Evidence-Based Recommendations for Monitoring Safety of Second Generation Antipsychotics in Children and Youth

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Abstract

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:** Our objective was to synthesize the evidence for specific metabolic and neurological side effects associated with the use of SGAs in children and make evidence-based recommendations for the monitoring of these side effects. **Methods:** We performed a systematic review of controlled clinical trials of SGAs in children. Recommendations for monitoring SGA safety were made according to a classification scheme based on the GRADE system. When there was inadequate evidence to make recommendations, recommendations were based on consensus and expert opinion. A multi-disciplinary consensus group reviewed all relevant evidence and came to consensus on recommendations. **Results:** Evidence-based recommendations for monitoring SGA safety are provided in the guideline. The strength of recommendations for specific physical examination maneuvers and laboratory tests are provided for each SGA medication at specific time points. **Conclusion:** Multiple randomized controlled trials (RCTs) have established the efficacy of many of the SGAs in pediatric mental health disorders. These benefits however do not come without risk; both metabolic and neurological side effects occur in children treated with these SGAs. The risk of weight gain, increased BMI and abnormal lipids appears greatest with olanzapine, followed by clozapine and quetiapine. The risk of neurological side effects of treatment appears greatest with risperidone, olanzapine and aripiprazole. Appropriate monitoring procedures for adverse effects will improve the quality of care of children treated with these medications.

Background

The second generation antipsychotics (SGAs) are a group of antipsychotic medications which include seven drugs available for use in Canada: clozapine, olanzapine, risperidone, quetiapine, ziprasidone, paliperidone and aripiprazole. These medications are labeled "atypical" in comparison to first generation antipsychotics based on their chemical properties, which includes 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 a number of mental disorders, including aggressive and oppositional behaviour in children with ADHD, conduct disorder, irritability related to autism spectrum disorders, tic disorders, mood disorders, and schizophrenia. Randomized controlled trials (RCTs) have demonstrated efficacy for many of the atypical antipsychotics in these condi-

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tions. At present, since none of the SGAs have received official indications by Health Canada for the treatment of children under 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 (Pringsheim, Lam, & Patten, 2010). Antipsychotic drug recommendations for children and youth by physicians in Canada have increased by 114% from 2005 to 2009. The most common reasons an SGA was recommended for a child or adolescent from 2005 to 2009 was for a primary diagnosis of ADHD (17%), mood disorder (16%), conduct disorder (14%) and psychotic disorder (13%). The number of antipsychotic recommendations for ADHD more than tripled over this 5 year period. Increases in drug recommendations for children occurred each year despite population data from Statistics Canada which show that the number of children (persons aged 0 to 19) in Canada actually decreased slightly each year. Data on the average duration of antipsychotic use by children in Canada suggest that these medications are being used for long periods. For risperidone, average duration of use was 179 days in children age 1 to 6, 334 days in children age 7 to 12, and 408 days in youth age 13 to 18.

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 make evidence-based recommendations for the monitoring of these side effects. The clinical questions addressed in this guideline are:

1. What is the evidence for metabolic and neurological side effects associated with SGA treatment of pediatric 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?

This guideline is intended to apply to children and youth 18 years of age and younger who have been prescribed a second generation antipsychotic medication for the treatment of a mental health disorder. Target users of this guideline include psychiatrists, pediatricians, developmental pediatricians, neurologists, and family practitioners. This guideline attempts to build on previous work in the area of SGA monitoring (Correll, 2008; Panagiotopoulos, Ronsley, Elbe, Davidson, & Smith, 2010) by providing a systematic review of the evidence and linking monitoring recommendations to the level of evidence. It should be noted that the performance of electrocardiograms, absolute neutrophil counts and slit lamp eye examinations as a part of monitoring were considered out of scope for this guideline. Clinicians may refer to the work of Blair (Blair & Taggart, 2004) for guidance on electrocardiogram monitoring. Clinicians may consult the clozapine product monograph regarding absolute neutrophil count requirements (Novartis, 2010) for the prescription of clozapine, and the quetiapine product monograph (AstraZeneca, 2008) regarding slit lamp eye examinations.

Methods

We performed a systematic review of controlled clinical trials of SGAs in children and adolescents. We included any double blind randomized controlled trial of SGA medications done specifically in a pediatric population for a mental health disorder. We also included open label and prospective cohort studies longer than 12 weeks in duration to gather information about longer term side effects. When data on medication side effects were unavailable from clinical trials or prospective cohort studies, we searched for data from retrospective cohort studies, case series, case reports or drug surveillance programs. While unpublished trials of SGA medications exist, they were not included in our evidence review unless published data were scarce. The SGA medications were all assessed individually. This includes the medications: risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone and paliperidone. The primary outcomes assessed were metabolic and neurological side effects as measured using physical examination maneuvers 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 pediatric population. Abstracts retrieved from the searches were reviewed independently by two different reviewers for potentially relevant articles. Full text articles were then read in detail independently by two different reviewers to see if inclusion criteria were fulfilled.

Clinical trials were evaluated for methodological quality using quality criteria developed by the US Preventive Services Task Force (Harris et al., 2001) (see Appendix 1, http://www.cacap-acpea.org/uploads/documents//Aug2011_RecommendationsforMonitoringSGAs). Trials were also rated using the GRADE system (Guyatt et al., 2008) (see Appendix 2, http://www.cacap-acpea.org/uploads/documents//Aug2011_RecommendationsforMonitoringSGAs). 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 done for commonly reported outcomes for each medication individually, in comparison to placebo or another drug. Both random effects 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. Randomized controlled trials of three months or shorter in duration were combined, and randomized controlled trials of longer than three months were combined in separate analyses.

The separate analyses were conducted to understand if differences occur with respect to side effects in short term versus long term studies. Odds ratios with 95% confidence intervals 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 to sampling error, statistical heterogeneity was assessed. In addition, a chi-square test of homogeneity was also performed in order to determine strength of evidence that heterogeneity is genuine.

