Review

Antipsychotics Medication Use and its Metabolic Challenges for Autism Spectrum Disorders

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There has been a growth in the knowledge about autism and autism spectrum disorders (ASD) in the United States and worldwide. As the prevalence rates have grown, so has the awareness of the need to develop effective and safe treatments for children with ASD. In addition to the behavioral interventions such as applied behavioral analysis, parent training, and adaptive skills training, there has been an increase in the use of medications for the treatment of ASD symptoms. At this time, there are two antipsychotics approved by the FDA for the use in children with ASD, risperidone and aripiprazol. Generally, the use of this classification has been more recently associated with changes in metabolic function in children. The purpose of this article is to review briefly the use of psychotropic medications, focusing on antipsychotics, and discuss the metabolic risks and risk factors associated with their use within children with autism.

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Key Words: *autism, autism spectrum disorders (ASD), antipsychotics, metabolic syndrome, treatment and management of autism*

INTRODUCTION

Autism and autism spectrum disorders (ASD) are neurodevelopmental disorders that cause impairments in social interactions and communication. In addition, ASD can manifests with symptoms of irritability, cognitive rigidity, stereotyped/restricted patterns of behavior, and often aggression. Although symptoms are usually present from the age of 3, there is increasing evidence that there is a wide range of impairments within children and adolescents leading to wide variation in the long-term impact of ASD on quality of life.

Since 1943, when Kanner originally described and coined the term "autism", there have been huge advancements in autism research and the awareness of ASD.[1] A recent study published by the Autism Developmental Disabilities Monitoring Network in the US estimated the prevalence across 14 sites to be 11.3 per 1,000 (1/88).[2] Additionally, a 2012 report on the global prevalence of autism and ASD reported a lower prevalence rate of 62 per 10,000 and stated, "while existing estimates are variable, the evidence reviewed does not support differences in PDD prevalence by geographic region nor a strong impact of ethnic/cultural or socioeconomic factors".[3] Regardless, there have been great advancements in the development of diagnostic tools to identify and distinguish children with ASD, allowing us to further our understanding about the disorder and develop ways to treat and manage symptoms related to ASD.

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Given the increased awareness of ASD and its worldwide prevalence, there have been amplified efforts and research into treatments to reduce the impact of the disorder and improve the quality of life for these children. Home based and school based behavioral interventions to improve social interactions and improve communication skills have been developed. Children with ASD are now able to have social skills training, adaptive skills training, applied behavioral analysis (ABA), and other cognitive therapies based on their needs. Of the behavioral interventions, ABA therapy has been the most successful and been found effective in several hundred evidence based trials and indicating improvements in intellectual functioning, language development, development of activities of daily living skills, and social functioning.[4,5,6]

In addition to the behavioral interventions, psychopharmacological interventions have also been developed for children with ASD. Unfortunately, medications are often reserved for children with more severe impairments in functioning and target symptoms of irritability, aggression, hyperactivity, inattention, and stereotyped/repetitive behaviors/or cognitions. Due to difficulties with attention, children with ASD are often impulsive in their actions resulting in an increased risk of harm to themselves or others. Specifically, medications are sometimes used to reduce self-injurious behavior (SIB) and aggression that can occur in children with ASD.[7,8]

Current estimates of the use of antipsychotics in ASD in the United States range from 30 to 60%.[7] Of those on

medications, it is estimated that almost half of the children with ASD who are prescribed antipsychotic medications are on two or more medications.[8,9] As our medication usage in this population increases, so has our awareness of the risk of serious side effects that can impact children treated with antipsychotic medications. The focus of this article is to briefly review the psychopharmacological treatment of ASD with antipsychotics and their risk of metabolic derangements in children and adolescents.

Table 1. Antipsychotic Medication Trials used in Autism Spectrum Disorder (ASD)**.**

Antipsychotic Medication	Studies	Target symptom(s)
Aripiprazole[a, b]	Marcus et al. (2009) Owen et al. (2009)	Irritability, hyperactivity, stereotypy, social withdrawal, inappropriate speech
Haloperidol	Anderson et al. (1989) Miral et al. (2008)	Behavioral symptoms, global function
Risperidone[a, b]	RUUP (2002) Shea et al (2004) McDougle et al (2005) Nagaraj et al. (2006) Padina et al. (2007) Miral et al. (2008)	Irritability, hyperactivity, repetitive behavior, stereotypy, social withdrawal, inappropriate speech, social and communication impairment, sensory, language
Olanzapine[b]	Hollander et al. (2006)	Global functioning, aggression, compulsions, irritability

a. Indicates FDA approval for the use in ASD
b. Indicates an FDA warning for diabetes

Table 2. Metabolic Syndrome Criteria as defined by the International Diabetes Federation for Children (<16 yrs) and Adolescents (>16 yrs).

