Management Recommendations for Metabolic Complications Associated with Second Generation Antipsychotic Use in Children and Youth

Josephine Ho, Constadina Panagiotopoulos, Brian McCrindle, Silviu Grisaru and Tamara Pringsheim for the CAMESA guideline group

The Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Project

The CAMESA guideline group includes:

Stacey Belanger, Neurologist, University of Montreal

Lisa Casselman, Consultant, Mental Health Commission of Canada

Jana Davidson, Child Psychiatrist, University of British Columbia

Asif Doja, Pediatric Neurologist, University of Ottawa

Silviu Grisaru, Pediatric Nephrologist, University of Calgary

Josephine Ho, Pediatric Endocrinologist, University of Calgary

Rekha Jabbal, Pharmacist, Alberta Children's Hospital Mental Health Program

Gail MacKean, Consultant, Mental Health Commission of Canada

Brian McCrindle, Pediatric Cardiologist, University of Toronto

John McLennan, Child Psychiatrist, University of Calgary

Valerie Palda, General Internist and Clinical Epidemiologist, University of Toronto

Constadina Panagiotopoulos, Pediatric Endocrinologist, University of British Columbia

Scott Patten, Psychiatrist and Clinical Epidemiologist, University of Calgary

Michelle Pearce, Child Psychiatrist, University of Toronto

Jonathan Ponesse, Developmental Pediatric Neurologist, University of Ottawa

Tamara Pringsheim, Neurologist and Clinical Epidemiologist, University of Calgary

Roger Thomas, Family Physician, University of Calgary

Waqar Waheed, Child Psychiatrist, University of Calgary

Chris Wilkes, Child Psychiatrist, University of Calgary

Abstract

Background: Second generation antipsychotics (SGAs) are commonly associated with metabolic complications. These medications are being used more frequently for the treatment of mental health disorders in children, which has stimulated the need for creating formal guidelines on monitoring their safety and effectiveness. Previous guidelines have been developed for monitoring for metabolic and neurological complications. In order to assist practitioners who perform these monitoring procedures, we have created a complementary set of treatment recommendations if abnormal measurements or results are encountered. **Objective:** To create evidence-based recommendations to assist in managing metabolic complications in children being treated with second generation antipsychotics. **Methods:** A systematic review of the literature on metabolic complications of second generation antipsychotic medications in children was conducted. Members of the consensus group evaluated the information gathered from the systematic review of the literature and used a nominal group process to come to consensus on treatment recommendations. Wherever possible, references were made to existing guidelines on the evaluation and treatment of metabolic abnormalities in children. **Results:** Evidence-based recommendations are presented to assist in managing metabolic complications, including weight gain, increased waist circumference, elevation in cholesterol, triglycerides and glucose, liver function tests, abnormal thyroid studies, and elevation in prolactin. **Conclusion:** The use of SGAs requires proper monitoring procedures. This treatment guideline provides guidance to clinicians on clinical management of metabolic complications if they occur.

Background

Metabolic complications of second generation antipsychotics are a common and unfortunate consequence of therapy. The rising use of these medications in Canada and internationally for the treatment of mental health disorders in children has stimulated the creation of formal guidelines on monitoring their safety and effectiveness. The CAMESA guideline group has made evidence-based recommendations on monitoring for metabolic and neurological complications. In order to assist practitioners who perform these monitoring procedures, we have created a complementary set of treatment

Correspondence to: Tamara Pringsheim, tmprings@ucalgary.ca

recommendations if abnormal measurements or results are encountered.

The purpose of this article is to provide guidance to clinicians on the appropriate course of action to follow when abnormal metabolic results are detected over the course of screening examinations. Abnormal values for each parameter are specified, and recommendations on further investigations, repeat testing, and management are listed. The target users of these guidelines are prescribers of antipsychotic medications for children and adolescents, which include psychiatrists, pediatricians, neurologists, and family physicians.

Methods

The following metabolic complication treatment recommendations are based on the assumption that the clinician has completed an appropriate diagnostic assessment and that treatment with a second generation antipsychotic medication is indicated. This guideline is intended to assist in managing metabolic complications in situations where the decision to treat with a second generation antipsychotic has already been made by the clinician based on an assessment of the potential risks and benefits for the patient. It is beyond the scope of the article to provide guidance as to whether a second generation antipsychotic should be used as a treatment method.