Results of the systematic review of the literature are presented in this manuscript in brief; readers interested in the full analysis and discussion of the systematic review findings are referred to a separate manuscript by Pringsheim (Pringsheim, Lam, Ching, & Patten, 2011).

Grading of Recommendations

Recommendations for monitoring SGA safety were made according to a classification scheme based on the GRADE system (Guyatt et al., 2008) (see 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 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 effects 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 circumstances. When there was inadequate evidence to make recommendations, recommendations were based on consensus and expert opinion. A consensus group of twenty individuals with expertise in the fields of psychiatry, neurology, pediatrics, endocrinology, cardiology, nephrology and family medicine engaged in a two day conference. The CAMESA guideline group did not receive any industry sponsorship and were able to independently develop this manuscript with no restrictions of any kind. The evidence was presented and discussed, and nominal group techniques were employed using a skilled facilitator to come to consensus on recommendations. Separate recommendations were made for monitoring procedures at baseline (before medication is started), at 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 an updated guideline. The guideline has been externally reviewed by members of the Canadian Pediatric Society and the Canadian Academy of Child and Adolescent Psychiatry prior to publication.

Results

Risperidone

948 abstracts on risperidone were retrieved from searches performed with MEDLINE and EMBASE. Of these, 74 full text articles were reviewed and 57 were included in the analysis (see Appendix 3 Risperidone Summary Table, http://www.cacap-acpea.org/uploads/documents//Aug2011_RecommendationsforMonitoringSGAs).

There are 10 RCTs on the use of risperidone versus placebo which are shorter than 12 weeks (Aman et al., 2002; Armenteros, Lewis, & Davalos, 2007; Buitelaar, van der Gaag, Cohen-Kettenis, & Melman, 2001; Findling et al., 2000; Haas, DelBello, et al., 2009; Haas, Unis, et al., 2009; Research Units on Pediatric Psychopharmacology Autism Network, 2002; Shea, 2004; Snyder et al., 2002; Van Bellinghen & De Troch, 2001). Meta-analysis was performed on side effect data obtained from these 10 trials. Mean weight gain was higher with risperidone compared to placebo, with a mean difference of 1.72 kg (95% CI 1.17, 2.26). Prolactin levels at endpoint were elevated with risperidone relative to placebo, with a mean difference of 20.70 ng/mL (95% CI 16.78, 24.62). Risperidone treated patients had a significantly higher odds ratio of extrapyramidal side effects relative to placebo, with an OR of 3.55 ($p<0.00001$). Laboratory testing for cholesterol, triglycerides, and fasting blood sugar were only performed in one study (Haas, DelBello, et al., 2009); no clinically significant changes were found. Additionally, two studies reported no adverse effects on glucose metabolism (Haas, Unis, et al., 2009; Reyes, Buitelaar, Toren, Augustyns, & Eerdekens, 2006). Five studies (Armenteros et al., 2007; Buitelaar et al., 2001; Research Units on Pediatric Psychopharmacology Autism Network, 2002; Snyder et al., 2002; Van Bellinghen & De Troch, 2001) reported no significant difference in blood pressure. One study (Shea, 2004) reported a significantly greater increase in systolic blood pressure by 4 mmHg in risperidone treated patients.

Table 1. Recommendation grades

Grade of recommendation	Benefit vs. 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

There are two randomized controlled trials in which children were randomized to risperidone, olanzapine or a first generation antipsychotic for 8 weeks (Sikich et al., 2008; Sikich, Hamer, Bashford, Sheitman, & Lieberman, 2004). Meta-analysis of the two studies shows that the amount of weight gain is higher with olanzapine than risperidone, with a mean difference of 2.41 kg (95% CI 0.98, 3.83). Change in body mass index (BMI) was also greater with olanzapine than risperidone, with a mean difference of 0.90 kg/m^2 (95% CI 0.42, 1.38). It is worth noting that in Sikich's 2008 study (Sikich et al., 2008), random assignment to olanzapine treatment was discontinued by the National Institute of Mental Health's Data and Safety Monitoring Board following review of interim data which revealed a greater increase in weight with olanzapine than molindone or risperidone, without evidence of greater efficacy. The number of subjects requiring anticholinergic therapy for extrapyramidal symptoms was high in both the olanzapine and risperidone treated groups. While meta-analysis of the data shows a higher odds of anticholinergic therapy with risperidone than olanzapine, the difference was not statistically significant.

Correll (Correll et al., 2009) studied the association of SGAs with body composition and metabolic parameters in pediatric patients without prior antipsychotic medication exposure in a prospective cohort study of 3 months duration. 135 of 338 children enrolled in the study received risperidone and were included in the analysis. After a median of 10.8 weeks of therapy, weight increased by 5.3 kg (95% CI 4.8, 5.9) in children treated with risperidone, compared to 0.2 kg (95% CI -1.0, 1.4) in the untreated control group. BMI increased by 1.92 kg/m$^{2.}$ Waist circumference increased by a mean of 5.1 cm ($p<0.001$). Triglycerides were significantly increased at endpoint compared to baseline measurements (9.74 mg/dl, 95% CI 0.45, 19.03). Glucose homeostasis was not significantly affected. Doses of risperidone greater than 1.5 mg per day were associated with significantly greater increases in weight, waist circumference, fat mass, and BMI *z* score.

Using data from the MedWatch Surveillance Program, Koller (Koller, Cross, Doraiswamy, & Schneider, 2003) searched for spontaneously reported adverse events (diabetes and hyperglycemia) in risperidone treated patients from 1993 to February 2002, and pooled these results with published case

reports of risperidone associated diabetes mellitus. They identified 131 distinct cases of risperidone associated diabetes or hyperglycemia, with 12 occurring in patients younger than 19 years of age. In most patients hyperglycemia occurred within three months of the start of risperidone therapy. The severity of reported pediatric cases was not described.