Clinical Parameters	Measures
Obesity	Central/abdominal obesity, waist: hip ratio, BMI
Glucose metabolism impairment	Increased fasting glucose, decreased glucose tolerance
Dyslipidemia	Triglyceride
Decreased HDL-Cholesterol	HDL-cholesterol
Hypertension	Systolic or diastolic elevations

PSYCHOPHARMACOLOGICAL TREATMENT OF AUTISM SPECTRUM DISORDERS

The use of medications in ASD has been a very complex process due to the heterogeneous nature of the disorder and clinical presentations. In reviewing the literature, some barriers to interpreting the published findings include: controversy as to the reliability and validity of the current diagnostic criteria of ASD; difficulties in screening, identifying, and targeting ASD behaviors as opposed to symptoms of co-morbid psychiatric disorders; systemic difficulties in the recruitment of homogeneous ASD participants in randomized controlled trials; and the lack of the consistent use of standardized and validated measures for monitoring target behavior/outcomes in response to medication treatment.

Medication treatment of ASD is challenging because most of the medications being used were originally designed to target different symptoms (e.g. depression, anxiety, mood stability) as opposed to ASD symptoms. As result, medications are often prescribed off-label in children with ASD. The majority of medication studies in ASD target symptoms such as hyperactivity, irritability, stereotypy, social withdrawal, inappropriate speech, and repetitive and restrictive behaviors.[10] Several intervention studies use the Aberrant Behavior Checklist (ABC) in their studies to monitor for symptoms of irritability, aggression, and self-injurious behavior.[11] Reviews of the published literature indicates that atypical antipsychotics are the first line of treatment of the symptoms of ASD.[12,13]

Generally, the classifications of medications used in ASDtrials include alpha 2 agonists, antipsychotics, mood stabilizers, norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and stimulants. A recent systematic review of psychotropic medications used for children 18 years and younger with ASD used the Reichow methodology for evaluating autism evidence based practices found; only aripiprazole, haloperidol, and risperidone had “established evidence” for irritability, behavioral symptoms,

hyperactivity, and stereotypy.[10] Although other classifications of medications such as mood stabilizers, stimulants, and antidepressants are regularly used in patients with ASD, none of them has been classified as having sufficient evidence for their use.[10] Of these medications, only aripiprazole (2009) and risperidone (2006) are FDA approved for the treatment of irritability associated with ASD (FDA reference) (**Table 1**). Of note, none of the studies published in recent reviews provided information on the use of more than one antipsychotic in children with ASD.[10,13]

METABOLIC SYNDROME AND ANTIPSYCHOTICS

Children with ASD can suffer from sensory integration difficulties, food aversions, and restrictive patterns of behavior/or eating that can put that am an increased risk for weight gain and poor nutritional habits.[4,6] The impact on children with ASD can be compounded by the use of antipsychotics, which although useful in the treatment of ASD, has been found to have a significant impact medically on weight gain and metabolic functioning. Metabolic Syndrome, also as referred to in the literature as Syndrome X, insulin resistance syndrome, or dysmetabolic syndrome, was first identified nearly 50 years ago when it was described by the World Health Organization and the United States Cholesterol Education Program (NECAP) Adult Treatment Panel (ATP). The National Health and Nutritional Examination Survey (NHANES) from 1999-2002 has reported that the rate of metabolic syndrome in adolescents in the US varies from 2% to > 9% depending on the diagnostic criteria applied.[25] The key components of metabolic syndrome include: obesity, blood pressure, cholesterol, and glucose intolerance (**Table 2**).

