Evidence-based recommendations for monitoring safety of second-generation antipsychotics in children and youth

Tamara Pringsheim MD MSc[1], Constadina Panagiotopoulos MD[2], Jana Davidson MD[3], Josephine Ho MD MSc[4];
The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group

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

BACKGROUND: The use of antipsychotics, especially second-generation antipsychotics (SGAs), for children with mental health disorders in Canada has increased dramatically over the past five years. These medications have the potential to cause major metabolic and neurological complications with chronic use.
OBJECTIVE: To synthesize the evidence for specific metabolic and neurological side effects associated with the use of SGAs in children, and provide evidence-based recommendations for the monitoring of these side effects.
METHODS: A systematic review of controlled clinical trials of SGAs involving children was performed. Recommendations for monitoring SGA safety were made according to a classification scheme based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. When there was inadequate evidence, recommendations were based on consensus and expert opinion. A multidisciplinary consensus group reviewed all relevant evidence and reached consensus on the recommendations.
RESULTS: The present guidelines provide evidence-based recommendations for monitoring SGA safety. The strength of recommendations for specific physical examination manoeuvres and laboratory tests are provided for each SGA medication at specific time points.
CONCLUSION: Multiple randomized controlled trials evaluated the efficacy of many of the SGAs in paediatric mental health disorders. These benefits, however, are not without risks – both metabolic and neurological side effects occur in children treated with SGAs. The risk of weight gain, increased body mass index and abnormal lipid levels is greatest with olanzapine, followed by clozapine and quetiapine. The risk of neurological side effects of the treatment is greatest with risperidone, olanzapine and aripiprazole. Appropriate monitoring procedures for adverse effects will improve the quality of care of children treated with these medications.

Key Words: *Antipsychotics; Children and adolescents; Drug safety; Extrapyramidal symptoms; Metabolic syndrome*

Des recommandations probantes pour surveiller l'innocuité des antipsychotiques de deuxième génération chez les enfants et les adolescents

HISTORIQUE : Au Canada, l'utilisation d'antipsychotiques, notamment les antipsychotiques de deuxième génération (ADG), a augmenté de façon considérable depuis cinq ans chez les enfants ayant des troubles de santé mentale. Ces médicaments ont le potentiel de causer de graves complications métaboliques et neurologiques lorsqu'on les utilise de manière chronique.
OBJECTIF : Synthétiser les données probantes relatives aux effets secondaires métaboliques et neurologiques précis associés à l'usage d'ADG chez les enfants et fournir des recommandations probantes sur la surveillance de ces effets secondaires.
MÉTHODOLOGIE : Les auteurs ont procédé à une analyse systématique des essais cliniques contrôlés des ADG auprès d'enfants. Ils ont fait des recommandations à l'égard de la surveillance de l'innocuité des ADG d'après un modèle de classification fondé sur le système GRADE (système de notation de l'évaluation et de l'élaboration des recommandations). Lorsque les données probantes n'étaient pas suffisantes, ils fondaient leurs recommandations sur le consensus et l'avis d'experts. Un groupe consensuel multidisciplinaire a analysé toutes les données probantes pertinentes et est parvenu à un consensus à l'égard des recommandations.
RÉSULTATS : Les recommandations probantes portant sur la surveillance de l'innocuité des ADG figurent dans les présentes lignes directrices. Les auteurs indiquent la qualité des recommandations relatives à des examens physiques et tests de laboratoire précis à l'égard de chaque ADG à des moments déterminés.
CONCLUSION : De multiples essais aléatoires et contrôlés ont permis d'évaluer l'efficacité de bon nombre des ADG utilisés pour traiter les troubles de santé mentale en pédiatrie. Toutefois, leurs avantages ne sont pas sans risques : on observe à la fois des effets secondaires métaboliques et neurologiques chez les enfants traités au moyen d'ADG. Le risque de prise de poids, d'augmentation de l'indice de masse corporelle et de taux lipidiques anormaux est plus élevé à l'utilisation d'olanzapine, suivie de la clozapine et de la quétiapine. Quant au risque d'effets secondaires neurologiques des traitements, il est plus élevé à l'utilisation de rispéridone, d'olanzapine et d'aripiprazole. Des interventions de surveillance pertinentes des effets secondaires amélioreront la qualité des soins des enfants traités à l'aide de ces médicaments.

Second-generation antipsychotics (SGAs) are a group of antipsychotic medications that include seven drugs available for use in Canada: clozapine, olanzapine, risperidone, quetiapine, ziprasidone, paliperidone and aripiprazole. These medications are labelled 'atypical' in comparison with first-generation antipsychotics, based on their chemical properties, which include rapid dissociation from dopamine type 2 receptors and blockade of serotonin type 2A receptors. The SGAs have been used 'off-label' in Canadian children and youth for many mental health disorders including aggressive and oppositional behaviour in children with attention-deficit hyperactivity disorder (ADHD), conduct disorder, irritability related to autism spectrum disorders, tic disorders, mood disorders

[1]*Department of Clinical Neurosciences and Pediatrics, University of Calgary, Calgary, Alberta;* [2]*Department of Pediatrics, University of British Columbia;*
[3]*Department of Psychiatry, University of British Columbia, Vancouver, British Columbia;* [4]*Department of Pediatrics, University of Calgary, Calgary, Alberta*
Correspondence: Dr Tamara Pringsheim, Department of Clinical Neurosciences and Pediatrics, University of Calgary, Alberta Children's Hospital, C4-431, 2888 Shaganappi Trail Northwest, Calgary, Alberta T3B 6A8. Telephone 403-955-5982, fax 403-955-5990; e-mail tmprings@ucalgary.ca
Accepted for publication August 29, 2011

and schizophrenia. Randomized controlled trials (RCTs) have demonstrated efficacy for many of the atypical antipsychotics used for these conditions. At present, because none of the SGAs have received official indications by Health Canada for the treatment of children younger than 18 years of age, all prescriptions for children are off-label.

