triglycerides and LDL and negatively correlated with HDL.

#### *Blood Pressure*

The odds of developing incident hypertension have been reported to be significantly higher for antipsychotic-treated adolescents 13 years of age or older (OR 2.78; 95% CI: 1.69-4.55), but are not correlated to which antipsychotic they received (McIntyre & Jerrell, 2008). Consistent with these data, the cross-sectional prevalence of elevated blood pressure (defined as systolic or diastolic  $\geq 90^{\text{th}}$  percentile for age, sex, and height percentile) within the CAPE unit at BCCH was 54% in AAP-treated youth, three times that seen in AAP-naïve youth (18%) (Panagiotopoulos, Davidson, Weiss, 2009). However, two other studies in AAP-treated children and adolescents (Fraguas et al., 2008; Laita et al., 2007)

have not found significant changes in blood pressure even when assessing long-term treatment.

#### *Metabolic syndrome*

The 'metabolic syndrome' refers to a condition in which there is central obesity and at least 2 additional criteria (high blood pressure, high triglyceride level, low HDL-cholesterol level, high fasting glucose) (Zimmet et al., 2007). Metabolic syndrome is a predictor of cardiovascular disease risk, particularly of atherosclerosis and stroke in adults (Li et al., 2003; Raitakari et al., 2003). The definition of metabolic syndrome is derived from adult studies and is not universally accepted in pediatrics. There is ongoing debate about the relative importance of the diagnosis compared to the individual abnormalities. The current literature indicates that the atherosclerotic process begins in childhood and that indices of metabolic syndrome track from childhood to adulthood (Berenson et al., 1998).

Studies assessing the impact of AAPs on metabolic syndrome in children are limited. Following short-term treatment (mean follow-up 10.8 weeks) with AAPs, the mean prevalence of metabolic syndrome was 1.6% with the highest rate documented in the quetiapine sub-group (6.5%) (Correll et al., 2009). In contrast, in the CAPE unit at BCCH, where the mean duration of AAP treatment at the time of assessment was 12 months, the prevalence of metabolic syndrome was 9 times higher in AAP-treated (27%) compared to AAP-naïve (2.9%) children and adolescents ( $p < 0.001$ ) with an increased prevalence of the following components, respectively: elevated waist circumference (49.1 vs. 17.9%;  $p < 0.0001$ ); hypertriglyceridemia (42.6 vs. 22.4%;  $p = 0.015$ ); impaired fasting glucose (16.1 vs. 2.6%;  $p = 0.005$ ); and hypertension (54 vs. 18%;  $p < 0.0001$ ). In addition, low HDL-cholesterol was seen in 16% of AAP-treated youth compared to 11% of AAP-naïve youth; however, this result was not statistically significant (Panagiotopoulos, Davidson, Weiss, 2009).

#### *Hepatic Transaminases*

Studies in children and adolescents regarding effects on hepatic transaminases during AAP treatment are limited. Woods (Woods, Martin, Spector, & McGlashan, 2002) reviewed the FDA MedWatch Drug Surveillance System regarding olanzapine and noted significantly higher risk ratios for hepatic transaminase abnormalities in children [under 10 years of age] (RR 3.4, 95% CI: 1.9-6.1) and adolescents [10-19 years of age] (RR 1.9, 95% CI: 1.5-2.4) compared to adults. These findings are consistent with other clinical trials (Gonzalez-Heydrich, Raches, Wilens, Leichtner, & Mezzacappa, 2003; Sikich et al., 2008). However, in risperidone-treated youth, data are conflicting. One case series (Kumra, Herion, Jacobsen, Briguglia, & Grothe, 1997) identified steatohepatitis in 2 of 13 children treated with risperidone, while other prospective studies (Erdogan et al., 2008;

Szigethy, Wiznitzer, Branicky, Maxwell, & Findling, 1999) have reported low rates of clinically significant hepatic transaminase elevation. More research is needed to evaluate these abnormalities and the potential for steatohepatitis in this population.

