STRATEGIES TO ADDRESS THE METABOLIC SIDE EFFECTS OF SECOND-GENERATION ANTIPSYCHOTICS IN YOUTH

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CASE SUMMARY

A 13-year-old male presents with a diagnosis of bipolar disorder and severe aggression after multiple unsuccessful trials of behavioral interventions. He has a personal history of obesity and a family history of dyslipidemia and early cardiac death in his paternal grandfather. His parents are interested in medication management with a second-generation antipsychotic (SGA). However, they are concerned about the side effects.

Questions to Consider:

- What are the risk factors that one would need to look for related to lipids, blood sugar, and weight gain?
- What are the current recommendations indicating when to screen and what to screen for?
- When should a clinician send a patient to an endocrinologist, and what can endocrinologists or other specialists do to help?

METABOLIC SYNDROME IN YOUTH

Pediatric psychiatrists are often involved in the care of youth with conditions for which a second-generation antipsychotic (SGA) is considered. These medications are associated with risks of dyslipidemia, weight gain, and hyperglycemia (abnormal blood sugar levels resulting from a disorder of metabolism). In this article, we review current data and recommendations for screening for these side effects as well as management options. The article will discuss what screening labs to obtain, and the indications for referral to endocrinology for managing the associated side effects.

Although the cause is still unknown, multiple studies show a clear association between the use of SGAs and the progression of metabolic syndrome, hyperglycemia, and type 2 diabetes (T2DM). The American Diabetes Association (ADA) classifies all children >16 years old into the adult classification of metabolic syndrome.[1] For youth under 16, three of the five criteria are needed to meet a diagnosis of metabolic syndrome (Table 1).[1] The criteria set forth by the ADA for diagnosing T2DM are listed in Table 2.[2]

Table 1: Metabolic Syndrome Criteria for Children

Waist Circumference	>90% for age
Blood Pressure	If <10 then >90% for blood pressure, If >10 then >130 systolic or >85 diastolic
Triglycerides	>150 or >95% for age
HDL	<40 or <5% for age
Glucose Intolerance	Fasting blood glucose >100

Table 2: Criteria for Diabetes Mellitus

Fasting Glucose	> 126
Non-fasting Glucose	> 200 with symptoms of diabetes
Oral Glucose Tolerance Test	> 200 post prandial
HgbA1c	> 6.5

In general, there is a dearth of studies examining SGAs in youth, and most information is extracted from studies of adults. Research examining SGAs use in the adult population shows a prevalence of metabolic syndrome between 13%-52%. Compared to the general population, the risk for metabolic syndrome in adults is 2-4 times greater for those taking SGAs. There is also a higher risk for developing T2DM[3] and a twofold increased risk of cardiovascular disease.[8]

Metabolic syndrome in youth is not as straightforward as in adults due to developmental metabolic changes, growth, and changes in normal vital signs during childhood. Studies that consider a range of age groups suggest there may be a *higher* risk of metabolic syndrome for youth on SGAs.[3,4] It is not well established why the prevalence might be higher in younger populations, though there are theories that younger populations are drug na-

Table 3: Signs of Diabetes Mellitus, Pre-diabetes, DKA

Diabetes and Pre-diabetes	Polyuria, polyphagia, polydipsia, nocturia, urinary incontinence, fatigue, acanthosis nigricans (hyperpigmented, thickened skin in skin creases, e.g. neck, armpits, groin), yeast infections
DKA	Symptoms of diabetes as above, may also have altered mental status, Kussmal breathing (deep and labored breathing), nausea, vomiting, abdominal pain, "fruity" breath

ïve and therefore much more susceptible to the medications' metabolic effects.

There is also a significant increase in the amount of T2DM that has developed in patients taking SGAs.[12] Studies showed that the chance of getting T2DM while on SGAs is significantly higher in youth than in adults.[4] One concern is how quickly the dysglycemia appears, as children are being diagnosed with T2DM as early as within a year of starting SGAs. This highlights the importance of early screening, and possibly more frequent screening than what is currently recommended for adults.

Beyond more slowly-progressing metabolic concerns, there are also acute concerns, including a higher chance of developing diabetic ketoacidosis (DKA). Proper education around signs and symptoms of DKA, diabetes, and hyperglycemia is essential (Table 3).