Available evidence indicates that the use of antipsychotics, especially SGAs, for children and youth with mental health disorders has increased dramatically (1). From 2005 to 2009, antipsychotic drug recommendations by physicians for children and youth in Canada have increased by 114%. The most common reasons an SGA was recommended for a child or adolescent from 2005 to 2009 were for a primary diagnosis of ADHD (17%), mood disorder (16%), conduct disorder (14%) or psychotic disorder (13%). The number of antipsychotic recommendations for ADHD more than tripled over this five-year period. Increases in drug recommendations for children occurred each year despite population data from Statistics Canada, which showed that the number of children (zero to 19 years of age) in Canada actually decreased slightly each year. Data on the average duration of antipsychotic drug use by children in Canada suggest that these medications are being used for long time periods. For risperidone, the average duration of use was 179 days in children one to six years of age, 334 days in children seven to 12 years of age, and 408 days in youth 13 to 18 years of age.

Given the increasing frequency and length of use of SGAs in children and youth, a detailed evaluation of the risk for metabolic and neurological side effects in children is appropriate. Our objective was to synthesize the evidence for specific metabolic and neurological side effects associated with the use of SGAs in children, and to make evidence-based recommendations for the monitoring of these side effects. The following clinical questions are addressed in the present guidelines:

1. What is the evidence for metabolic and neurological side effects associated with SGA treatment of paediatric mental health disorders?
2. When and how should clinicians monitor for metabolic and neurological side effects when an SGA has been initiated in a child/adolescent?

The present guidelines are intended to apply to children and youth 18 years of age or younger who have been prescribed an SGA medication for the treatment of a mental health disorder. Target users of these guidelines include psychiatrists, paediatricians, developmental paediatricians, neurologists and family practitioners. The present guidelines attempt to build on previous work in the area of SGA monitoring (2,3) by providing a systematic review of the evidence and linking monitoring recommendations to a level of evidence. It should be noted that the performance of electrocardiograms, absolute neutrophil counts and slit lamp eye examinations as part of monitoring were considered to be beyond the scope of the present guidelines. Clinicians may refer to the work of Blair and Taggart (4) for guidance on electrocardiogram monitoring. Clinicians may consult the clozapine product monograph regarding absolute neutrophil count requirements (5) for the prescription of clozapine, and the quetiapine product monograph (6) regarding slit lamp eye examinations.

METHODS

A systematic review of controlled clinical trials using SGAs in children and adolescents was performed. Any double-blind, RCT of SGA medications performed specifically in a paediatric population for a mental health disorder was included. In addition, open-label and prospective cohort studies longer than 12 weeks in duration were included to gather information on longer-term side effects. When data on medication side effects were unavailable from clinical trials or prospective cohort studies, retrospective cohort studies, case series, case reports or drug surveillance programs were searched. While unpublished trials of SGA medications exist, they were not included in the evidence review unless published data were scarce. The SGA medications were all assessed individually including risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone and paliperidone. The primary outcomes assessed were metabolic and neurological side effects as measured using physical examination manoeuvres or rating scales, or laboratory tests. To find relevant articles for the review, the Medline (1996 to May 2010) and Embase (1996 to May 2010) databases were searched using highly sensitive search strategies for clinical trials and cohort studies in a paediatric population. Abstracts retrieved from the searches were reviewed independently by two reviewers for potentially relevant articles. Full-text articles were then independently read in detail by two reviewers to determine whether inclusion criteria were fulfilled.

Clinical trials were evaluated for methodological quality using criteria developed by the United States Preventive Services Task Force (7). Trials were also rated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (8). Two authors independently assessed methodological quality for each included study. Based on the fulfillment of quality criteria, studies were rated as good, fair or poor, and graded as high or low levels of evidence.

Meta-analysis was performed on the data for synthesis. Meta-analysis was performed for commonly reported outcomes for each medication individually, in comparison with placebo or another drug. Both random-effect and fixed-effect models were used. Random-effects models were used when the I^2 statistic was greater than 40%. Results from open-label and prospective cohort studies were described individually. RCTs spanning three months or less were combined, and those longer than three months were combined in separate analyses. The separate analyses were conducted to understand whether differences with respect to side effects in short-term versus long-term studies were present. ORs with 95% CIs for binary outcomes were used. For continuous outcomes, mean differences were used to analyze the data. All analyses included all participants in the treatment groups to which they were allocated. Clinical heterogeneity was assessed by comparing trial design and the distribution of important participant factors. By examining the I^2 statistic (an approximate quantity that describes the proportion of variation in point estimates that is due to heterogeneity of studies rather than sampling error), statistical heterogeneity was assessed. In addition, a χ^2 test was performed to determine the strength of the evidence supporting genuine heterogeneity.

Results of the systematic review of the literature are presented in the current article in summary form only; readers interested in the full analysis and discussion of the systematic review findings should refer to the studies by Pringsheim et al (9,10).

Grading of recommendations

Recommendations for monitoring SGA safety were made according to a classification scheme based on the GRADE system (8) (Table 1). Modifications to the GRADE system were made to reflect that while there is good evidence that specific side effects occur with the use of SGAs, there is no evidence on the outcome of monitoring for these side effects. The system created for grading recommendations thus accepts that if there is good evidence that a specific side effect occurs with SGA treatment, monitoring for