There is a complex relationship between metabolic syndrome and obesity indicating that it may be a bidirectional relationship with significant impact on cardiovascular morbidity and mortality.[26-28] Additionally, children with ASD often suffer from restrictive patterns of eating and sensory integration difficulties that can contribute to their weight gain. Due to the complex spectrum of ASD and their related behaviors, it is difficult to quantify their impact on the development of metabolic syndrome and obesity. Weight gain and obesity have been associated with an increase in elevated blood pressure, coronary artery disease, dyslipidemia, colorectal cancer, insulin resistance, type 2 diabetes, and inflammatory responses.[28,29] Although the specific mechanisms are unknown, a growing body of evidence supports the impact of histaminic receptor antagonism contribution towards weight gain and indirectly to insulin resistance.[27,30] Some evidence comes from studies indicating that there is a dose dependent risk of developing diabetes mellitus in medications with the higher histamine receptor affinity.[30,31] At this time, one specific receptor or target causing insulin resistance remains unclear, and it is likely that the etiology of insulin resistance is a complex interplay between neurotransmitters within the brain neuroendocrine receptors and transmitters peripherally and at specific organ sites.[32,33] On review of the weight gain and metabolic risks associated with antipsychotic use, it is concerning that children in general are at an increased risk weight gain when using antipsychotic medication in comparison to adults.[27] It has also been identified that younger children with ASD who possibly had less exposure to antipsychotic use were at an increased risk of weight gain.[27] Children treated with antipsychotics, independent of ASD diagnosis, have been found to have a significantly higher risk of weight gain (Odds ration [OR], 2.28), type 2 diabetes (OR, 2.36), and dyslipidemia (OR, 5.26).[35] Given that antipsychotics have been found to be effective in the treatment of psychiatric disorders, it is of critical importance that practitioners understand the metabolic risks of treatment and monitor patients carefully for metabolic syndrome.

METABOLIC MONITORING OF ASD PATIENTS RECEIVING ANTIPSYCHOTICS TREATMENT

At this time, there are no consensus guidelines around the monitoring of antipsychotic medications in children with or without ASD. Practitioners working with children with ASD should carefully weigh the risk of weight gain, dyslipidemia, diabetes, and metabolic syndrome against the possibly benefit of reduced irritability, aggression, and improved social/emotional functioning when considering the use of medication treatment of children with ASD. Treatment and management of children and adolescents with antipsychotics should include the following key components: review and identification of risk factors, regular monitoring of metabolic markers, and identification of potential modifiers to the development of metabolic syndrome (i.e. lifestyle, polypharmacy). Easily identifiable risk factors to review include: patient history of weight gain, familial obesity, familial diabetes, family history of hypercholesterolemia, and family history of cardiovascular disease and/or events. Given the risk factors, prescribers can tailor the treatment regimen using the evidence-based research. For example, patients with a history of weight gain and/or diabetes may avoid medications known to increase the risk of these side effects such as risperidone and olanzapine.[27,31] Certain cardiovascular risk factors (QTc prolongation, diabetes, and weight gain) also appear to have dose dependent side effect profiles that may require monitoring at dose changes.[31, 35, 36]

Several groups such as the International Diabetes Association, World Health Organization, American Diabetes Association, and others have attempted to create guidelines for the monitoring and management of metabolic side effects with antipsychotics. Unfortunately, most of the guidelines are difficult to translate to the pediatric population due to discrepancies in measuring and determining cut offs of variables such as insulin insensitivity, weight gain, and lipids. Additionally, pediatric measurements have to take into consideration modifying factors such as growth velocity, genetic predisposition, pubertal onset, and other physiological developmental differences between and among children and adolescents. Given these difficulties it seems prudent to measure certain metabolic variables prior to initiation of antipsychotic treatment and at intervals such as dose changes, medication changes, or time from medication initiation (**Table 3**).

Table 3. Proposed Metabolic Screening Measures for Children and Adolescents on Antipsychotics.

Proposed Screening Parameters	Clinical Comments
Fasting plasma glucose	Increases or decreases in glucose metabolism
Fasting insulin	Fasting insulin is a more accurate indicator of insulin resistance, HgA1c may not show dysregulation until metabolic abnormalities have progressed
OGTT	Indicated if signs of fasting glucose or insulin dysregulation
Waist circumference	Central obesity
BMI (kg/m2)	Might consider the use of a BMI-z score to account for normal growth
Blood pressure (mm/Hg)	Hypertension and hypotension can be present with antipsychotic use
Cholesterol panel (fasting cholesterol, LDL, HDL, Triglycerides)	Emphasis should be placed on triglycerides as indicated by the IDF
Liver function panel (AST, ALT)	Certain antipsychotics are associated with an increased risk of liver dysfunction
Thyroid stimulating hormone	Alterations in thyroid function can be found with typical antipsychotics, atypical antipsychotics, antiepileptics, and lithium
Prolactin	Primarily with risperidone
Electrocardiogram	Assess for Qtc prolongation

CONCLUSION

There has been a growth in the use of atypical antipsychotics in the treatment of children with autism and ASD. At this time, there is a growing body of data on the usage patterns, side effects, and monitoring of the use of antipsychotics in children in general. Given that children with ASD appear to be at an increased risk of weight gain, insulin resistance, the metabolic syndrome, and type 2 diabetes, as well as possibly other metabolic derangement, it seems prudent for providers to be aware of the side effect potentials and begin monitoring children prior to initiation of the medications. There also are studies indicating that some medications can be used to protect or counteract the impact the metabolic effects of antipsychotics. There are some indications that omega-3 may be used in children with ASD against cardiovascular abnormalities and metformin has been used in pediatric and adult populations to address weight gain and glucose metabolism.[37,38] Unfortunately, there is limited data on the use of omega-3 in ASD and metformin in children, often necessitating consultation with subspecialists in child psychiatry and/or endocrinology. There appears to be a great need for further discussions and guidelines to be developed and provided so that prescribers can best prescribe medication interventions for children with ASD in the future.