The choice of *specific* SGAs may be important in metabolic syndrome, as adult studies indicate risk for weight gain, T2DM, and dyslipidemia varies by SGA (Table 4).[5] The FDA-approved indications for SGAs in patients under 18 are listed in Table 5.[6] Studies in children demonstrate general increased weight gain with clozapine, olanzapine and quetiapine, and risperidone's rate of hyperglycemia and metabolic syndrome is the highest.[7]

GUIDELINES FOR MONITORING

There are multiple guidelines that exist for monitoring for complications such as T2DM or metabolic syndrome (Table 6),[5,9,10] although the majority of data is derived from studies in adults. In 2004, the ADA, American Psychiatric Association (APA), American Association of Clinical Endocrinologists (AACE), and North American Association for the Study of Obesity (NAASO) met to develop prescribing guidelines.[5] The consensus suggests that when prescribing SGAs, the physician should obtain screening studies for any patient starting an SGA, including glucose and lipid levels, patients' height, weight, blood pressure, and waist circumference, and a patient and family history to better ascertain risks. There is also agreement that blood pressure and laboratory studies, including fasting lipids and glucose, should be repeated after starting treatment, though the frequencies vary among recommendations. However, even five years following the consensus guidelines, fewer than 50% of child providers were following the recommendations.[11] Information on AACAP Practice Parameter development can be found online at:

http://www.aacap.org/AACAP/Resources_for_Primary_Care/Practice_Parameters_and_Resource_Centers/Practice_Parameters.aspx

Table 4: Risk of Metabolic Symptoms Based on Specific SGA

Drug	Risk for weight gain	Risk for DM	Risk for dyslipidemia
Clozapine	Severely increased	Increased	Increased
Olanzapine	Severely increased	Increased	Increased
Risperidone	Severely increased	Moderately increased	Moderately increased
Quetiapine	Increased	Moderately increased	Moderately increased
Aripiprazole	Moderately increased	None	None
Ziprasidone	Moderately increased	None	None

PREVENTION OF METABOLIC SYNDROME AND T2DM

When prescribing an SGA, it is important to be ready to discuss ways to help prevent metabolic syndrome and T2DM through education and lifestyle changes. The American Academy of Pediatrics (AAP) has published recommendations for important lifestyle changes to protect against cardiovascular disease.[13] Ensuring greater than 60 minutes of physical activity and less than two hours of screen time per day is important for increasing cardiovascular fitness. Monitoring blood pressure routinely is important, and this might require having the child follow up with the school nurse or his or her pediatrician's office often to have blood pressure checked.

In terms of diet, beverages can be a significant source of calories for some children, so encourage low fat or fat-free milk and reduced sugar-sweetened beverages including juices, sodas, energy drinks, and sports drinks. Other important dietary recommendations include encouraging portion control, increased fiber, and eating as a family, avoiding fast-food restaurants, and following the "Healthy Plate." The Healthy Plate is a government initiative (www.choosemyplate.gov) that suggests dividing the plate into four roughly equal portions based on food groups (grains, proteins, fruits, and vegetables)[13], and a side of dairy. One important factor to assess for is tobacco

Table 5: FDA-Approved SGAs for Youth

Drug Name	Indications	Age
Aripiprazole	Schizophrenia	>13
Aripiprazole	Bipolar Disorder	>10
Aripiprazole	Irritability with Autism	6-17
Olanzapine	Schizophrenia, Bipolar	>13
Paliperidone	Schizophrenia	>17
Quetiapine	Bipolar	>10
Quetiapine	Schizophrenia	>13
Risperidone	Schizophrenia	>13
Risperidone	Bipolar	>10

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Table 6: Consensus Monitoring Recommendations	
Baseline info	Personal and family history of obesity, T2DM, dyslipidemia, HTN, or heart disease
Baseline studies	Weight, height, waist circumference, BP, fasting blood glucose, fasting lipid profile
Follow-up labs during the first year of treatment	4, 8 and 12 weeks and quarterly get waist circumference. 12 weeks get BP, fasting glucose and fasting lipids
Follow-up labs after 1 year of treatment	Annual updates of personal and family history, waist circumference, BP and fasting glucose. Fasting lipids to be obtained every 5 years

use, and if necessary, it is strongly recommended that patients work on smoking cessation. When starting an SGA, clinicians should sit down and go through current lifestyle habits and develop a plan with the family to make realistic changes, and during follow-up visits, it is important to revisit these lifestyle goals.