TABLE 1
Recommendation grades

Grade of recommendation	Benefit versus risk and burdens	Methodological quality of supporting evidence	Implications
1A: Strong recommendation, high-quality evidence	Benefits of monitoring clearly outweigh risk and burdens	Consistent evidence from RCTs without important limitations that the specific side effect occurs, or overwhelming evidence from observational studies	Strong recommendation Can apply to most patients in most circumstances without reservation
1B: Strong recommendation, moderate-quality evidence	Benefits of monitoring clearly outweigh risk and burdens	RCTs with important limitations, or exceptionally strong evidence from observational studies that specific side effect occurs	Strong recommendation Can apply to most patients in most circumstances without reservation
1C: Strong recommendation, low-quality or very low-quality evidence	Benefits of monitoring clearly outweigh risk and burdens	Several observational studies or case series suggest that specific side effect occurs	Strong recommendation, but may change when higher-quality evidence becomes available
2A: Weak recommendation, high- or moderate-quality evidence	Uncertainty in the estimates of benefits, risks and burden	RCT or exceptionally strong evidence from observational studies that specific side effects occur, but clinical significance of test is questionable or there is conflicting evidence between studies	Weak recommendation; best action may differ depending on circumstances
2B: Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks and burden	Limited observational studies or case series suggest that the specific side effect occurs. Clinical significance is questionable or evidence is conflicting	Weak recommendation; best action may differ depending on circumstances
3: Weak recommendation, no evidence, consensus based	Uncertainty in the estimates of benefits, risks and burden	No data from RCTs or observational studies to support presence of specific side effect. Recommended on the basis of expert opinion	Weak recommendation; best action may differ depending on circumstances

RCTs Randomized controlled trials

the specific side effect may improve health outcomes in the long term. Recommendations, therefore, are graded on the quality of evidence that the specific side effect occurs with use of the drug, and the perceived benefits and burdens of monitoring. A strong recommendation can apply to most patients in most circumstances without reservation. With a weak recommendation, the best action may differ depending on the circumstances. When there was inadequate evidence to make recommendations, they were based on consensus and expert opinion. A consensus group of 20 individuals, with expertise in the fields of psychiatry, neurology, paediatrics, endocrinology, cardiology, nephrology and family medicine engaged in a two-day conference. The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group did not receive any industry sponsorship and were able to independently develop the present manuscript with no restrictions. The evidence was presented and discussed, and nominal group techniques involving a skilled facilitator was used to reach consensus on the recommendations. Separate recommendations were made for monitoring procedures at baseline (before medication is started), three months, six months and one year.

Stakeholder involvement

Patients' views and preferences with respect to SGA side effects and monitoring were sought by holding two focus group sessions involving families of children and adolescents with mental health disorders. These focus group sessions were led by two experienced qualitative researchers, who reported their findings to the consensus group panel. The consensus group panel incorporated this information when making recommendations. The guideline will be piloted at two academic centres over the next one to two years to evaluate feasibility. When results of this pilot evaluation are analyzed, refinements to the monitoring protocol will be made, and any emerging evidence on SGA side effects published in the intervening period will be incorporated into subsequent updated guidelines. These guidelines have been externally reviewed by members of the Canadian Paediatric Society and the Canadian Academy of Child and Adolescent Psychiatry before publication.

RESULTS

Risperidone

Fifty-seven articles on the use of risperidone in children were included in the analysis. Evidence was found for the following adverse effects related to risperidone therapy:

- Higher mean weight gain with risperidone compared with placebo, with a mean difference of 1.72 kg (95% CI 1.17 to 2.26) in RCTs lasting 12 weeks or less, and a mean difference of 2.09 kg (95% CI 1.64, 2.55) in RCTs lasting six months.
- Elevated prolactin levels at endpoint compared with placebo (RCTs 12 weeks or less), with a mean difference of 899.99 pmol (95% CI 729.56 to 1074.78).
- Significantly higher odds of extrapyramidal side effects relative to placebo, with an OR of 3.55 (P<0.00001), and high rates of anticholinergic treatment for extrapyramidal side effects.
- Mean body mass index (BMI) increase of 1.92 kg/m^2, mean increase in waist circumference of 5.1 cm, and a significant increase in triglyceride level after 10.8 weeks of therapy.
- Case reports of risperidone-associated diabetes or hyperglycemia in children.
- Continuous weight gain and increase in BMI in open-label studies up to two years duration; variable elevation in prolactin levels, with a tendency for prolactin levels to decrease over time.

Based on the evidence, the recommendations for monitoring the safety of risperidone in children are presented in Tables 2 and 3.

Olanzapine

Twenty-five articles on the use of olanzapine in children were included in the analysis. Evidence was found for the following adverse effects related to olanzapine therapy:

- Higher mean weight gain and increase in BMI with olanzapine compared with placebo, with a mean difference of 3.47 kg (95% CI 2.94 to 3.99) and 1.28 kg/m^2 (95% CI 0.96 to 1.59), respectively, in RCTs lasting less than eight weeks.
- Higher mean weight gain and increase in BMI with olanzapine than risperidone, with a mean difference of