The CAMESA guideline group did not receive any industry sponsorship and were able to independently develop this manuscript with no restrictions of any kind. Recommendations were created by incorporating the results of a systematic review of the literature on metabolic complications of second generation antipsychotic medications in children (see monitoring guideline for detailed discussion of search methods and knowledge synthesis) with a consensus group process involving experts in the fields of endocrinology, cardiology, nephrology, psychiatry, neurology and paediatrics. Members of the consensus group evaluated the information gathered from the systematic review of the literature and used a nominal group process to come to consensus on treatment recommendations. A nominal group process is a method of small group discussion in which information is gathered by asking individuals to respond to questions posed by a moderator, and then having participants prioritize the suggestions of all group members. This process allows all group participants to contribute to the prioritization of recommendations. Wherever possible, we have made references to existing guidelines on the evaluation and treatment of metabolic abnormalities in children. Prior to the consensus group process, individual interviews were conducted with community paediatricians, psychiatrists, and family practitioners as a needs assessment. The need for formal treatment recommendations was identified, and preferences on format were sought. This information was incorporated into the development of these guidelines. Upon completion, this guideline was externally reviewed by the Canadian Academy of Child and Adolescent Psychiatry and the Canadian Pediatric Society.

The level of evidence (LOE) associated with treatment recommendations is provided. Randomized controlled trials are considered "high" levels of evidence, observational studies are "low", and any other evidence (retrospective study, case series, or case report) are "very low". Recommendations have been graded using a classification scheme based on the GRADE system (Brozek, Akl, Alonso-Coello, & al., 2009; Brozek, Akl, Alonso-Coello, Lang, et al., 2009) (Table 1). As with many other paediatric conditions, there is often a lack of large randomized, controlled trials on which to make evidence-based recommendations. Therefore, expert consensus recommendations can still be important even in the absence of strong evidence. Recommendations are listed in the order by which prescribers should pursue them.

Recommendations

MINIMIZING METABOLIC COMPLICATIONS

Treatment recommendations for minimizing weight gain:

1. Lifestyle intervention

Since second generation antipsychotic medication use in children and youth is associated with weight gain and resultant metabolic complications, it is strongly recommended that patients receive counselling (nutrition, lifestyle and exercise) at the initiation of therapy regardless of baseline body mass index. This is particularly important in a child who is overweight or obese prior to treatment with a second generation antipsychotic medication (Grade 3).

2. Re-evaluate use of antipsychotic medication to minimize weight gain (Grade 3):

a. Can the medication be stopped?

Strong consideration should be made to stopping the medication if severe metabolic side effects are encountered. In placebo discontinuation studies, discontinuation of the antipsychotic medication can result in improvement of weight (Lindsay, Leone, & Aman, 2004; Reyes, Buitelaar, Toren, Augustyns, & Eerdekens, 2006).

b. Is the lowest effective dose of medication being used?

Higher doses of both risperidone (LOE high) (Haas et al., 2009) and olanzapine (LOE low) (Correll et al., 2009) have been associated with greater weight gain and an increased likelihood of metabolic abnormalities in children.

Table 1. Summary of strength of recommendations using the GRADE approach (Brozek, Akl, Alonso-Coello, Lang, et al., 2009)

Grade of recommendation	Benefit vs risk and burdens	Methodological quality of supporting evidence	Implications
1A/ strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations 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 clearly outweigh risk and burdens, or vice versa	RCTs with important limitations, or exceptionally strong evidence from observational studies	Strong recommendation Can apply to most patients in most circumstances without reservation
1C/ strong recommendation, low quality or very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/ weak recommendation, high quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations, or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B/ weak recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations, or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2C/ weak recommendation, low quality or very low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable
3/ weak recommendation, no evidence, consensus based	Uncertainty in the estimates of benefits, risks, and burden	No data from RCTs or observational studies. Recommended on the basis of expert opinion	Weak recommendation, best action may differ depending on circumstances

c. Can the antipsychotic medication be switched to a different antipsychotic?

Weight gain is the highest with olanzapine (LOE high) (Correll et al., 2009) and clozapine (LOE high) (Kumra et al., 2008), and the risk of high cholesterol, triglycerides and fasting blood sugar is greatest with olanzapine (LOE low) (Correll et al., 2009). Could the patient be switched to risperidone or aripiprazole, which are associated with lower amounts of weight gain and lipid abnormality (LOE low) (Correll et al., 2009)? Ziprasidone has been associated with comparatively less weight gain than other atypical antipsychotics in adult patients (LOE high) (Komossa et al., 2009); however, data is lacking in young children. Switching to ziprasidone may be a consideration in older adolescent patients.

d. Is the patient taking any other medications in addition to the antipsychotic which also causes weight gain? If yes, can these medications be stopped, changed, or reduced?