METFORMIN

Metformin represents another "off-label" option to help prevent or treat metabolic syndrome, especially if it is not possible or optimal to change medications, and lifestyle modification has failed. Metformin has shown mixed benefit for children and adolescents in preventing the weight gain that occurs with SGA's, and most trials so far have only had a small sample size.[14] As such, there is no clear consensus, and practitioners should consult the latest treatment recommendations before prescribing metformin.

Patients who are already at risk for metabolic syndrome represent good candidates for starting metformin. These patients include those who are obese or have impaired glucose tolerance ("pre-diabetes"). Patients who have a rapid weight gain when starting an SGA may also benefit from metformin. The population at highest risk for metabolic syndrome is young children who are starting an SGA for the first time, and most studies indicate that this group would benefit the most from starting an SGA.[15]

Currently metformin is only FDA approved to treat T2DM in children 10 years or older, but otherwise metformin does not have FDA approval for other usage. As such, the use of metformin is off-label in this setting. Prescribers must take this into consideration when deciding to start metformin and may consider referring to an endocrinologist first. When taking metformin, there is risk of increased lactic acidosis if a person has renal failure, necessitating frequent checks of both a blood urea nitrogen (BUN) and creatinine (Cr) level. If the patient has lung disease, congestive heart failure, or liver disease, referral to an endocrinologist or other specialist should be considered before starting metformin.

REFERRAL TO ENDOCRINOLOGY

Specialists, including endocrinologists, who focus on dyslipidemia or weight management, often see children with metabolic symptoms in their clinics. There are no consensus guidelines or recommendations for when that referral should take place or when a change to a new medication should be considered, but if a child is trending towards any of these stated criteria, then more frequent follow-up to closely monitor weight, blood pressure, and laboratory parameters would be advisable.

If an abnormality arises during monitoring, early referral to a specialist may be advisable to prevent long-term negative outcomes such as T2DM or cardiovascular disease. These abnormalities include any change in waist circumference, blood pressure, triglycerides, HDL, or glucose that is approaching or in the range of what is considered metabolic syndrome or DM (Tables 1 and 2) or if they are starting to develop symptoms of DM, pre-diabetes, or DKA (Table 3). There are no firm guidelines for when to stop the medication, so good collaboration between the child psychiatrist and endocrinologist is needed to weigh future safety risks of continuing the medication against the benefit provided by it.

Referral may come from the patient's primary care provider (e.g. pediatrician), or a child psychiatrist. Prior to referral, there are some considerations to be made. First, additional labs may be collected in collaboration with the primary care provider, such as HgA1c or thyroid studies. Communication with the primary care provider is also crucial to identify who will be following laboratory studies and to determine if a specialist referral is needed.

As discussed before, it is essential that proper information is given to families about weight gain, nutrition, dyslipidemia and signs of hyperglycemia/DKA to help prevent complications. If healthy lifestyle choices are already being implemented, the specialist can focus more on what needs to be done for further risk reduction, such as considering lipid-lowering medication or metformin. Finally, it is essential to work in conjunction with the specialist to consider changing the psychiatric medication to one with fewer metabolic side effects.

Conclusions

In conclusion, it is important to consider that SGAs are associated with metabolic risks in both children and

adults. When the teenager described in the case above walks into your office, keep in mind that there are guidelines to help with the risks, and referral to specialists in endocrinology, dyslipidemia, and weight management may be necessary. Although most of the guidelines focus on adults, at present they are the best evidence-based guidelines available.

Additional research is needed to advance our understanding of the etiology, prevention, diagnosis, and treatment of metabolic side effects of SGAs in youth. In particular, a better understanding of the reasons why SGAs seem to promote weight gain, metabolic syndrome, and T2DM would potentially allow for better treatment options to be developed. It has been speculated that there is a genetic component that promotes these symptoms, and identifying genetic markers could help to guide appropriate therapy.

Take-Home Summary:

Use of second generation antipsychotics can result in metabolic side effects and hyperglycemia. Management of these side effects occurs though prevention, education, monitoring, and partnership with specialists and primary care providers.

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