#### *Prolactin*

There is accumulating evidence (Anderson et al., 2007) that children treated with risperidone often exhibit modest to marked elevations in prolactin. In a post-hoc analysis of 5 clinical trials (Findling et al., 2003) in children between 5-15 years of age with disruptive behaviour disorders who were treated with risperidone, there was a rapid rise of serum prolactin peaking at 1-2 months following initiation of therapy and returning to normal levels after 3-5 months. However, in a different study (Anderson et al., 2007) of children with autism between 5-17 years of age, the risperidone-induced increase in prolactin reached a 4-fold increase within the first 2 months, and remained significantly increased at 6 months (3-fold) and at 22 months of treatment (2-fold). While data (Alfaro et al., 2002) do not suggest any correlation between prolactin levels and risperidone dosage, a reduction in dosage has been associated with significantly decreased levels (Masi, Cosenza, & Mucci, 2001). While increases in prolactin levels are especially noted with risperidone, they can also occur with other AAPs, including olanzapine and clozapine (Alfaro et al., 2002; Dittmann et al., 2008; Laita et al., 2007; Wudarsky et al., 1999). These elevations appear to be particularly concerning in adolescents (Woods et al., 2002). In contrast, aripiprazole appears to decrease prolactin levels (Findling et al., 2008). While the majority of patients remain asymptomatic with mild prolactin elevation, more marked elevation has been reported to lead to gynecomastia in males, and galactorrhea and amenorrhea in females (Madhusoodanan & Moise, 2006). Although there is evidence that AAP-induced increases in prolactin tend to diminish over time, the impact of chronic prolactin increases on gonadal hormones, growth and pubertal development and bone mineral density are unknown (Anderson et al., 2007).

#### *Metabolic monitoring*

Prompted by the growing body of evidence highlighting significant metabolic effects associated with AAP treatment in adults, the American Diabetes Association with the American Psychiatric Association published a consensus statement (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, & North American Association for the Study of Obesity, 2004) in 2004 that specified a monitoring protocol including baseline assessments of personal/family history, body mass index, waist circumference, blood pressure, as well as fasting plasma glucose and lipid levels. In spite of these recommendations, and in conjunction with FDA warnings about metabolic adverse

effects of AAPs, adherence to these monitoring recommendations has been low in adults (Haupt et al., 2009; Morrato et al., 2009).

In our retrospective chart review of 432 youth admitted to the CAPE unit at BCCH during a 2.5-year period, we found that only 39% of patients had their height and weight measured, 34% had their fasting glucose measured, and 32% had a lipid profile measured (Panagiotopoulos et al., 2009). Similarly, Haupt reported (Haupt et al., 2009) that baseline and 12-week testing rates for lipids and glucose in children were the lowest of all age groups. A survey of Australian child psychiatrists

(Walter et al., 2008) revealed the following monitoring rates following AAP-initiation: height (50%); waist circumference (28%); blood pressure (46%); fasting glucose (52%); lipids (48%); prolactin (32%); hepatic transaminases (53%).

Based on the current literature regarding the time course of onset of metabolic complications, and other national consensus guidelines (American Diabetes Association et al., 2004; Woo, Harris, Houlden, 2005), we have created a metabolic monitoring protocol. Table 3 summarizes the proposed history, anthropometric and laboratory measures with suggested time intervals in the first year of treatment. Although beyond the scope of this

**Table 3. Proposed metabolic monitoring protocol**

Assessment	Baseline	1 month	2 months	3 months	6 months	9 months	12 months†
Family History (diabetes, high cholesterol, cardiovascular disease, psychiatric history)	x						
Risk Factors (smoking, physical activity, screen time, sugar-sweetened beverages)	x						
Height	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x
Waist Circumference	x	x	x	x	x	x	x
Blood Pressure	x	x	x	x	x	x	x
Fasting Plasma Glucose	x			x	x		x
Fasting Insulin	x			x	x		x
Fasting Total Cholesterol	x			x	x		x
Fasting LDL-Cholesterol	x			x	x		x
Fasting HDL-Cholesterol	x			x	x		x
Fasting Triglycerides	x			x	x		x
Aspartate Aminotransferase	x			x	x		x
Alanine Aminotransferase	x			x	x		x
Gamma Glutamyltransferase	x			x	x		x
Prolactin	x			x*	x*		x*
Amylase‡	x			x	x		x
Thyroid Stimulating Hormone‡	x			x			x