TABLE 2
Monitoring summary table: Physical examination manoeuvres

		Grade of recommendation			
	Antipsychotic medication	**Baseline**	**3 months**	**6 months**	**1 year**
Height	Risperidone	Strong 1A	Strong 1A	Strong 1A	Strong 1C
	Olanzapine	Strong 1A	Strong 1A	Strong 1C	Strong 1C
	Quetiapine	Strong 1A	Strong 1A	Strong 1C	Weak 3
	Aripiprazole	Strong 1A	Strong 1A	Strong 1C	Strong 1C
	Clozapine	Strong 1A	Strong 1A	Strong 1C	Weak 3
	Ziprasidone	Strong 1C	Weak 3	Strong 1C	Weak 3
Weight	Risperidone	Strong 1A	Strong 1A	Strong 1A	Strong 1C
	Olanzapine	Strong 1A	Strong 1A	Strong 1C	Strong 1C
	Quetiapine	Strong 1A	Strong 1A	Strong 1C	Weak 3
	Aripiprazole	Strong 1A	Strong 1A	Strong 1C	Strong 1C
	Clozapine	Strong 1A	Strong 1A	Strong 1C	Weak 3
	Ziprasidone	Strong 1C	Weak 3	Strong 1C	Weak 3
Body mass index	Risperidone	Strong 1A	Strong 1A	Strong 1A	Strong 1C
	Olanzapine	Strong 1A	Strong 1A	Strong 1C	Strong 1C
	Quetiapine	Strong 1A	Strong 1A	Strong 1C	Weak 3
	Aripiprazole	Strong 1A	Strong 1A	Strong 1C	Strong 1C
	Clozapine	Strong 1A	Strong 1A	Strong 1C	Weak 3
	Ziprasidone	Strong 1C	WEAK 3	Strong 1C	Weak 3
Waist circumference (at the level of the umbilicus)	Risperidone	Strong 1C	Strong 1C	Weak 3	Weak 2B
	Olanzapine	Strong 1C	Strong 1C	Weak 3	Weak 3
	Quetiapine	Strong 1C	Strong 1C	Weak 3	Weak 3
	Aripiprazole	Strong 1C	Strong 1C	Weak 3	Weak 3
	Clozapine	Weak 3	Weak 3	Weak 3	Weak 3
	Ziprasidone	Weak 3	Weak 3	Weak 3	Weak 3
Blood pressure	Risperidone	Strong 1A	Strong 1A	Weak 3	Weak 3
	Olanzapine	Strong 1A	Strong 1A	Weak 3	Weak 3
	Quetiapine	Strong 1A	Strong 1A	Weak 3	Weak 3
	Aripiprazole	Weak 3	Weak 3	Weak 3	Weak 3
	Clozapine	Weak 3	Weak 3	Weak 3	Weak 3
	Ziprasidone	Weak 3	Weak 3	Weak 3	Weak 3
Neurological examination for extrapyramidal symptoms and signs	Risperidone	Strong 1A	Strong 1A	Strong 1A	Strong 1C
	Olanzapine	Strong 1A	Strong 1A	Strong 1C	Weak 3
	Quetiapine	Weak 2B	Weak 3	Weak 2B	Weak 3
	Aripiprazole	Strong 1A	Strong 1A	Weak 2B	Strong 1C
	Clozapine	Weak 2B	Weak 2B	Weak 3	Weak 3
	Ziprasidone	Strong 1C	Strong 1C	Strong 1C	Weak 3

2.41 kg (95% CI 0.98 to 3.83) and 0.90 kg/m^2 (95% CI 0.42 to 1.38), respectively.

- Higher odds of elevated triglyceride levels anytime during treatment with olanzapine compared with placebo, with an OR of 5.13 (95% CI 2.78 to 9.45).
- Increase in total cholesterol levels with olanzapine relative to placebo, with a mean difference of 0.095 mmol/L (P<0.001).
- Olanzapine-treated patients had higher odds of elevated prolactin levels any time during treatment compared with placebo, with an OR of 30.52 (P<0.00001).
- Children treated with olanzapine showed a greater change in aspartate aminotransferase level from baseline, with a mean difference of 8.98 U/L (95% CI 5.1 to 12.78), and a greater change in alanine aminotransferase level from baseline, with a mean difference of 22.5 (95% CI 14.26 to 30.74). The odds of a clinically significant increase in alanine aminotransferase level was higher with olanzapine, with an OR of 18.74 (P=0.0005).
- High rates of anticholinergic treatment for extrapyramidal symptoms.
- After a mean of 10.8 weeks of therapy, mean weight increase of 8.5 kg, mean increase in waist circumference of 8.55 cm, and significant adverse baseline to endpoint changes in cholesterol, triglycerides, glucose and insulin levels.

Based on the evidence, the recommendations for monitoring the safety of olanzapine in children are presented in Tables 2 and 3.

Quetiapine

Seventeen articles on the use of quetiapine were included in the analysis. Evidence was found for the following adverse effects related to quetiapine therapy:

- Higher mean weight gain with quetiapine compared with placebo, with a mean difference of 1.41 kg (95% CI 1.10 to 1.81) in RCTs lasting less than eight weeks.
- The mean change in prolactin levels was not significantly different between treatment groups.
- Significant changes in fasting triglyceride levels with quetiapine versus placebo.
- No significant difference between quetiapine and placebo with regard to extrapyramidal symptom scales.