There were three trials greater than 12 weeks comparing risperidone to placebo. The duration of these trials were all six months. Mean weight gain was higher with risperidone compared to placebo, with a mean difference of 2.09 kg (95% CI 1.64, 2.55). Reyes (Reyes, Croonenberghs, Augustyns, & Eerdekens, 2006) found endpoint levels of prolactin were 20.3 ± 21.3 ng/mL and 9.6 ± 9.5 ng/mL, for risperidone treated patients and placebo, respectively ($p<0.00001$). Children treated with risperidone had a higher odds of extrapyramidal side effects than those treated with placebo (OR 3.71), however, this difference was not statistically significant ($p=0.07$).

Open label studies of risperidone up to two years have been reported. In general, these studies report significant weight gain and increase in BMI with risperidone use, and variable elevation in prolactin levels. In general, prolactin levels decrease over time. Anderson (Anderson et al., 2007) prospectively followed prolactin levels in children treated with risperidone who participated in an RCT of eight weeks, followed by an open label study. Twenty children had their prolactin measured at four time points: baseline, eight weeks, six months and 22 months. Mean prolactin levels were 11.8 ng/mL at baseline, 37.2 ng/mL at 8 weeks, 32.2 ng/mL at six months, and 22.9 ng/mL at 22 months. While prolactin levels were significantly elevated at all three on-drug time points compared to baseline, levels were significantly lower at twenty-two month follow-up compared to six month levels. In a one year open label study by Croonenberghs (Croonenberghs et al., 2005) 367 children completed treatment at a mean dose of risperidone was 1.6 mg/day. Peak levels in prolactin occurred at week 4 (mean for boys 28.2 ng/mL, mean for girls 35.4 ng/mL), then decreased to 16.1 ng/mL in boys and 21.6 ng/mL in girls at end point. Adverse events that could potentially be attributed to prolactin elevation were reported in 32 patients. Mild (15 patients) and moderate (10 patients) gynecomastia was reported in a total of 25 patients, 22 of 419 boys, and three of 85 girls. Seven patients reported menstrual disturbances and 1 patient developed galactorrhea.

Additional information on metabolic side effects associated with risperidone was obtained from a naturalistic study by Calarge (Calarge, Acion, Kuperman, Tansey, & Schlechte, 2009), who performed anthropometric measurements and laboratory tests on 99 children treated with risperidone for an average of 2.9 years. 34 of the 99 children were found to be overweight (BMI between 85th and 95th percentile) or obese (BMI over 95th percentile). In comparison to children with a normal BMI on risperidone, overweight/obese children had significantly higher insulin and triglyceride levels, and significantly lower HDL. The prevalence of metabolic abnormalities was also significantly higher in overweight/obese children, with 3/27 children having an abnormal insulin, 5/28 children having triglycerides over 110 mg/dl, 6/28 children having HDL lower than 40 mg/dl, in comparison to none of the 57 children with a normal BMI percentile. It should be noted however, that in the absence of a comparison group, these abnormalities in lipids and insulin may be a consequence of obesity, rather than directly related to risperidone use. Based on the evidence presented, the recommendations for monitoring the safety of risperidone in children are presented in Tables 2 and 3.

Olanzapine

640 abstracts pertaining to olanzapine were retrieved through the MEDLINE and EMBASE searches. Of these, 28 full text articles were reviewed and 25 were included in the analysis (see Appendix 4 Olanzapine Summary Table, http://www.cacap-acpea.org/uploads/documents//Aug2011_RecommendationsforMonitoringSGAs).

There are three RCTs of olanzapine versus placebo for the treatment of pediatric mental health conditions (Hollander et al., 2006; Kryzhanovskaya et al., 2009; Tohen et al., 2007). These trials ranged in duration from three to eight weeks. Meta-analysis was performed on side effect data. Weight gain was higher with olanzapine compared to placebo, with a mean difference of 3.47 kg (95% CI 2.94, 3.99). The odds of clinically significant weight gain was higher with olanzapine, with an OR of 10.66 ($p<0.003$) of a more than 7% increase in baseline weight. BMI increased with olanzapine, with a mean difference of 1.28 kg/m^2 (95% CI 0.96, 1.59) compared to placebo. The odds of high triglycerides anytime during treatment was higher with olanzapine compared to placebo, with an OR of 5.13 (95% CI 2.78, 9.45). Compared to baseline, fasting total cholesterol increased with olanzapine compared to placebo, with a mean difference of 3.67 mg/dl ($p<0.001$). There was no difference in the change in fasting glucose from baseline between treatment groups. Olanzapine treated subjects had a higher odds of an elevated prolactin any time during treatment compared to placebo, with an OR of 30.52 ($p<0.00001$). Children treated with olanzapine had a greater change in AST from baseline, with a mean difference of 8.98 U/l (95% CI 5.19, 12.78), and a greater change in ALT from baseline, with a mean difference of 22.5 (95% CI 14.26, 30.74). The odds of a clinically significant increase in ALT was higher with olanzapine with an OR of 18.74 ($p=0.0005$).

With respect to extrapyramidal side effects, there were no differences in the rate of abnormal movements between groups. However, data from the trials comparing risperidone and olanzapine (described above in the risperidone section) found a high rate of extrapyramidal signs and symptoms in olanzapine treated patients. Blood pressure was measured in all three trials. One study reported an increase of 3.61 mmHg in olanzapine treated patients ($p=0.001$).