† and yearly thereafter or sooner if clinically indicated

\* as clinically indicated [ie. abnormalities in menstruation, galactorrhea/nipple discharge, sexual dysfunction, delays in pubertal development; signs of osteoporosis (fractures)]

‡ quetiapine-treatment only



review, reports of thyroid stimulating hormone and amylase abnormalities following quetiapine treatment (Feret & Caley, 2000; Gropper & Jackson, 2004; Kelly & Conley, 2005) support inclusion of these parameters in our metabolic monitoring protocol. More frequent assessments of metabolic parameters may be required based on clinical circumstances. This monitoring protocol is currently being piloted at BC Children's Hospital and Vancouver Coastal Child & Youth Mental Health Teams.

## Discussion

There are no approved indications for AAP use in children and adolescents in Canada. In this paper, we have summarized the limited number of indications and target symptoms within specific age groups by AAP for which there is evidence to support efficacy in this population. Our review confirms that there is no evidence to support the use of these medications for insomnia or major depression. While naturalistic studies assessing clinical effectiveness would be helpful to guide clinical practice, these studies are limited to non-existent for these published indications. In view of the fact that AAPs are being prescribed for a wide range of symptoms and mental health conditions in children and adolescents (Doey et al., 2007; Harrison-Woolrych, Garcia-Quiroga, Ashton, & Herbison, 2007; Olfson et al., 2006) that are not supported by our comprehensive review of the literature, we strongly encourage health care professionals to review their prescribing practices in this vulnerable population. Furthermore, based on recent FDA warnings (US Food and Drug Administration, 2010) and our literature review, it is clear that olanzapine should not be used as a first-line treatment in youth. Given that a growing number of physicians without specialty training are also prescribing these medications, practice guidelines that provide an evidence-based algorithm for treatment (including alternatives to AAP use) are vital for ensuring that all children and adolescents with mental health conditions receive the best care.

In view of the substantial body of literature suggesting that AAPs have a wide range of metabolic effects on individuals who are still growing and developing, consistent metabolic monitoring including anthropometric measurements and laboratory testing at baseline and at appropriate intervals thereafter is necessary. As part of the routine psychiatric history, baseline documentation of familial and lifestyle risk factors for obesity, type 2 diabetes, dyslipidemia and cardiovascular disease should be performed to assist the prescriber in assessing and providing anticipatory guidance regarding potential metabolic risks. We propose that national consensus guidelines for monitoring and management of metabolic complications of AAPs are urgently required and will serve as a starting point for improving awareness and monitoring uptake in Canada. As a first step, following synthesis of the current evidence, we have prepared a metabolic monitoring proto-

col which is currently being piloted at BC Children's Hospital and local community mental health teams.

## Conclusion

Prescription of AAPs in children and adolescents should be guided by the available evidence in this age group, and not extrapolated from adult studies. It is incumbent on physicians to ensure that the benefits of AAP treatment outweigh the risks. There is an urgent need for clinical practice guidelines in Canada that provide, not only appropriate treatment algorithms for AAP-use based on indications, but also address metabolic monitoring and subsequent management of complications in this vulnerable population. In preparation for the development of such guidelines, the authors invite readers' comments and feedback.

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Nous voulons sincèrement remercier le Dr. André Gagnon pour son travail assidu, notre premier rédacteur-adjoint pour les soumissions francophones au Journal.

Malheureusement le Dr. Gagnon doit tirer sa révérence de notre équipe. On recherche une personne dynamique avec une bonne connaissance des deux langues officielles pour le remplacer aussitôt que possible. SVP envoyez un bref paragraphe exprimant votre intérêt et votre CV, le tout sera gardé confidentiellement, au Dr. Normand Carrey, normand.carrey@iwk.nshealth.ca

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