Guidelines

Management recommendations for metabolic complications associated with second-generation antipsychotic use in children and youth

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BACKGROUND: Second-generation antipsychotics 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 metabolic and neurological complications. To assist practitioners who perform these monitoring procedures, a complementary set of treatment recommendations have been created for situations in which 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 reach a 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 prolactin, cholesterol, triglyceride and glucose levels; abnormal liver function tests and abnormal thyroid studies.

CONCLUSION: The use of second-generation antipsychotics requires proper monitoring procedures. The present treatment guideline provides guidance to clinicians on the clinical management of metabolic complications if they occur.

Key Words: Antipsychotic medications; Children; Metabolic syndrome

Les recommandations de prise en charge des complications métaboliques associées aux antipsychotiques de deuxième génération chez les enfants et les adolescents

HISTORIQUE : Les antipsychotiques de deuxième génération s’associent souvent à des complications métaboliques. Ces médicaments sont utilisés plus souvent pour le traitement des troubles de santé mentale chez les enfants, ce qui a requis l’élaboration de lignes directrices officielles sur la surveillance de leur innocuité et de leur efficacité. Des lignes directrices ont déjà été élaborées pour surveiller les complications métaboliques et neurologiques. Afin d’aider les praticiens qui effectuent ces interventions de surveillance, une série de recommandations thérapeutiques complémentaires a été élaborée pour les cas où l’on observe des mesures ou des résultats anormaux.

OBJECTIF: Créer des recommandations probantes afin de contribuer à la prise en charge des complications métaboliques chez les enfants traités au moyen d’antipsychotiques de deuxième génération.

MÉTHODE: Les auteurs ont procédé à une analyse systématique des publications sur les complications métaboliques des antipsychotiques de deuxième génération chez les enfants. Les membres du groupe consensuel ont évalué l’information recueillie grâce à l’analyse bibliographique systématique et ont fait appel à un processus de groupe nominal pour parvenir à un consensus à l’égard de recommandations thérapeutiques. Dans la mesure du possible, ils se sont reportés aux lignes directrices existantes sur l’évaluation et le traitement des anomalies métaboliques chez les enfants.

RÉSULTATS: Des recommandations probantes sont présentées pour contribuer à la prise en charge des complications métaboliques, y compris la prise de poids, l’augmentation du tour de taille, l’élévation des taux de prolactine, de cholestérol, de triglycérides et de glucose, les épreuves de fonction hépatique anormales et les études thyroïdiennes anormales.

CONCLUSION: Il faut recourir à des mesures de surveillance convenables lorsqu’on prescrit des antipsychotiques de deuxième génération. Les présentes lignes directrices thérapeutiques orientent les cliniciens quant à la prise en charge clinique des complications métaboliques lorsqu’elles se produisent.

Metabolic complications of second-generation antipsychotics are a common and unfortunate consequence of therapy. The increasing 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 Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) guideline group has made evidence-based recommendations on monitoring for metabolic and neurological complications. To assist practitioners who perform these monitoring procedures, we have created a complementary set of treatment recommendations if abnormal measurements or results are encountered.

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The purpose of the present 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, paediatricians, 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 in which 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 was able to independently develop the present article 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 (refer to monitoring guidelines 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 reach a consensus on treatment recommendations. A nominal group process is a 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 enables all group participants to contribute to the prioritization of recommendations. Wherever possible, references have been made to existing guidelines on the evaluation and treatment of metabolic abnormalities in children. Before 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. On completion, the present guideline was externally reviewed by the Canadian Academy of Child and Adolescent Psychiatry and the Canadian Paediatric Society (Ottawa, Ontario).

The level of evidence (LOE) associated with treatment recommendations is provided. Randomized controlled trials are considered to be ‘high’ levels of evidence, observational studies are ‘low’, and any other studies (retrospective study, case series or case report) are ‘very low’. Recommendations have been graded using a classification scheme based on the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system (1) (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 adhere to them.

**RECOMMENDATIONS FOR MINIMIZING METABOLIC COMPLICATIONS**

**Treatment recommendations for minimizing weight gain**

**Lifestyle intervention:** Because 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 their baseline body mass index (BMI). This is particularly important in a child who is overweight or obese before treatment with a second-generation antipsychotic medication (Grade of recommendation: 3).