Table 2. Monitoring summary table: physical examination maneuvers

	Antipsychotic	Baseline	3 months	6 months	1 year
Height (cm):	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 (kg):	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
BMI (kg/WEAK 3):	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

Table 3. Monitoring summary table: laboratory tests

	Antipsychotic	Baseline	3 months	6 months	12 months
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[5]	STRONG 1C
	Clozapine	STRONG 1C	WEAK 3	STRONG 1C	WEAK 3
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Insulin:	Risperidone	WEAK 3	WEAK 3	WEAK 3	WEAK 2B[3]
	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[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[4]
	Quetiapine	STRONG 1C	STRONG 1C	STRONG 1C	WEAK 3[4]
	Aripiprazole	STRONG 1C	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Fasting LDL-C:	Risperidone	WEAK 3	WEAK 3	WEAK 3[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3[4]
	Quetiapine	STRONG 1C	STRONG 1C	WEAK 3	WEAK 3[4]
	Aripiprazole	STRONG 1C	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Fasting HDL-C:	Risperidone	WEAK 3	WEAK 3	WEAK 3[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3[4]
	Quetiapine	STRONG 1C	STRONG 1C	WEAK 3	WEAK 3[4]
	Aripiprazole	STRONG 1C	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	WEAK 3	WEAK 3	WEAK 3	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Fasting triglycerides:	Risperidone	STRONG 1C	STRONG 1C	WEAK 3[2]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 2B[4]
	Quetiapine	STRONG 1A	STRONG 1A	WEAK 3	WEAK 3[4]
	Aripiprazole	WEAK 2B	Not recommended	WEAK 2B[5]	STRONG 1C
	Clozapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[4]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
AST:	Risperidone	WEAK 3	Not recommended	WEAK 2B[3]	WEAK 2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[3]
	Quetiapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Aripiprazole	WEAK 3[3]	Not recommended	WEAK 3[3]	WEAK 3[3]
	Clozapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]

continued

Table 3. Monitoring summary table: laboratory tests *continued*

	Antipsychotic	Baseline	3 months	6 months	12 months
ALT:	Risperidone	WEAK 3	Not recommended	WEAK 2B[3]	WEAK2B[3]
	Olanzapine	STRONG 1A	STRONG 1A	STRONG 1C	WEAK 3[3]
	Quetiapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Aripiprazole	WEAK 3[3]	Not recommended	WEAK 3[3]	WEAK 3[3]
	Clozapine	WEAK 3	WEAK 3[3]	WEAK 3[3]	WEAK 3[3]
	Ziprasidone	WEAK 3	Not recommended	WEAK 3[6]	WEAK 3[4]
Prolactin:	Risperidone	STRONG 1A	STRONG 1A	WEAK2A[1]	WEAK 3[1]
	Olanzapine	STRONG 1A	STRONG 1A	WEAK 3[1]	WEAK 3[1]
	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[1]
Thyroid stimulating hormone (TSH):	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

1 To determine height, weight and BMI percentiles, use age and sex specific growth charts at http://www.cdc.gov/growthcharts.

2 To determine age and sex specific percentiles, go to http://www.idf.org/webdata/docs/Mets definition children.pdf (pages 18–19).

3 To determine age and sex specific percentiles, go to http://pediatrics.aappublications.org/cgi/content/full/114/2/S2/555.

4 Tools available for monitoring extrapyramidal symptoms include: Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale, Extrapyramidal Symptom Rating Scale, Barnes Akathisia Rating Scale.

5 For FPG values of 5.6–6.0 mmol/L, consideration should be given to performing an oral glucose tolerance test (OGTT).

6 Note that this assessment is NOT recommended for aripiprazole or ziprasidone, but IS appropriate for all other SGAs.

7 For fasting insulin levels 100pmol/L, consideration should be given to performing an OGTT. Normal reference range may vary between centres.

8 Assessment of prolactin levels should be completed according to protocol except when the patient is displaying clinical symptoms of hyperprolactinemia (i.e. menstrual irregularity, gynecomastia, or galactorrhea), in which case more frequent monitoring may be warranted. Please also note that risperidone has the greatest effect on prolactin.

9 It is recommended that amylase levels be monitored in case where the patient presents with clinical symptoms of pancreatitis (i.e. abdominal pain, nausea, vomiting).

Correll's (Correll et al., 2009) cohort study (discussed in Risperidone section) included 45 children receiving olanzapine. After a median of 10.8 weeks of therapy, weight increased by 8.5 kg (95% CI 7.4, 9.7) in children treated with olanzapine, compared to 0.2 kg (95% CI -1.0, 1.4) in the untreated control group. Waist circumference increased by a mean of 8.55 cm ($p<0.001$). Adverse baseline to endpoint changes reached statistical significance for total cholesterol, triglycerides, non-HDL cholesterol, and ratio of triglycerides to HDL cholesterol in olanzapine treated children. In addition, there was a statistically significant increase in glucose (3.14 mg/dL, $p=0.02$) and insulin (2.71 µIU/mL, $p=0.02$). Patients treated with doses of olanzapine greater than 10 mg per day experienced significantly greater increases in total cholesterol and non-HDL cholesterol. The total daily olanzapine dose was not associated with body composition parameter changes.

Data on longer term side effects (three months or longer of therapy) was obtained from eight open label studies and five prospective cohort studies. All studies found continued weight gain. Weight gain in studies of 12 weeks duration varied from 4.69 to 7.20 kg (Milin et al., 2006; Mozes, Ebert, Michal, Spivak, & Weizman, 2006; Mozes et al., 2003; Ratzoni et al., 2002). In studies of 24 weeks, weight gain ranged from 11.1 to 15.5 kg (Arango et al., 2009; Castro-Fornieles et al., 2008; Dittmann et al., 2008; Fraguas et al., 2008), and in studies of one year, weight gain ranged from 12.8 to 16.2 kg (Fleischhaker et al., 2008; Ross, Novins, Farley, & Adler, 2003). BMI increased at all time points, from 2.5 kg/m^2 at 12 weeks, 3.8 to 5.4 kg/m^2 at 24 weeks, and 5.2

kg/m^2 at one year. Increases in total cholesterol (Fraguas et al., 2008) and extrapyramidal side effects (Dittmann et al., 2008) were also reported in studies of six months duration.