TABLE 3
Monitoring summary table: Laboratory tests

		Grade of recommendation			
Tests	**Antipsychotic medication**	**Baseline**	**3 months**	**6 months**	**1 year**
Fasting plasma glucose	Risperidone	Strong 1C	Strong 1C	Weak 2B	Weak 2B
	Olanzapine	Strong 1C	Strong 1C	Weak 3	Weak 2B
	Quetiapine	Strong 1C	Strong 1C	Strong 1C	Weak 3
	Aripiprazole	Strong 1C	Not recommended	Weak 3†	Strong 1C
	Clozapine	Strong 1C	Weak 3	Strong 1C	Weak 3
	Ziprasidone	Weak 3	Not recommended	Weak 3‡	Weak 3**
Insulin	Risperidone	Weak 3	Weak 3	Weak 3	Weak 2B*
	Olanzapine	Strong 1A	Strong 1A	Weak 3	Weak 3
	Quetiapine	Weak 3	Weak 3	Weak 3	Weak 3
	Aripiprazole	Not recommended	Not recommended	Not recommended	Not recommended
	Clozapine	Weak 3	Weak 3	Weak 3	Weak 3
	Ziprasidone	Weak 3	Not recommended	Not recommended	Not recommended
Total cholesterol	Risperidone	Weak 3	Weak 3	Weak 3§	Weak 2B*
	Olanzapine	Strong 1A	Strong 1A	Strong 1C	Weak 3**
	Quetiapine	Strong 1C	Strong 1C	Strong 1C	Weak 3**
	Aripiprazole	Strong 1C	Not recommended	Weak 2B†	Strong 1C
	Clozapine	Strong 1A	Strong 1A	Strong 1C	Weak 3**
	Ziprasidone	Weak 3	Not recommended	Weak 3‡	Weak 3**
Fasting low-density lipoprotein – cholesterol	Risperidone	Weak 3	Weak 3	Weak 3§	Weak 2B*
	Olanzapine	Strong 1A	Strong 1A	Weak 3	Weak 3**
	Quetiapine	Strong 1C	Strong 1C	Weak 3	Weak 3**
	Aripiprazole	Strong 1C	Not recommended	Weak 2B†	Strong 1C
	Clozapine	Weak 3	Weak 3	Weak 3	Weak 3**
	Ziprasidone	Weak 3	Not recommended	Weak 3‡	Weak 3**
Fasting high-density lipoprotein – cholesterol	Risperidone	Weak 3	Weak 3	Weak 3§	Weak 2B*
	Olanzapine	Strong 1A	Strong 1A	Weak 3	Weak 3**
	Quetiapine	Strong 1C	Strong 1C	WeakK 3	Weak 3**
	Aripiprazole	Strong 1C	Not recommended	Weak 2B†	Strong 1C
	Clozapine	Weak 3	Weak 3	Weak 3	Weak 3**
	Ziprasidone	Weak 3	Not recommended	Weak 3‡	Weak 3**
Fasting triglycerides	Risperidone	Strong 1C	Strong 1C	Weak 3§	Weak 2B*
	Olanzapine	Strong 1A	Strong 1A	Weak 3	Weak 2B**
	Quetiapine	Strong 1A	Strong 1A	Weak 3	Weak 3**
	Aripiprazole	Weak 2B	Not recommended	Weak 2B†	Strong 1C
	Clozapine	Strong 1A	Strong 1A	Strong 1C	Weak 3**
	Ziprasidone	Weak 3	Not recommended	Weak 3‡	Weak 3**
Aspartate aminotransferase	Risperidone	Weak 3	Not recommended	Weak 2B*	Weak 2B*
	Olanzapine	Strong 1A	Strong 1A	Strong 1C	Weak 3*
	Quetiapine	Weak 3	Weak 3*	Weak 3*	Weak 3*
	Aripiprazole	Weak 3*	Not recommended	Weak 3*	Weak 3*
	Clozapine	Weak 3	Weak 3*	Weak 3*	Weak 3*
	Ziprasidone	Weak 3	Not recommended	Weak 3‡	Weak 3**
Alanine aminotransferase	Risperidone	Weak 3	Not recommended	Weak 2B*	Weak 2B*
	Olanzapine	Strong 1A	Strong 1A	Strong 1C	Weak 3*
	Quetiapine	Weak 3	Weak 3*	Weak 3*	Weak 3*
	Aripiprazole	Weak 3*	Not recommended	Weak 3*	Weak 3*
	Clozapine	Weak3	Weak 3*	Weak 3*	Weak 3*
	Ziprasidone	Weak 3	Not recommended	Weak 3‡	Weak 3**
Prolactin	Risperidone	Strong 1A	Strong 1A	Weak 2A¶	Weak 3¶
	Olanzapine	Strong 1A	Strong 1A	Weak 3¶	Weak 3¶
	Quetiapine	Weak 3	Not recommended	Not recommended	Not recommended
	Aripiprazole	Weak 3	Not recommended	Not recommended	Not recommended
	Clozapine	Weak 3	Not recommended	Not recommended	Not recommended
	Ziprasidone	Weak 2B	Not recommended	Weak 2B	Weak 3¶

Continued on next page

TABLE 3 – CONTINUED
Monitoring summary table: Laboratory tests

		Grade of recommendation			
	Antipsychotic medication	**Baseline**	**3 months**	**6 months**	**1 year**
Thyroid-stimulating hormone	Risperidone	Not recommended	Not recommended	Not recommended	Not recommended
	Olanzapine	Not recommended	Not recommended	Not recommended	Not recommended
	Quetiapine	Strong 1C	Not recommended	Strong 1C	Not recommended
	Aripiprazole	Not recommended	Not recommended	Not recommended	Not recommended
	Clozapine	Not recommended	Not recommended	Not recommended	Not recommended
	Ziprasidone	Not recommended	Not recommended	Not recommended	Not recommended

*Due to the absence of data, paliperidone was not included in the evidence tables. *Testing recommended in overweight or obese children; †Given the very limited data on abnormalities on laboratory tests of metabolic parameters at this time point, if the child is not overweight, consider deferring laboratory testing until the one-year period; ‡Given the paucity of long-term data on ziprasidone in children, clinicians should consider performing laboratory testing for metabolic side effects at six months, especially if body mass index percentile scores increase above the 85th percentile, or waist circumferences increase above the 90th percentile; §If three-month screening laboratory tests are normal, the body mass index percentile has remained under the 85th percentile, and the waist circumference has remained at less than the 90th percentile, repetition of laboratory work for cholesterol, low-density lipoprotein – cholesterol, high-density lipoprotein – cholesterol and triglyceride levels can be made on a yearly basis; ¶The decision to measure prolactin levels at these time points may be based on the presence of clinical symptoms of hyperprolactinemia such as menstrual irregularity, gynecomastia or galactorrhea. If no symptoms of hyperprolactinemia are present, prolactin monitoring is recommended on a yearly basis; **If six-month screening laboratory tests are normal, body mass index remains below the 85th percentile and waist circumference remains below the 90th percentile, repetition of laboratory work for cholesterol, low-density lipoprotein – cholesterol, high-density lipoprotein – cholesterol and triglyceride levels can be made on a yearly basis*

- After 10.8 weeks of therapy, significant increase in BMI, waist circumference, and adverse baseline to end point changes in total cholesterol and triglyceride levels.
- Trials lasting longer than three months reported continuous weight gain, increase in BMI, significant increases in thyroid-stimulating hormone levels and decreases in free thyroxine levels.
- Paediatric case reports of quetiapine-associated hyperglycemia or diabetes.

Based on the evidence, the recommendations for monitoring the safety of quetiapine in children are presented in Tables 2 and 3.