BODY MASS INDEX (BMI)

BMI is determined using a height and weight measurement. For proper technique in measuring, please see the Canadian Pediatric Society position statement regarding the use of growth charts ("A health professional's guide to using growth charts," 2004). Age and sex-adjusted growth charts and BMI charts are available at http://www.cdc.gov/growthcharts/clinical_charts.htm#Set1 (Source: Centers for Disease Control and Prevention).

The Canadian clinical practice guidelines on the management and prevention of obesity in adults and children recommends comprehensive healthy lifestyle intervention as the first line therapy for obese children (Lau et al., 2007). Behavioural lifestyle intervention in children has been shown to be effective in managing obesity (Oude Luttikhuis et al., 2009). Single blind, randomized controlled trials have been done in adults being treated with antipsychotic medication and have shown that cognitive behavioural therapy aimed at healthy lifestyles improves weight loss compared to no cognitive

behavioural therapy (Alvarez-Jimenez et al., 2006; Khazaal et al., 2007; Weber & Wyne, 2006).

Metformin has been used in some small trials of children on antipsychotic medication (Arman, Sadramely, Nadi, & Koleini, 2008; Klein, Cottingham, Sorter, Barton, & Morrison, 2006; Morrison, Cottingham, & Barton, 2002; Shin, Bregman, Breeze, Noyes, & Frazier, 2009). In a double blind, randomized, placebo controlled study, Arman et al. (2008) found that mean weight and BMI improved in patients on risperidone treated with metformin for the first four weeks compared to placebo, but by 12 weeks there was no significant difference. However, Klein et al. (2006) noted an improvement in weight, BMI z-score and insulin sensitivity in patients treated with metformin compared to placebo in a 16 week double blind, randomized controlled study of children on olanzapine, risperidone or quetiapine. In an open label, prospective cohort study of 12 weeks duration, Morrison et al. (2002) found that 15 of 19 patients on various antipsychotic medications lost weight while on metformin. Another open label, prospective cohort study by Shin et al. (2009) of 12 weeks duration did not show weight loss in those on antipsychotic medication treated with metformin, but did demonstrate that overall, the patients did not continue to gain weight. To date, study findings are discordant and are limited by the short duration of follow-up, small subject numbers, and variability in the antipsychotic medication with which the patients were being treated.

Other medications have been used in the management of weight gain associated with antipsychotic use. Maayan (Maayan, Vakhrusheva, & Correll, 2010) conducted a systematic review which included 32 studies and 15 different medications: amantadine, dextroamphetamine, d-fenfluramine, famotidine, fluoxetine, fluvoxamine, metformin, nizatidine, orlistat, phenypropanolamine, reboxetine, rosiglitazone, sibutramine, topiramate and metformin plus sibutramine. The total number of patients was small and only five of these demonstrated small weight loss when compared to placebo: metformin (n=334), d-fenfluramine (n=16), sibutramine (n=55), topiramate (n=133) and reboxetine (n=79). This systematic review demonstrated that there is insufficient evidence to support routine clinical usage of these agents.

Treatment recommendations for abnormal BMI:

1. Normal BMI = 5th percentile to 85th percentile

Recommend: Repeat BMI measurement at next scheduled screen (refer to screening document).

2. Overweight BMI = ≥ 85th percentile and < 95th percentile

Recommend: Re-evaluate use of antipsychotic medication to minimize weight (Grade 3).

Consider cognitive/behavioral lifestyle intervention aimed at weight loss (Grade 1B).

3. Obese BMI = BMI ≥ 95th percentile

Recommend: Re-evaluate use of antipsychotic medication to minimize weight (Grade 3).

Consider cognitive/behavioral lifestyle intervention aimed at weight loss (Grade 1B).

Consider metformin in consultation with a specialist (Grade 2B).

WAIST CIRCUMFERENCE

Waist circumference percentiles are sex and age-adjusted and vary for different ethnicities. Technique for waist circumference measurement is described by Douketis et al. (Douketis, Paradis, Keller, & Martineau, 2005). Age and sex-adjusted waist circumference percentiles are available at http://www.idf.org/webdata/docs/Mets_definition_children.pdf (Source: International Diabetes Federation).