**Re-evaluate the use of antipsychotic medication to minimize weight gain** (Grade of recommendation: 3):

- **Can the medication be discontinued?**
  - Strong consideration should be made to discontinue the medication if severe metabolic side effects are encountered. In placebo discontinuation studies, discontinuation of the antipsychotic medication can result in weight improvement (2,3).

- **Is the lowest effective dose of medication being used?**
  - Higher doses of both risperidone (LOE high) (4) and olanzapine (LOE low) (5) have been associated with greater weight gain and an increased likelihood of metabolic abnormalities in children.

- **Can the medication be switched to a different antipsychotic?**
  - Weight gain is the highest with olanzapine (LOE high) (5) and clozapine (LOE high) (6), and the risk of high cholesterol, triglyceride and fasting blood sugar levels is greatest with olanzapine (LOE low) (5). Could the patient be switched to risperidone or aripiprazole, which are associated with lower amounts of weight gain and lipid abnormality (LOE low) (5)? Ziprasidone has been associated with comparatively less weight gain than other atypical antipsychotics in adult patients (LOE high) (7); however, data are lacking in young children. Switching to ziprasidone could be considered for older adolescent patients.

- **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?**

**BMI**

BMI is determined by using a height and weight measurement. For proper technique in measuring, please refer to the Canadian Paediatric Society position statement regarding the use of growth charts (8). Age- and sex-adjusted growth charts and BMI charts are available at [www.cdc.gov/growthcharts/clinical_charts.htm](http://www.cdc.gov/growthcharts/clinical_charts.htm#Set1) (Centers for Disease Control and Prevention, USA).

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 (9). Behavioural lifestyle intervention in children has been shown to be effective in managing obesity (10). Single-blind, randomized controlled trials have been performed in adults treated with antipsychotic medication, and have shown that cognitive behavioural therapy aimed at healthy lifestyles improves weight loss compared with no cognitive behavioural therapy (11-13).

Metformin has been used in some small trials involving children who were taking antipsychotic medication (14-17). In a
double-blind, randomized, placebo-controlled study, Arman et al (14) found that mean weight and BMI improved in patients on risperidone treated with metformin for the first four weeks compared with placebo, but by 12 weeks, there was no significant difference. However, Klein et al (15) noted an improvement in weight, BMI z-score and insulin sensitivity in patients treated with metformin compared with 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 (16) found that 15 of 19 patients on various antipsychotic medications lost weight while on metformin. Another open-label, prospective cohort study of 12 weeks’ duration by Shin et al (17) did not report weight loss in patients who were on antipsychotic medications 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 et al (18) conducted a systematic review that included 32 studies and 15 different medications: amantadine, dextroamphetamine, d-fenfluramine, famotidine, fluoxetine, fluvoxamine, metformin, niacin and orlistat, phenylpropanolamine, 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 with 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.

**Overweight BMI = 5th to 85th percentile**

Recommendation: Re-evaluate the use of antipsychotic medication to minimize weight (Grade of recommendation: 3), and consider cognitive/behavioural lifestyle intervention aimed at weight loss (Grade of recommendation: 1B).

**Obese BMI = ≥95th percentile**

Recommendation: Re-evaluate the use of antipsychotic medication to minimize weight (Grade of recommendation: 3), consider cognitive/behavioural lifestyle intervention aimed at weight loss (Grade of recommendation: 1B), and consider metformin in consultation with a specialist (Grade of recommendation: 2B).

**WAIST CIRCUMFERENCE**

Waist circumference percentiles are sex and age adjusted, and vary for different ethnicities. The technique for waist circumference measurement is described by Douketis et al (19). Age- and sex-adjusted waist circumference percentiles are available at www.idf.org/webdata/docs/Mets_definition_children.pdf (International Diabetes Federation, Belgium).

**Treatment recommendations for abnormal waist circumference:**

**Normal waist circumference = 5th percentile to 75th percentile**

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

**Elevated waist circumference (abnormally overweight) = ≥75th percentile and <90th percentile**

Recommendation: Re-evaluate use of antipsychotic medication to minimize weight (Grade of recommendation: 3), and consider cognitive/behavioural lifestyle intervention aimed at weight loss (Grade of recommendation: 1B).