Aripiprazole

Eight articles on the use of aripiprazole were included in the analysis. Evidence of the following adverse effects relating to aripiprazole therapy was found:

- Higher mean weight gain and increase in BMI with aripiprazole compared with placebo, with a mean difference of 0.85 kg (95% CI 0.57 to 1.13) and 0.27 kg/m^2 (95% CI 0.11 to 0.42) in RCTs lasting less than eight weeks.
- The incidence of elevated blood glucose, triglyceride, low-density lipoprotein or total cholesterol levels, or low high-density lipoprotein levels were not significantly different between treatment groups.
- Significantly greater decrease in prolactin levels after treatment, with a mean difference of –218.69 pmol (95% CI –339.13 to –98.26) relative to placebo.
- Higher odds of extrapyramidal side effects compared with the placebo group, with an OR of 3.70 (P<0.0001).
- After a median of 10.8 weeks of therapy, increase in waist circumference by 5.4 cm.

Based on the side effect data presented in these studies, the recommendations for monitoring safety of aripiprazole in children are presented in Tables 2 and 3.

Clozapine

Eight articles on the use of clozapine were included in the analysis. Evidence of the following adverse effects relating to clozapine therapy was found:

- Weight gain and increase in BMI comparable with olanzapine in trials lasting less than 12 weeks.
- Elevation in cholesterol and triglyceride levels related to clozapine treatment.

Based on the side effect data from these studies, recommendations for monitoring the safety of clozapine in children are presented in Tables 2 and 3.

Ziprasidone

Five articles on the use of ziprasidone were included in the analysis. Evidence of the following adverse effects relating to ziprasidone therapy was found:

- Similar weight gain between ziprasidone and placebo-treated groups in an RCT lasting eight weeks.
- No adverse changes in glucose, cholesterol or triglyceride levels in open-label studies lasting up to six months.
- Extrapyramidal side effects including akathisia, dyskinesias and acute dystonic reactions.

Based on the available data, recommendations for monitoring the safety of ziprasidone in children are presented in Tables 2 and 3. Given the paucity of both short- and long-term data with respect to side effects of ziprasidone in children, many recommendations are consensus rather than evidence based. As more RCTs are completed with ziprasidone in children, recommendations on monitoring safety will likely change.

Paliperidone

No RCTs or prospective open-label studies of paliperidone in children have been published. No evidence-based recommendations can be made at this time on monitoring adverse effects of paliperidone in children.

DISCUSSION

Multiple RCTs have evaluated the efficacy of many of the SGAs in paediatric mental health disorders. These medications have been a useful addition to the treatment options available for a number of paediatric mental health disorders. These benefits, however, do not come without risks: both metabolic and neurological side effects occur in children treated with these SGAs. The risk of weight gain, increased BMI and abnormal lipid levels is greatest with olanzapine, followed by clozapine and quetiapine. The risk of neurological side effects of treatment is greatest with risperidone, olanzapine and aripiprazole. Neurological side effects are very uncommon in children treated with quetiapine and clozapine; not enough paediatric data on ziprasidone exists to draw a conclusion.

The present guidelines specifically focused on metabolic and neurological side effects, and how they should be monitored. SGAs can cause other side effects that were not discussed in the present article including sedation, drooling, a decrease in absolute neutrophil count (with clozapine), cataracts (with quetiapine) and prolongation of the QTc interval. Clinicians prescribing these medications should familiarize themselves with the most common adverse events associated with the SGA they are prescribing, and consult appropriate resources on when to perform absolute neutrophil counts (5), electrocardiograms (4) and slit lamp eye examinations (6). Users of these guidelines should be aware that we have also created separate guidelines on the management of SGA-related metabolic and neurological complications that are detected over the course of monitoring procedures.

With respect to the noted metabolic side effects of SGA treatment, the long-term health consequences of obesity and dyslipidemia in children are concerning. Higher BMI during childhood is associated with an increased risk of coronary artery disease in adulthood (11). A prospective cohort study of 2195 children followed for 21 years (12) showed that youth determinants of adult metabolic syndrome include obesity, and high triglyceride, insulin and C-reactive protein levels, as well as a family history of hypertension and type 2 diabetes. Obesity, high low-density lipoprotein cholesterol and low high-density lipoprotein cholesterol in childhood are associated with a decrease in carotid artery elasticity in adulthood – an early pathophysiological change relevant to the development of atherosclerosis (13). The social and emotional consequences of obesity in a child who may already be seen as different due to his/her mental health disorder is also worth considering. A prospective study demonstrated that women with childhood metabolic syndrome showed higher levels of depressive symptoms in adulthood than women who did not have childhood metabolic syndrome (14).

Given the evidence for metabolic side effects in children treated with SGAs, and the long-term sequelae of these problems, monitoring of all children who are prescribed SGAs is appropriate. There has been a notable lag, however, in translation of the research evidence into changes in clinical practice. Data from the United States suggest that metabolic testing rates have showed little change following the 2003 Food and Drug Administration warning on diabetes risk for SGAs and recommendations from the American Diabetes Association and American Psychiatric Association (15) in 2004 that all patients receiving SGAs undergo glucose and lipid testing. In the evaluation of 109,451 individuals receiving Medicaid who began taking an SGA (sample included 25% children), initial testing rates (prewarning) were low (glucose 27% and lipids 10%). The Food and Drug Administration warning and the American Diabetes Association/American Psychiatric Association recommendations were not associated with an increase in glucose testing among SGA-treated patients, and was associated with only a marginal increase in lipid testing rates (1.7% [$P<0.02$]) (16).