Treatment recommendations for abnormal waist circumference:

1. Normal waist circumference = 5th percentile to 75th percentile

Recommend: Repeat waist circumference measurement at next scheduled screen (refer to screening document).

2. Elevated waist circumference (abdominally overweight) = ≥75th percentile and <90th percentile

Recommend: Re-evaluate use of antipsychotic medication to minimize weight (Grade 3).

Consider cognitive/behavioral lifestyle intervention aimed at weight loss (Grade 1B).

3. Elevated waist circumference (abdominally obese) = ≥90th percentile or exceeding the adult cut-off

Recommend: Re-evaluate use of antipsychotic medication to minimize weight (Grade 3).

Consider cognitive/behavioral lifestyle intervention aimed at weight loss (Grade 1B).

Consider metformin in consultation with a specialist (Grade 2B).

BLOOD PRESSURE (BP)

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) percentiles are sex, age and height percentile-adjusted. Proper technique for blood pressure measurement in children has been published by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents ("The fourth report on the

diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004). Specific BP percentiles are available at http://pediatrics.aappublications.org/cgi/content/full/114/2/S2/555. The following recommendations are based on the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

Treatment recommendations for abnormal BP:

1. Normal BP = SBP and DBP <90th percentile

Recommend: Repeat BP check at next scheduled screen (refer to screening document).

2. Pre-hypertension = SBP or DBP ≥90th percentile and <95th percentile or BP exceeds 120/80 mmHg

Recommend: Recheck BP reading in six months ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

If still elevated, consider specialist consultation ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

3. Stage 1 Hypertension = SBP and/or DBP 95th to 99th percentile plus 5mmHg

Recommend: Recheck BP reading in one to two weeks or sooner if symptomatic ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

If persistently elevated on two additional occasions, consider specialist consultation for evaluation and treatment within one month ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

Example: For a three year old girl with a height at the 95th percentile, a BP of 110/69 would be at the 95th percentile (from table provided in the Fourth Report ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004)). She would be at stage 1 hypertension with a BP of 115/74 (5 mmHg above the 95th percentile).

4. Stage 2 Hypertension = SBP and/or DBP >99th percentile plus 5mmHg

Recommend: Consult specialist within one week or immediately if patient is symptomatic ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

Example: For a 12 year old boy with a height at the 95th percentile, a BP of 135/91 would be at the 99th percentile (from table provided in the Fourth Report ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004)). He would be at stage 2 hypertension with a BP of 140/96 (5 mmHg above the 99th percentile).

5. Severe hypertension = SBP or DBP >95th percentile plus > 20 mmHg and above or symptomatic

Recommend: Immediate assessment by specialist for investigation and management ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

Patients with symptomatic malignant hypertension (sudden, severe hypertension with threat of organ damage) should be referred to the nearest emergency room ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004).

Example: For a 10 year old girl with a height at the 95th percentile, a BP of 122/80 would be at the 95th percentile (from table provided in the Fourth Report ("The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents," 2004)). She would have severe hypertension with a BP of >142/100 (>20 mmHg above the 95th percentile).

FASTING PLASMA GLUCOSE (FPG) & INSULIN

The following recommendations are based on the Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008).

Treatment recommendations for abnormal FPG & fasting insulin:

1. Normal FPG = FPG < 6.1 mmol/L

*Recommend:*Repeat FPG at next scheduled screen (refer to screening document).

If the fasting insulin is above the upper limit of normal for the assay being used, consider oral glucose tolerance test (OGTT) and specialist consultation (Grade 3).

For those individuals with a FPG value of 5.6 - 6.0 mmol/L, consideration should be given to performing an OGTT (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008).

2. Impaired FPG = FPG 6.1 - 6.9 mmol/L

Recommend: Consider OGTT and specialist consultation if abnormal (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008).

Consider metformin in consultation with a specialist (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008).

3. Abnormal FPG (Diabetes) = FPG ≥ 7 mmol/L

Recommend: Consult with specialist for the management of diabetes (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008).

FASTING LIPID PROFILE

Normal lipid levels vary by sex and age (Daniels & Greer, 2008) and several clinical management guidelines have been published on the management of dyslipidemia in children (Daniels & Greer, 2008; Kavey et al., 2006; McCrindle et al., 2007). The following recommendations are based on the guidelines by McCrindle (McCrindle, in press).