Further information on adverse events associated with olanzapine treatment was found from a study by Koller (Koller, Cross, Doraiswamy, & Malozowski, 2003), who used the MedWatch surveillance program and MEDLINE to identify spontaneously reported cases of pancreatitis associated with the use of atypical antipsychotics. Sixty-two cases occurred in patients receiving olanzapine, and an additional seven cases occurred in patients receiving olanzapine plus clozapine, risperidone or haloperidol. Four of the cases occurred in children. Time to diagnosis of pancreatitis was less than six months in 63% of olanzapine treated cases.

Based on the review of these studies, recommendations for monitoring safety of olanzapine are presented in Tables 2 and 3.

Quetiapine

353 abstracts on quetiapine were retrieved from the MEDLINE and EMBASE searches. Of these, 20 full text articles were reviewed and 17 were included in the analysis. See Appendix 5 Quetiapine Summary Table, http://www.cacap-acpea.org/uploads/documents//Aug2011_RecommendationsforMonitoringSGAs, for a description of each included study.

There are three studies of quetiapine versus placebo ranging from six to eight weeks in duration (Connor, McLaughlin, & Jeffers-Terry, 2008; DelBello et al., 2009; DelBello, Schwiers, Rosenberg, & Strakowski, 2002). The only side effect data reported in all three trials was regarding mean weight gain and change in prolactin levels during therapy. This data was combined using meta-analysis. Weight gain was significantly higher in those treated with quetiapine, with a mean difference of 1.41 kg (95% CI 1.10, 1.81) compared to placebo. The mean change in prolactin levels was not significantly different between treatment groups.

The effect of the treatment on lipids and blood glucose were described in one study (DelBello et al., 2009). They reported a significant change in fasting triglycerides with quetiapine versus placebo, with a mean increase of 30 mg/dL in quetiapine treated patients (p=0.003). There was no significant change in fasting total cholesterol, LDL, HDL or glucose from baseline to endpoint.

With respect to neurological side effects, there was no significant difference between groups in extrapyramidal symptom scales. The effect of quetiapine on blood pressure and heart rate was studied in all three trials. DelBello (DelBello et al., 2009) reported a significant increase in supine systolic blood pressure at endpoint in the quetiapine group (mean change +6 mmHg). Heart rate was significantly higher in quetiapine treated patients (mean change +11 bpm).

Correll's (Correll et al., 2009) cohort study included 36 children receiving quetiapine. After a median of 10.8 weeks of therapy, weight increased by 6.1 kg (95% CI 4.9, 7.2) in children treated with quetiapine, compared to 0.2 kg (95% CI -1.0, 1.4) in the untreated control group. There was a significant increase in BMI and BMI *z*-scores compared to baseline. Waist circumference increased significantly by 5.27 cm. Adverse baseline to endpoint changes reached statistical significance for total cholesterol, triglycerides, non-HDL cholesterol, and ratio of triglycerides to HDL cholesterol in quetiapine treated children.

Data on longer term (3 months or greater) adverse events from quetiapine was obtained from nine open label and prospective cohort studies ranging from 12 to 48 weeks in duration. Studies of 12 weeks duration found weight gain ranging from 3.8 to 6.2 kg, and increases in BMI ranging from 1.4 to 2.1 kg/m^2 (DelBello, Adler, Whitsel, Stanford, & Strakowski, 2007; Schimmelmann et al., 2007). A significant increase in thyroid stimulating hormone and decrease in free thyroxine were also found. Studies of six months duration found weight gain ranging from 2.5 to 6.0 kg, and increases in BMI ranging from 1.4 to 1.8 kg/m^2 (Arango et al., 2009; Castro-Fornieles et al., 2008; Fraguas et al., 2008). Significant increases in total cholesterol, and decreases in free thyroxine were also found. Extrapyramidal symptoms were uncommon.

Data on quetiapine associated hyperglycemia and diabetes mellitus is available from a pharmacovigilance survey of spontaneously reported adverse events in quetiapine treated patients conducted using reports from the MedWatch Program (January 1, 1997 through July 31, 2002) and published cases. Koller (Koller, Weber, Doraiswamy, & Schneider, 2004) identified 46 reports of quetiapine associated hyperglycemia or diabetes, nine of which occurred in persons under the age of 19. The time to diagnosis of hyperglycemia was six months or less from the time quetiapine therapy was started in 75% of cases where this information was available. Eleven deaths were reported, including at least one child. The severity of reported cases ranged from mild glucose intolerance to diabetic ketoacidosis or hyperosmolar coma.

Based on analysis of the side effect data from the above described studies, recommendations for monitoring safety of quetiapine are presented in Tables 2 and 3.

Aripiprazole

The MEDLINE and EMBASE searches retrieved 175 abstracts on aripiprazole. Of these, nine were selected for review of the full text article, and eight met our inclusion criteria. See Appendix 6 Aripiprazole Summary Table, http://www.cacap-acpea.org/uploads/documents//Aug2011_RecommendationsforMonitoringSGAs, for a description of each included study .