We have attempted to create an evidence-based monitoring protocol for physicians to follow when prescribing an SGA to a child with a mental health condition. Because the risk of metabolic and neurological side effects varies between SGA medications, we have provided the levels of evidence associated with the specific side effects of each drug. While this adds a layer of complexity for physicians to follow, there are important differences in the side effect profiles of the SGAs that should be noted. Monitoring summary tables for physical examination manoeuvres and laboratory tests with recommendation grades according to each individual SGA have been created (Table 2 and 3). Recognizing that some clinicians may not have adequate resources to apply these drug-specific recommendations, we have also created a simplified single-screening and monitoring tool (Table 4) for ease of use in the clinical setting. The entire Metabolic Assessment, Screening and Monitoring Tool (from which Table 4 has been extracted) is available online (http://keltymentalhealth.ca/partner/provincial-mental-health-metabolic-program) under the Resources tab.

Experience suggests that, in situations in which an SGA is recommended, the average number of SGAs trialed for a given patient is between two to three (unpublished data). As a result, it is important to complete full baseline measurements on patients receiving any one of the SGAs. Notable in Table 4 is the recommendation to complete a clinical assessment including physical examination manoeuvres such as height, weight, waist circumference, and blood pressure at four and eight weeks following initiation of the SGA. In addition to determining effectiveness of the medications following their initiation, careful monitoring at these time points is necessary given the current evidence, which suggests that significant changes may occur in weight and waist circumference within four weeks of initiating SGAs (17). Early intervention with conservative lifestyle measurements, if weight and/or waist circumference increase within the first three months of treatment with an SGA, may mitigate these metabolic side effects.

Prolactin monitoring is recommended after three months of treatment with risperidone or olanzapine, and after six months with ziprasidone and, if normal, on a yearly basis thereafter in asymptomatic children. This is because prepubertal children may not develop clinical symptoms or signs of hyperprolactinemia (menstrual irregularity, gynecomastia or galactorrhea); the long-term consequences of chronic elevation of prolactin levels on future sexual, bone and breast development are unknown. While there is evidence to suggest that prolactin levels may normalize over time in children on chronic treatment (18,19), this is not always the case; therefore, we have adopted a conservative stance until further information is available. Prolactin undergoes diurnal fluctuations, and can be altered by medication (20) and food intake. Prolactin levels should, therefore, be determined after fasting with scheduled blood work – some of which also requires a 12 h fast (eg, blood lipids). Because we found no evidence of abnormalities in the electrolytes or renal function tests, such as urea or creatinine, with the use of SGAs, we have not made any screening recommendations for these tests as a part of routine monitoring of SGA safety.

We have not made evidence-based recommendations for monitoring beyond one year due to the lack of long-term studies. As more information becomes available from long-term prospective cohort studies, we expect this evidence will be used to inform practice. At this time, we recommend that clinicians use their clinical judgment to make decisions about monitoring children beyond one year of treatment based on the results of their monitoring to date. Beyond the first year of monitoring, it is the clinical practice of the members of our guideline group to repeat laboratory tests yearly in stable patients with a normal physical examination and previous normal laboratory tests. Physical examination manoeuvres are completed during all follow-up visits as a part of routine care.

We recognize that there may be organizational barriers to applying the recommendations of these guidelines. Clinicians have a number of demands on their time; the need to perform specific physical examination manoeuvers and laboratory tests will add time to clinical visits. We advise that, given the good evidence for specific metabolic and neurological side effects associated with SGAs, clinicians who are unprepared to monitor children for side effects should choose not to prescribe these medications. A

TABLE 4
A practical tool for metabolic monitoring of children and youth treated with second-generation antipsychotics

Parameter	Pretreatment baseline	1 month	2 months	3 months	6 months	9 months	1 year
Assessment date							
Height, cm*							
Height percentile							
Weight, kg*							
Weight percentile							
BMI, kg/m^2*							
BMI percentile							
Waist circumference (at the level of the umbilicus)†							
Waist circumference percentile							
Blood pressure, mmHg‡							
Blood pressure percentile							
Neurological examination§	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed
Laboratory evaluations							
Fasting plasma glucose (normal ≤6.1 mmol/L)¶		NR	NR			NR	
Fasting insulin** (normal ≤100 pmol/L)††		NR	NR			NR	
Fasting total cholesterol (normal <5.2 mmol/L)		NR	NR			NR	
Fasting low-density lipoprotein – cholesterol (normal <3.35 mmol/L)		NR	NR			NR	
Fasting high-density lipoprotein – cholesterol (normal ≥1.05 mmol/L)		NR	NR			NR	
Fasting triglycerides (normal <1.5 mmol/L)		NR	NR			NR	
Aspartate aminotransferase		NR	NR	NR		NR	
Alanine aminotransferase		NR	NR	NR		NR	
Thyroid-stimulating hormone (quetiapine only)		NR	NR	NR		NR	
Prolactin‡‡		NR	NR		NR	NR	
Other_____ (eg, Amylase, A1C, OGTT etc)§§							
Physician initials: →							

**To determine height, weight and body mass index (BMI) percentiles, use age- and sex-specific growth charts (http://www.cdc.gov/growthcharts/); †To determine age- and sex-specific percentiles, visit http://www.idf.org/webdata/docs/Mets definition children.pdf (pages 18-19); ‡To determine age- and sex-specific percentiles, visit http://pediatrics.aappublications.org/cgi/content/full/114/2/S2/555; §Tools available for monitoring extrapyramidal symptoms include Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale, Extrapyramidal Symptom Rating Scale and Barnes Akathisia Rating Scale; ¶For fasting plasma glucose values of 5.6 mmol/L to 6.0 mmol/L, an oral glucose tolerance test (OGTT) should be considered; **This assessment is not recommended for aripiprazole or ziprasidone, but is appropriate for all other second-generation antipsychotics; ††For fasting insulin levels >100 pmol/L, an OGTT should be considered. Normal reference range may vary between centres; ‡‡Assessment of prolactin levels should be completed according to protocol, except when the patient is displaying clinical symptoms of hyperprolactinemia (ie, menstrual irregularity, gynecomastia or galactorrhea), in which case more frequent monitoring may be warranted. Also note that risperidone has the greatest effect on prolactin; §§It is recommended that amylase levels be monitored in cases in which the patient presents with clinical symptoms of pancreatitis (ie, abdominal pain, nausea and vomiting). NR Not recommended*

website is currently under construction (www.camesaguideline.org), which will include downloadable forms for physicians to help facilitate adoption of the recommendations. While there are cost implications with respect to the use of laboratory tests for monitoring safety, we believe that the cost of these preventive measures will be far less than the costs of managing the long-term effects of obesity and hyperlipidemia in cardiovascular disease.