Treatment recommendations for abnormal fasting lipid profile:

Low Density Lipoprotein (LDL)

1. Normal LDL < 3.35 mmol/L (McCrindle, in press).

Recommend: Repeat LDL measurement at next scheduled screen (refer to screening document).

2. Abnormal LDL ≥ 3.35 mmol/L or a non-HDL cholesterol (total cholesterol minus HDL) ≥ 3.75 mmol/L (McCrindle, in press).

Recommend: Re-evaluate use of antipsychotic medication to minimize weight (Grade 3).

Consider cognitive/behavioral lifestyle intervention aimed at weight loss (Grade 1B).

3. Elevated LDL ≥ 4.15 mmol/L despite aggressive lifestyle/diet/exercise modification as above for 3-6 months (McCrindle, in press).

Recommend: Consider consultation with specialist for possible medical therapy (McCrindle, in press).

High Density Lipoprotein (HDL)

1. Normal HDL ≥ 1.05 mmol/L (McCrindle, in press).

Recommend: Repeat HDL measurement at next scheduled screen (refer to screening document).

2. Abnormal HDL <1.05 mmol/L (McCrindle, in press).

Recommend: Re-evaluate use of antipsychotic medication to minimize weight (Grade 3).

Consider cognitive behavioural lifestyle intervention aimed at weight loss (Grade 1B).

Triglycerides (TG)

1. Normal TG < 1.5 mmol/L (McCrindle, in press).

Recommend: Repeat TG measurement at next scheduled screen (refer to screening document).

2. Abnormal TG ≥ 1.5 mmol/L (McCrindle, in press).

Recommend: Re-evaluate use of antipsychotic medication to minimize weight (Grade 3).

Consider cognitive behavioural lifestyle intervention aimed at weight loss (Grade 1B).

Consider consultation with specialist if TG ≥ 5 mmol/L for possible medical therapy (McCrindle, in press).

LIVER FUNCTION

Due to the lack of evidence, the following recommendations are based on expert consensus opinion.

Treatment recommendations for abnormal liver function tests:

1. Normal AST/ALT

Recommend: Repeat AST/ALT measurement at next scheduled screen (refer to screening document).

2. Abnormal AST/ALT

Recommend: Consider repeating AST/ALT (Grade 3).

Consider specialist consultation for further investigation and management (Grade 3).

THYROID STIMULATING HORMONE

Thyroid stimulating hormone measurements have been recommended for children and youth taking quetiapine. Due to the lack of evidence, the following recommendations are based on expert consensus opinion.

Treatment recommendations for abnormal TSH:

1. Normal TSH

Recommend: Repeat TSH measurement at next scheduled screen (refer to screening document).

2. Abnormal TSH

Recommend: Consider assessment of free thyroxine level (Grade 3).

Consider specialist consultation for further investigation and management (Grade 3).

PROLACTIN

Elevations in prolactin may be associated with signs and symptoms such as gynecomastia, galactorrhea, infertility,

menstrual irregularities, oligomenorrhea, amenorrhea, sexual dysfunction, decreased libido, acne and hirsutism in females. However, hyperprolactinemia may be asymptomatic in some individuals, and in particular, in pre-pubertal children. Due to the lack of evidence, the following recommendations are based on expert consensus opinion.

Treatment recommendations for abnormal prolactin:

1. Normal prolactin

Recommend: Repeat prolactin measurement at next scheduled screen (refer to screening document).

2. Elevated prolactin

Recommend: Re-evaluate use of antipsychotic medication (Grade 3):

a. Is the lowest effective dose of the antipsychotic being used? There is evidence to support that higher doses of both risperidone (LOE high) (Kleinberg, Davis, de Coster, Van Baelen, & Brecher, 1999) and olanzapine (LOE low) (Alfaro et al., 2002) cause more prolactin elevation and prolactin-related side effects in comparison to lower doses.

b. Can the antipsychotic medication be switched to a prolactin-sparing agent? Risperidone is the second generation antipsychotic with the greatest effect on prolactin (LOE high), while aripiprazole, quetiapine and clozapine do not elevate prolactin (LOE high) (Haddad & Wieck, 2004; Roke, van Harten, Boot, & Buitelaar, 2009). Switching to a prolactin-sparing agent results in return to normal levels of prolactin within weeks (LOE low) (Lee, Kim, & Park, 2006).

c. If continued treatment with the current antipsychotic medication is essential for the patient's psychiatric illness, consult with a specialist regarding further management of the hyperprolactinemia.

d. If clinical concerns, consider specialist consultation for further investigation regarding other causes of hyperprolactinemia and/or amenorrhea.