There are five randomized controlled trials on the use of aripiprazole for pediatric mental health disorders (Findling, Nyilas, et al., 2009; Findling et al., 2008; Marcus et al., 2009; Owen et al., 2009; Tramontina et al., 2009). These trials ranged from four to eight weeks in duration. Meta-analysis was performed on side effect data obtained from these five

trials. Mean weight gain was higher with aripiprazole compared to placebo, with a mean difference of 0.85 kg [(95% CI 0.57, 1.13) p<0.00001]. The odds of clinically significant weight gain (more than 7% of total body weight) was significantly higher with aripiprazole, with an OR of 3.66 (p=0.0003). Aripiprazole treated patients had a significantly greater increase in BMI post treatment compared to placebo, with a mean difference of 0.27 kg/m^2 (95% CI 0.11, 0.42). The incidence of elevated fasting blood glucose, elevated triglycerides, elevated LDL or total cholesterol, or low HDL were not significantly different between treatment groups. Aripiprazole treated patients had a significantly greater decrease in prolactin levels after treatment, with a mean difference of -5.03 ng/mL (95% CI -7.80, -2.26) relative to placebo. Aripiprazole treated patients had a higher odds of extrapyramidal side effects compared to the placebo group, with an OR of 3.70 (p<0.0001). No significant changes in blood pressure or heart rate were reported.

Further information on short term side effects is available from Correll's (Correll et al., 2009) study. 41 children in this study received aripiprazole. After a median of 10.8 weeks of therapy, weight increased by 4.4 kg (95% CI 3.7, 5.2) in children treated with aripiprazole, compared to 0.2 kg (95% CI -1.0, 1.4) in the untreated control group. Waist circumference also increased significantly by 5.4 cm, and BMI increased by 1.67 kg/m^2. Baseline to endpoint changes in total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, ratio of triglycerides to HDL, glucose, and insulin were not significant in aripiprazole treated patients.

Data on longer term side effects (three months or longer of therapy) was obtained from two open label trials of aripiprazole. Seo (Seo, Sung, Sea, & Bai, 2008) studied the use of aripiprazole in 15 children in a 12 week trial. The authors reported mean BMI scores at baseline of 20.53±6.62 kg/m^2 and 20.61±7.25 kg/m^2 at endpoint (p=0.749). No other metabolic or neurological side effects were reported. Stigler (Stigler et al., 2009) studied the use of aripiprazole in a trial of 14 weeks duration. Nineteen of 25 subjects gained weight (mean 2.7 kg), with mean BMIs increasing from 20.3±6.1 kg/m^2 at baseline to 21.1±5.7 kg/m^2 at endpoint (p<0.04). No significant changes in fasting glucose or lipid measures compared to baseline were found. Three subjects developed abnormal lipid measures (total cholesterol, LDL and triglycerides) after treatment. Four patients developed mild tremor.

Information on side effects of chronic treatment with aripiprazole is available from a poster presentation by Findling at the 2009 Annual Meeting of the American College of Neuropsychopharmacology (Findling, Marcus, et al., 2009). Findling and colleagues performed a 52 week open label study of the safety and tolerability of flexibly dosed aripiprazole. 330 children entered the 52 week treatment phase, and 199 completed. Weight gain as an adverse event was reported in 23% of patients. 33% of children had a BMI over the 90th percentile at baseline, and 44% of children had a BMI over the 90th percentile at the trial endpoint. Of the 153 children undergoing metabolic laboratory testing at endpoint, 2% had a fasting glucose over 115 mg/dl, 5% had a total cholesterol over 200 mg/dl, 7% had an LDL over 130 mg/dl, 30% had an HDL less than 40 mg/dl and 5% had triglycerides over 200 mg/dl. Tremor was reported in 3%, psychomotor hyperactivity in 2.7%, akathisia in 2.4%, and dyskinesia in 2.4%.

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

370 abstracts were retrieved pertaining to clozapine from the MEDLINE and EMBASE searches. Of these, 10 articles were read in full, and eight were included in the analysis (see Appendix 7 Clozapine Summary Table, http://www.cacap-acpea.org/uploads/documents//Aug2011_RecommendationsforMonitoringSGAs).

Data on short term side effects of clozapine are available from three randomized controlled trials of clozapine for pediatric schizophrenia, all with an active comparator (Kumra et al., 1996; Kumra et al., 2008; Shaw et al., 2006). These trials ranged in length from 6 to 12 weeks. Two trials compared clozapine to olanzapine and one trial compared clozapine to haloperidol. Meta-analysis of trial data was not possible due to clinical heterogeneity, and differences in the reporting of outcomes between trials.

Shaw (Shaw et al., 2006) compared clozapine to olanzapine in 25 children with schizophrenia refractory to at least two medications in an eight week trial. Mean weight gain with clozapine was 3.8±6.0 kg, and with olanzapine was 3.6±4.0 kg (p=0.96). Change in BMI was 1.6±2.5 kg/m^2 with clozapine and 1.4±1.6 kg/m^2 with olanzapine (p=0.76). One of 12 patients on clozapine developed elevated triglycerides and cholesterol requiring treatment. Kumra (Kumra et al., 2008) compared clozapine to olanzapine for 12 weeks in 39 children with schizophrenia who were resistant to at least two antipsychotics. At baseline, 16 of the 18 clozapine treated patients were overweight or obese, and 16 of the 21 olanzapine treated patients were overweight or obese. At trial endpoint, this increased to 17 of 18 clozapine treated patients, and 17 of 21 olanzapine treated patients. Four of 18 clozapine treated patients and five of 21 olanzapine treated patients had fasting triglycerides over 110 mg/dl at trial endpoint. Kumra (Kumra et al., 1996) compared clozapine to haloperidol in 21 children with schizophrenia in a trial of 6 weeks duration. Mean weight gain was 0.9±6.47 kg in clozapine treated patients, compared to 0.94±2.89 kg in the haloperidol treated patients.

Data on longer term side effects of clozapine are available from two open label trials of 12 and 16 weeks duration in children with schizophrenia, and one prospective cohort study of 45 weeks duration in a group of children with mental health disorders. Kumra (Kumra et al., 2008) conducted a 12 week open label follow-up study of children previously participating in the 12 week double blind clozapine/olanzapine

comparative trial. At week 24, 11 of the 14 subjects were overweight or obese according to their BMI percentile. Two children had elevated total serum cholesterol, 10 children had elevated fasting triglycerides, and four children had impaired fasting glucose. Fleischhaker (Fleischhaker et al., 2008) monitored 15 children initially on clozapine for 45 weeks. The weight and body mass index of children were obtained at initial hospitalization and prospectively monitored. The mean weight change over 45 weeks was 9.5±10.4 kg. 9 of the 15 patients gained more than 7% of their body weight over this time period. BMI increased from 22.0±3.2 kg/m^2 at baseline to 25.0±4.3 kg/m^2 at week 45.