We anticipate that the use of these evidence-based guidelines on monitoring SGA safety in children will improve the quality of care of children with mental health disorders, and help improve awareness among patients and practitioners of the side effects associated with these drugs.

THE CAMESA GUIDELINE GROUP: Stacey Belanger, University of Montreal (Montreal, Quebec); Lisa Casselman, Mental Health Commission of Canada (Calgary, Alberta); Jana Davidson, University of British Columbia (Vancouver, British Columbia); Asif Doja, University of Ottawa (Ottawa, Ontario); Silviu Grisaru, University of Calgary (Calgary); Josephine Ho, University of Calgary; Rekha Jabbal, Alberta Children's Hospital Mental Health Program (Calgary); Gail MacKean, Mental Health Commission of Canada; Brian McCrindle, University of Toronto (Toronto, Ontario); John McLennan, University of Calgary; Valerie Palda, University of Toronto; Constadina Panagiotopoulos, University of British Columbia; Scott Patten, University of Calgary; Michelle Pearce, University of Toronto; Jonathan Ponesse, University of Ottawa; Tamara Pringsheim, University of Calgary; Roger Thomas, University of Calgary; Waqar Waheed, University of Calgary; and Chris Wilkes, University of Calgary.

NOTE: The present guideline has been endorsed by the Canadian Paediatric Society.

CONFLICTS OF INTEREST: The authors of the CAMESA guideline have no conflicts of interest to declare.

ACKNOWLEDGEMENTS: The authors thank the Canadian Academy of Child and Adolescent Psychiatry and the Canadian Paediatric Society for their external review of the manuscript.

FINANCIAL SUPPORT: The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline project was funded by the Canadian Institutes of Health

Research. Dr Panagiotopoulos receives Clinician Scientist salary support from the Child & Family Research Institute and the Canadian Diabetes Association.

REFERENCES

1. Pringsheim T, Lam D, Patten S. The pharmacoepidemiology of antipsychotic medications in Canadian children. J Child Adolesc Psychopharmacol. (In press)
2. Correll C. Monitoring and management of antipsychotic-related metabolic and endocrine adverse events in pediatric patients. Int Rev Psychiatry 2008;20:195-201.
3. Panagiotopoulos C, Ronsley R, Elbe D, Davidson J, Smith D. First do no harm: Promoting an evidence-based approach to atypical antipsychotic use in children and adolescents. J Can Acad Child Adolesc Psychiatry 2010;19:124-37.
4. Blair J, Taggart B. Electrocardiographic safety profile and monitoring guidelines in pediatric psychopharmacology. J Neural Transm 2004;111:791-815.
5. Novartis. Clozaril. East Hanover: Novartis Pharmaceutical Corporation, 2010:1-32.
6. AstraZeneca. Seroquel. Mississauga: Astra Zeneca Canada Inc, 2008:1-50.
7. Harris R, Helfand M, Woolf S, et al. Current methods of the U.S. Preventive Services Task Force. A review of the process. Am J Prevent Med 2001;20(3S):21-35.
8. Guyatt G, Oxman A, Vist G, et al. GRADE: An emerging consensus on rating quality of evidence and strength or recommendations. BMJ 2008;336.
9. Pringsheim T, Lam D, Ching H, Patten S. Metabolic and neurological complications of second generation antipsychotic use in children: A systematic review and meta-analysis of randomized controlled trials. Drug Safety 2011;34:651-68.
10. Pringsheim T, Panagiotopoulos C, Davidson J, Ho J; for the CAMESA guideline group. Evidence-based recommendations for monitoring safety of second generation antipsychotics in children and youth. J Can Acad Child Adolesc Psychiatry 2011;20:218-33.
11. Baker J, Olesen L, Sorensen T. Childhood body mass index and the risk of coronary heart disease in adulthood. N Engl J Med 2007;357:2329-37.
12. Mattson N, Ronnemaa T, Juonala M. Childhood predictors of the metabolic syndrome in adulthood. The cardiovascular risk in young finns study. Ann Med 2008;40:542-52.
13. Juonala M, Järvisalo MJ, Mäki-Torkko N, Kähönen M, Viikari JS, Raitakari OT. Risk factors identified in childhood and decreased carotid artery elasticity in adulthood. Circulation 2005;112:1486-93.
14. Pulkki-Raback L, Elovainio M, M. K. Depressive symptoms and the metabolic syndrome in childhood and adulthood: A prospective cohort study. Health Psychology 2009;28:108-16.
15. American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. Diabetes Care 2004;27:596-601.
16. Morato E, Druss B, Harung D. Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second generation antipsychotic drugs. Arch Gen Psychiatry 2010;67:17-24.
17. Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. J Am Med Assoc 2009;302:1765-73.
18. Anderson G, Scahill L, McCracken J, et al. Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. Biol Psychiatry 2007;61:545-50.
19. Croonenberghs J, Fegert JM, Findling RL, De Smedt G, Van Dongen S; Group RDBS. Risperidone in children with disruptive behavior disorders and subaverage intelligence: a 1-year, open-label study of 504 patients. J Am Acad Child Adolesc Psychiatry 2005;41:64-72.
20. Turrone P, Kapur S, Seeman M, Flint A. Elevation in prolactin levels by atypical antipsychotics. Am J Psychiatry 2002;159:133-5.