Conclusion

These treatment recommendations have been formulated to advise practitioners of an appropriate course of action if metabolic or other laboratory abnormalities are encountered over the course of screening activities related to second generation antipsychotic use. Practitioners should incorporate these recommendations with their clinical judgement, as the individual and unique nature of patient and drug related complications cannot be ignored. As further long term data becomes available, revisions to these recommendations may be required. It is our hope that the recommendations made will allow practitioners to feel more confident about their monitoring procedures, and more prepared to act if adverse events occur.

There are potential organizational barriers in applying these recommendations, particularly in the area of allied health support. One large potential barrier is the lack of access to appropriate cognitive behavioral therapy for weight loss in obese children, as well as support from registered dieticians and exercise therapists. Given that the main first line intervention recommended for many of the metabolic complications is lifestyle intervention, it is important to ensure that appropriate resources are available for patients to access. The screening and interventions recommended are anticipated to be cost-effective, since early detection and treatment of metabolic side effects would prevent progression to more severe disease states and long term complications.

Acknowledgements / Conflicts of Interest

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References

Alfaro, C. L., Wudarsky, M., Nicolson, R., Gochman, P., Sporn, A., Lenane, M., & Rapoport, J. (2002). Correlation of antipsychotic and prolactin concentrations in children and adolescents acutely treated with haloperidol, clozapine, or olanzapine. *Journal of Child and Adolescent Psychopharmacology, 12*(2), 83-91.

Alvarez-Jimenez, M., Gonzalez-Blanch, C., Vazquez-Barquero, J. L., Perez-Iglesias, R., Martinez-Garcia, O., Perez-Pardal, T.,…Crespo-Facorro, B. (2006). Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naive first-episode psychosis patients: A randomized controlled trial. *Journal of Clinical Psychiatry, 67*(8), 1253-1260.

Arman, S., Sadramely, M. R., Nadi, M., & Koleini, N. (2008). A randomized, double-blind, placebo-controlled trial of metformin treatment for weight gain associated with initiation of risperidone in children and adolescents. *Saudi Medical Journal, 29*(8), 1130-1134.

Brozek, J. L., Akl, E. A., Alonso-Coello, P., & al., e. (2009). Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy, 64*(5), 669-677.

Brozek, J. L., Akl, E. A., Alonso-Coello, P., Lang, D., Jaeschke, R., Williams, J. W.,…GRADE Working Group. (2009). Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy, 64*(5), 669-677.

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee (2008). Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. *Canadian Journal of Diabetes, 32*(Suppl 1), S1-S201.

Correll, C. U., Manu, P., Olshanskiy, V., Napolitano, B., Kane, J. M., & Malhotra, A. K. (2009). Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *Journal of the American Medical Association, 302*(16), 1765-1773.

Daniels, S. R., & Greer, F. R. (2008). Lipid screening and cardiovascular health in childhood. *Pediatrics, 122*(1), 198-208.

Douketis, J. D., Paradis, G., Keller, H., & Martineau, C. (2005). Canadian guidelines for body weight classification in adults: Application in clinical practice to screen for overweight and obesity and to assess disease risk. *Canadian Medical Association Journal, 172*(8), 995-998.

The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents (2004). *Pediatrics, 114*(2 Suppl 4th Report), 555-576.

Haas, M., Eerdekens, M., Kushner, S., Singer, J., Augustyns, I., Quiroz, J.,…Kusumakar, V. (2009). Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: Double-blind study. *British Journal of Psychiatry, 194*(2), 158-164.

Haddad, P. M., & Wieck, A. (2004). Antipsychotic-induced hyperprolactinaemia: Mechanisms, clinical features and management. *Drugs, 64*(20), 2291-2314.

A health professional's guide to using growth charts (2004). *Paediatrics and Child Health, 9*(3), 174-188.

Kavey, R. E., Allada, V., Daniels, S. R., Hayman, L. L., McCrindle, B. W., Newburger, J. W.,… Steinberger, J. (2006). Cardiovascular risk reduction in high-risk pediatric patients: A scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: Endorsed by the American Academy of Pediatrics. *Circulation, 114*(24), 2710-2738.