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**TABLE 1**

Summary of strength of recommendations using the GRADE approach (1)

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

GRADE Grades of Recommendation Assessment, Development and Evaluation; RCTs Randomized controlled trials

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**Treatment recommendations for abnormal BMI**

**Normal BMI = 5th percentile to 85th percentile**

Recommendation: Repeat BMI measurement at next scheduled screen (refer to screening document).
Elevated waist circumference (abdominally obese) = ≥90th percentile or exceeding the adult cut-off

Recommendation: Re-evaluate the use of antipsychotic medication to minimize weight (Grade of recommendation: 3), consider cognitive/behavioural lifestyle intervention aimed at weight loss (Grade of recommendation: 1B), and consider metformin in consultation with a specialist (Grade of recommendation: 2B).

BLOOD PRESSURE
Systolic blood pressure (SBP) and diastolic blood pressure (DBP) percentiles are sex, age and height percentile adjusted. The proper technique for BP measurement in children has been published by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (20). 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” (20).

<table>
<thead>
<tr>
<th>Treatment recommendations for abnormal BP</th>
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</thead>
<tbody>
<tr>
<td>Normal BP = SBP and DBP &lt;90th percentile</td>
</tr>
<tr>
<td>Recommendation: Repeat BP check at next scheduled screen (refer to screening document).</td>
</tr>
</tbody>
</table>

Prehypertension = SBP or DBP ≥90th percentile and <95th percentile or BP exceeds 120/80 mmHg

Recommendation: Recheck BP reading in six months (20). If still elevated, consider specialist consultation (20).

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

Recommendation: Recheck BP reading in one to two weeks or sooner if symptomatic (20). If persistently elevated on two additional occasions, consider specialist consultation for evaluation and treatment within one month. (20) Example: For a three-year-old girl with height at the 95th percentile, a BP of 110/69 mmHg would be at the 95th percentile (20). She would be at stage 1 hypertension with a BP of 115/74 mmHg (5 mmHg above the 95th percentile).

Stage 2 hypertension = SBP and/or DBP >99th percentile plus 5 mmHg

Recommendation: Consult a specialist within one week or immediately if patient is symptomatic (20). Example: For a 12-year-old boy with height at the 95th percentile, a BP of 135/91 mmHg would be at the 99th percentile (20). He would be at stage 2 hypertension with a BP of 140/96 mmHg (5 mmHg above the 99th percentile).

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

Recommendation: Immediate assessment by a specialist for investigation and management (20). Patients with symptomatic malignant hypertension (sudden, severe hypertension with threat of organ damage) should be referred to the nearest emergency room (20). Example: For a 10-year-old girl with height at the 95th percentile, a BP of 122/80 mmHg would be at the 95th percentile (20). She would have severe hypertension with a BP >142/100 mmHg (>20 mmHg above the 95th percentile).

FASTING PLASMA GLUCOSE AND INSULIN
The following recommendations are based on the Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada (21).

<table>
<thead>
<tr>
<th>Treatment recommendations for abnormal fasting plasma glucose (FPG) and fasting insulin</th>
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<tbody>
<tr>
<td>Normal FPG = FPG &lt;6.1 mmol/L</td>
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<tr>
<td>Recommendation: 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 the oral glucose tolerance test (OGTT) and specialist consultation (Grade of recommendation: 3). For individuals with an FPG value of 5.6 mmol/L to 6.0 mmol/L, consideration should be given to performing an OGTT (21).</td>
</tr>
</tbody>
</table>

Impaired FPG = FPG 6.1 mmol/L to 6.9 mmol/L

Recommendation: Consider OGTT and specialist consultation if abnormal (21), and consider metformin in consultation with a specialist (21).

Abnormal FPG (diabetes) = FPG ≥7 mmol/L

Recommendation: Consult with a specialist for the management of diabetes (21).

FASTING LIPID PROFILE
Normal lipid levels vary according to sex and age (22); several clinical management guidelines have been published on the management of dyslipidemia in children (22-24). The following recommendations are based on the guidelines by McCrindle (25).