Gogtay (Gogtay, Sporn, Alfaro, Mulqueen, & Rapoport, 2002) reported akathisia as a neurological side effect of clozapine in two children with schizophrenia. Both children developed akathisia within days of starting clozapine which resolved with propranolol treatment.

Further information on adverse events associated with clozapine treatment was found from a study by Koller (Koller et al., 2003), who used the MedWatch surveillance program and MEDLINE to identify spontaneously reported cases of pancreatitis associated with the use of atypical antipsychotics. Seventy-two cases occurred in patients receiving clozapine, and an additional ten cases occurred in patients receiving clozapine with another antipsychotic medication. One case occurred in a 10 year old child on clozapine monotherapy, and one case occurred in a 17 year old child treated with a combination of clozapine and haloperidol. Time to diagnosis of pancreatitis was less than six months in 63% of clozapine treated cases.

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

160 abstracts pertaining to ziprasidone were obtained from the MEDLINE and EMBASE searches. Of these, five full text articles were reviewed in detail, and three met our inclusion criteria. Due to the paucity of data on this medication, we decided to also include open label studies shorter than 12 weeks, and case series commenting specifically on adverse events associated with ziprasidone use in children (see Appendix 8 Ziprasidone Summary Table, http://www.cacap-acpea.org/uploads/documents//Aug2011_Recommendations forMonitoringSGAs).

Data on short term side effects of ziprasidone is available from one randomized controlled trial in children with Tourette Syndrome of eight weeks duration (Sallee et al., 2000). Twenty-eight children were randomized to ziprasidone or placebo. Mean weight gain was similar in the two groups, with 0.7±1.5 kg gained in the ziprasidone group and 0.8±2.3 kg gained in the placebo group at trial endpoint. Mean serum prolactin levels were also similar between groups at trial endpoint. One of the 16 ziprasidone treated patients developed akathisia which resolved with lowering of the medication dosage. No clinically significant differences between the treatment groups were observed in assessment of vital signs.

There are two short term prospective open label studies of ziprasidone in children. Malone (Malone, Delaney, Hyman, & Cater, 2007) studied the use of ziprasidone in 12 adolescents in a six week open label pilot study. Mean BMI at baseline was 24.4±4.5 kg/m^2, and at endpoint was 24.3±4.7 kg/m^2. With respect to other metabolic effects, there was no change in triglycerides or HDL from baseline to endpoint. There was a net decrease in total cholesterol of 10.2 mg/dl from baseline to endpoint (p=0.04). Prolactin levels did not change. There were no significant changes in pulse or blood pressure. Two subjects had acute dystonic reactions; one resolved without treatment and one resolved with lowering of the ziprasidone dose.

Biederman (Biederman et al., 2007) studied the use of ziprasidone in an eight week open label prospective study in 21 children. Metabolic variables measured at baseline and endpoint included cholesterol, LDL, HDL, triglycerides, glucose, prolactin, blood pressure, weight and body mass index. There were no significant differences between baseline and endpoint in any of these variables. Neurological adverse events were not discussed.

McDougle (McDougle, Kem, & Posey, 2002) published a case series of 12 youths treated with ziprasidone for at least six weeks. Eleven of the 12 children in this case series had received previous antipsychotic treatment, and nine of these children had experienced substantial weight gain with their prior treatments. Patients were treated with ziprasidone for an average of 14.15±8.29 weeks (range 6-30 weeks). The mean weight change for the group was -2.7±5.7 kg (range -15.9 to +2.7 kg). Five patients lost weight, five had no change and one gained weight. One patient developed an oral dyskinesia which resolved on discontinuation of ziprasidone.

Data on longer term side effects is available from one open label study of ziprasidone. DelBello (DelBello, Versavel, Ice, Keller, & Miceli, 2008) studied the tolerability of ziprasidone in 63 children in an open label study of six months duration. The study was divided into two periods; in period 1, children were randomized to a low dose (80 mg per day) or high dose (160 mg per day) regimen for three weeks. In period two, children received a flexible dose of 20 to 160 mg per day for 24 weeks. The mean weight gain at week three (n=61) was 1.0±1.0 kg, and at week 27 (n=47) was 2.8±6.3 kg. No clinically significant changes in lipid profiles were observed. Changes in total cholesterol, HDL and LDL levels were minimal in both periods. Elevated prolactin (more than 1.5 times the upper limit of normal) occurred in four of 63 patients during period one and in nine of 56 subjects in period 2. The overall incidence of movement disorders was 22% (14 of 63 patients) during period one, and 16% (9 of 56 patients) in period two.

Based on the available data recommendations for monitoring 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

Twelve abstracts were retrieved pertaining to paliperidone with the MEDLINE and EMBASE searches. Of these none met our inclusion criteria.

No evidence-based recommendations can be made as there is no data available on the use of paliperidone in children at this time.

Discussion

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

Our guideline specifically focused on metabolic and neurological side effects, and how they should be monitored. Second generation antipsychotics can cause other side effects which were not discussed in this guideline, including sedation, drooling, a decrease in absolute neutrophil count (with clozapine), cataracts (with quetiapine) and prolongation of the QT_c 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 (Novartis, 2010), electrocardiograms (Blair & Taggart, 2004), and slit lamp eye examinations (AstraZeneca, 2008). Users of this guideline 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 (in press).