Khazaal, Y., Fresard, E., Rabia, S., Chatton, A., Rothen, S., Pomini, V.,…Zullino, D. (2007). Cognitive behavioural therapy for weight gain associated with antipsychotic drugs. *Schizophrenia Research, 91*(1-3), 169-177.

Klein, D. J., Cottingham, E. M., Sorter, M., Barton, B. A., & Morrison, J. A. (2006). A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *American Journal of Psychiatry, 163*(12), 2072-2079.

Kleinberg, D. L., Davis, J. M., de Coster, R., Van Baelen, B., & Brecher, M. (1999). Prolactin levels and adverse events in patients treated with risperidone. *Journal of Clinical Psychopharmacology, 19*(1), 57-61.

Komossa, K., Rummel-Kluge, C., Hunger, H., Schwarz, S., Bhoopathi, P. S., Kissling, W., & Leucht, S. (2009). Ziprasidone versus other atypical antipsychotics for schizophrenia. *Cochrane Database Systemic Review,* (4), CD006627.

Kumra, S., Kranzler, H., Gerbino-Rosen, G., Kester, H. M., De Thomas, C., Kafantaris, V.,…Kane J. (2008). Clozapine and "high-dose" olanzapine in refractory early-onset schizophrenia: A 12-week randomized and double-blind comparison. *Biological Psychiatry, 63*(5), 524-529.

Lau, D. C., Douketis, J. D., Morrison, K. M., Hramiak, I. M., Sharma, A. M., & Ur, E. (2007). 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children [summary]. *Canadian Medical Association Journal, 176*(8), S1-13.

Lee, B. H., Kim, Y. K., & Park, S. H. (2006). Using aripiprazole to resolve antipsychotic-induced symptomatic hyperprolactinemia: A pilot study. *Progress in Neuropsychopharmacology & Biological Psychiatry, 30*(4), 714-717.

Lindsay, R. L., Leone, S., & Aman, M. G. (2004). Discontinuation of risperidone and reversibility of weight gain in children with disruptive behavior disorders. *Clinical Pediatrics (Philadelphia)*, *43*(5), 437-444.

Maayan, L., Vakhrusheva, J., & Correll, C. (2010). Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: A systematic review and meta-analysis. *Neuropsychopharmacology, 35*(7), 1520-1530.

McCrindle, B. W. (in press). Pathogenesis and management of obesity-related dyslipidemia. New York, NY: Humana Press.

McCrindle, B. W., Urbina, E. M., Dennison, B. A., Jacobson, M. S., Steinberger, J., Rocchini, A. P.,… Daniels, S. (2007). Drug therapy of high-risk lipid abnormalities in children and adolescents: A scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. *Circulation, 115*(14), 1948-1967.

Morrison, J. A., Cottingham, E. M., & Barton, B. A. (2002). Metformin for weight loss in pediatric patients taking psychotropic drugs. *American Journal of Psychiatry, 159*(4), 655-657.

Oude Luttikhuis, H., Baur, L., Jansen, H., Shrewsbury, V. A., O'Malley, C., Stolk, R. P., & Summerbell, C. (2009). Interventions for treating obesity in children. *Cochrane Database Systemic Review,* (1), CD001872.

Reyes, M., Buitelaar, J., Toren, P., Augustyns, I., & Eerdekens, M. (2006). A randomized, double-blind, placebo-controlled study of risperidone maintenance treatment in children and adolescents with disruptive behavior disorders. *American Journal of Psychiatry, 163*(3), 402-410.

Roke, Y., van Harten, P. N., Boot, A. M., & Buitelaar, J. K. (2009). Antipsychotic medication in children and adolescents: A descriptive review of the effects on prolactin level and associated side effects. *Journal of Child and Adolescent Psychopharmacology, 19*(4), 403-414.

Shin, L., Bregman, H., Breeze, J. L., Noyes, N., & Frazier, J. A. (2009). Metformin for weight control in pediatric patients on atypical antipsychotic medication. *Journal of Child and Adolescent Psychopharmacology, 19*(3), 275-279.

Weber, M., & Wyne, K. (2006). A cognitive/behavioral group intervention for weight loss in patients treated with atypical antipsychotics. *Schizophrenia Research, 83*(1), 95-101.