<table>
<thead>
<tr>
<th>Treatment recommendations for abnormal fasting lipid profile</th>
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<tbody>
<tr>
<td>Low-density lipoprotein (LDL)</td>
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<tr>
<td>Normal LDL &lt;3.35 mmol/L (25)</td>
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<tr>
<td>Recommendation: Repeat LDL measurement at next scheduled screen (refer to screening document).</td>
</tr>
</tbody>
</table>

Abnormal LDL ≥3.35 mmol/L or a non-high-density lipoprotein (HDL) cholesterol (total cholesterol minus HDL) ≥3.75 mmol/L (25)

Recommendation: Re-evaluate the use of antipsychotic medication to minimize weight (Grade of recommendation: 3), and consider cognitive/behavioural lifestyle intervention aimed at weight loss (Grade of recommendation: 1B).

Elevated LDL ≥4.15 mmol/L despite aggressive lifestyle/diet/exercise modification as above for three to six months (25)

Recommendation: Consider consultation with specialist for possible medical therapy (25).

HDL
Normal HDL ≥1.05 mmol/L (25)

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

Abnormal HDL <1.05 mmol/L (25)

Recommendation: Re-evaluate the use of antipsychotic medication to minimize weight (Grade of recommendation: 3), and consider cognitive behavioural lifestyle intervention aimed at weight loss (Grade of recommendation: 1B).
Triglycerides (TG)

**Normal TG <1.5 mmol/L (25)**
Recommendation: Repeat TG measurement at next scheduled screen (refer to screening document).

**Abnormal TG ≥1.5 mmol/L (25)**
Recommendation: Re-evaluate the use of antipsychotic medication to minimize weight (Grade of recommendation: 3), consider cognitive behavioural lifestyle intervention aimed at weight loss (Grade of recommendation: 1B), and consider consultation with specialist if TG ≥5 mmol/L for possible medical therapy (25).

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

**Treatment recommendations for abnormal liver function tests**

**Normal aspartate aminotransferase/alanine aminotransferase (AST/ALT) levels**
Recommendation: Repeat AST/ALT measurement at next scheduled screen (refer to screening document).

**Abnormal AST/ALT levels**
Recommendation: Consider repeating AST/ALT measurement (Grade of recommendation: 3), and consider specialist consultation for further investigation and management (Grade of recommendation: 3).

**THYROID-STIMULATING HORMONE**
Thyroid-stimulating hormone (TSH) 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**

**Normal TSH levels**
Recommendation: Repeat TSH measurement at next scheduled screen (refer to screening document).

**Abnormal TSH levels**
Recommendation: Consider assessment of free thyroxine level (Grade of recommendation: 3), and consider specialist consultation for further investigation and management (Grade of recommendation: 3).

**PROLACTIN**
Elevations in prolactin levels 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, particularly in prepubertal children. Due to the lack of evidence, the following recommendations are based on expert consensus opinion.

**Treatment recommendations for abnormal prolactin**

**Normal prolactin levels**
Recommendation: Repeat prolactin measurement at next scheduled screen (refer to screening document).

**Elevated prolactin levels**
Recommendation: Re-evaluate the use of antipsychotic medication (Grade of recommendation: 3):
1. Is the lowest effective dose of the antipsychotic being used? There is evidence to support that higher doses of both risperidone (LOE high) (26) and olanzapine (LOE low) (27) cause more prolactin elevation and prolactin-related side effects compared with lower doses.
2. Can the antipsychotic medication be switched to a prolactin-sparing agent? Risperidone is a second-generation antipsychotic with the greatest effect on prolactin levels (LOE high), while aripiprazole, quetiapine and clozapine do not elevate prolactin levels (LOE high) (28,29). Switching to a prolactin-sparing agent results in return to normal levels of prolactin within weeks (LOE low) (30).
3. 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.
4. If there are 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, because the individual and unique nature of patient- and drug-related complications cannot be ignored. As further long-term data become available, revisions to these recommendations may be required. We hope that these recommendations will enable practitioners to feel more confident about their monitoring procedures, and more prepared to act in case of adverse events.

There are potential organizational barriers to applying these recommendations, particularly in the area of allied health support. One large potential barrier is the lack of access to appropriate cognitive behavioural 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 because early detection and treatment of metabolic side effects would prevent progression to more severe disease states and long-term complications.

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REFERENCES