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 heart disease in adulthood (Baker, Olesen, & Sorensen, 2007). A prospective cohort study of 2,195 children followed for 21 years has shown that youth determinants of adult metabolic syndrome include obesity, high triglycerides, high insulin, high CRP and a family history of hypertension and type 2 diabetes (Mattson, Ronnemaa, & Juonala, 2008). Obesity, high LDL cholesterol and low HDL cholesterol in childhood are associated with a decrease in carotid artery elasticity in adulthood, an early pathophysiological change relevant to the development of atherosclerosis (Juonala, Jarvisalo, & N., 2005). The social and emotional consequences of obesity in a child who may already be seen as different due to their mental health disorder is also worth considering. A prospective study has demonstrated that women with the metabolic syndrome in childhood have higher levels of depressive symptoms in adulthood than women free of the childhood metabolic syndrome (Pulkki-Raback, Elovainio, & M., 2009).

Given the evidence for metabolic side effects in children treated with SGAs, and the long term sequelae of these problems, monitoring of all children prescribed SGAs is appropriate. There has been a notable lag however in the 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 FDA warning on diabetes risk for SGAs and recommendations from the American Diabetes Association (ADA) and American Psychiatric Association (APA) (American Diabetes Association, 2004) in 2004 that all patients receiving SGAs have 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 (pre-warning) were low (glucose 27%, lipids 10%). The FDA warning and ADA/APA 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%, $p<0.02$) (Morato, Druss, & Harung, 2010).

We have attempted to create an evidence-based monitoring protocol for physicians to follow when prescribing an SGA to a child for a mental health condition. As 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 which should be noted. Monitoring summary tables for physical examination maneuvers 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. 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 (Panagiotopoulos & Davidson, unpublished data). As a result, it is important to complete full baseline measures on patients receiving any one of the SGAs. Notable in Table 4 is the recommendation to complete a clinical assessment

Table 4. A practical tool for metabolic monitoring of children & youth treated with second-generation antipsychotics

Parameter		Pre-treatment Baseline	1 month	2 month	3 month	6 month	9 month	12 month
Assessment date								
Height (cm)[1]								
Height percentile								
Weight (kg)[1]								
Weight percentile								
BMI: (kg/m^2)[1]								
BMI percentile								
Waist circumference (At the level of the umbilicus)[2]								
Waist circumference percentile								
Blood pressure (mm/Hg)[3]								
Blood pressure percentile								
Neurological examination[4]		☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed	☐ completed
Laboratory evaluations:	Normal values							
Fasting plasma glucose	≤ 6.1 mmol/L[5]		NR	NR			NR	
Fasting insulin[6]	≤ 100 pmol/L[7]		NR	NR			NR	
Fasting total cholesterol	< 5.2 mmol/L		NR	NR			NR	
Fasting LDL-C	< 3.35 mmol/L		NR	NR			NR	
Fasting HDL-C	≥ 1.05 mmol/L		NR	NR			NR	
Fasting triglycerides	< 1.5 mmol/L		NR	NR			NR	
AST			NR	NR	NR		NR	
ALT			NR	NR	NR		NR	
TSH **(Quetiapine ONLY)**			NR	NR	NR	NR	NR	
Prolactin[8]			NR	NR	NR	NR	NR	
Other_____ (e.g. Amylase, A1C, OGTT etc.)[9]								
Physician Initials: ➔								

1 To determine height, weight and BMI percentiles, use age and sex specific growth charts at http://www.cdc.gov/growthcharts/.

2 To determine age and sex specific percentiles, go to http://www.idf.org/webdata/docs/Mets definition children.pdf (pages 18-19).

3 To determine age and sex specific percentiles, go to http://pediatrics.aappublications.org/cgi/content/full/114/2/S2/555.

4 Tools available for monitoring extrapyramidal symptoms include: Abnormal Involuntary Movement Scale (AIMS), Simpson Angus Scale, Extrapyramidal Symptom Rating Scale, Barnes Akathisia Rating Scale.

5 For FPG values of 5.6-6.0 mmol/L, consideration should be given to performing an oral glucose tolerance test (OGTT).

6 Note that this assessment is NOT recommended for aripiprazole or ziprasidone, but IS appropriate for all other SGAs.

7 For fasting insulin levels >100pmol/L, consideration should be given to performing an OGTT. Normal reference range may vary between centres.

8 Assessment of prolactin levels should be completed according to protocol except when the patient is displaying clinical symptoms of hyperprolactinemia (i.e. menstrual irregularity, gynecomastia, or galactorrhea), in which case more frequent monitoring may be warranted. Please also note that risperidone has the greatest effect on prolactin.

9 It is recommended that amylase levels be monitored in case where the patient presents with clinical symptoms of pancreatitis (i.e. abdominal pain, nausea, vomiting).

NR = not recommended

including physical exam maneuvers, 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 (Correll et al., 2009). Early intervention with conservative lifestyle measures if weight and/or waist circumference are increasing 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 6 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), and the long-term consequences of chronic elevation of prolactin 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 (Anderson et al., 2007; Croonenberghs et al., 2005), this is not always the case, and therefore we have adopted a conservative stance until further information is available. Prolactin undergoes diurnal fluctuations, and can be altered by medication (Turrone, Kapur, Seeman, & Flint, 2002) and food intake. Prolactin levels should therefore be drawn fasting with the other scheduled blood work, some of which also requires a twelve hour fast (e.g. blood lipids). As we found no evidence of abnormalities in 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 evidenced-based recommendations for monitoring beyond one year due to the poverty of long term studies. As more information becomes available from long term prospective cohort studies, we expect this evidence can 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 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 maneuvers 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 this guideline. Clinicians have a number of demands on their time; the need to perform specific physical examination maneuvers 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 website is currently under construction (www.camesaguideline.org) which will include forms for download by 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 on 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.

Acknowledgements / Conflicts of Interest

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