CONFLICT OF INTEREST

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REFERENCES

1. Kanner, L. Autistic Disturbances of Affective Contact. Nervous Child. 1943;2:217-250.
2. Autism and Developmental Disabilities Monitoring Network Surveillance. Prevalence of Autism Spectrum Disorders-Autism and Developmental Disabilities Monitoring Network, 14 Sites, United States, 2008. MMWR Surveill Summ. 2012;61(3):1-19.
3. Elsabbagh M, Divan G, Yun-Joo K, et al. Global Prevalence on Autism and Other Pervasive Developmental Disorders. Autism Res. 2012;5(3):160-179.
4. Granpeesheh D, Tarbox J, Dixon DR. Applied behavior analytic interventions for children with autism: A description and review of treatment research. Ann Clin Psychiatry. 2009;21(3):162-173.
5. Spreckley M, Boyd R. Efficacy of Applied Behavioral Intervention in Preschool Children with Autism for Improving Cognitive, Language, and Adaptive Behavior: A Systematic Review and Meta-analysis. J Pediatr. 2009;154(3):338-344.
6. Virues-Ortega J. Applied behavior analytic intervention for autism in early childhood: Meta-analysis, meta-regression and dose-response meta-analysis of multiple outcomes. Clin Psychol Rev. 2010;30(4):387-399.
7. Logan SL, Nicholas JS, Carpenter LA, et al. High Prescription Drug Use and Associated Costs among Medicaid-Eligible Children with Autism Spectrum Disorders Identified by a Population-Based Surveillance Network. Ann Epidemiol. 2012;22(1):1-8.
8. American Academy of Pediatrics. Children with autism frequently receive psychotropic medications. Science Daily. Available at http://www.sciencedaily.com/releases/2010/05/100502080228.htm. June 2012.
9. Langworthy-Lam KS, Aman MG, Van Bourgondien ME. Prevalence and patterns of use of psychoactive medicines in individuals with autism in the autism society of North Carolina. J Child Psych. 2002(12);311-321.
10. Siegel M, Beaulieu AA. Psychotropic medications in children with autism spectrum disorders: A Systematic Review and Synthesis for Evidence-Based Practice. J Autism Dev Disord. 2011;e pub ahead of print.
11. Aman MG, Singh NN, Setwart AW, Field CJ. The Abberant Behavior Check-list:a behavior rating scale for the assessment of treatment effects. Am J Ment Defic. 1985;89(5):485-491.
12. McDougle CJ, Stigler KA, Erickson CA, et al. Atypical antipsychotics in children and adolescents with autistic and other pervasive developmental disorders. J Clin Psychiatry. 2008;69(Suppl 4):15-20.
13. McPheeters, ML, Warren Z, Sathe N, et al. A systematic review of medical treatments for children with autism spectrum disorders. Pediatrics. 2011;127(5);e1312-e1321.
14. Reichow B, Volkmar FR, Cicchetti DV. Development of the evaluative method for evaluating and determining evidence-based practices in autism. J Autism Dev Disord. 2008;38(7):1311-1319.
15. Marcus RN, Owen R, Kamen L, et al. A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability

associated with autistic disorder. J Am Acad Child and Adolesc Psychiatry. 2009;48(11);1110-1119.
16. Owen R, Sikich L, Marcus RN, et al. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. Pediatrics. 2009;124(6):1533-1540.
17. Anderson LR, Campbell M, Adams P, et al. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. J Autism Dev Disord. 1989;19(2):227-239.
18. McCracken JT, McGough J, Shah B, et al. Rispidone in children with autism and serious behavioral problems. N Engl J Med. 2002;347(5):314-321.
19. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics. 2004;114:e634-e641.
20. McDougal CJ, Scahill L, Aman MG, et al. Risperidone for the core symptom domains of autism: Results from the study by the autism network of the research units on pediatric psychopharmocology. Amer J Psychiatry. 2005;162(6):1142-1148.
21. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. J Child Neurol. 2006;21(6):450-455.
22. Pandina GJ, Bossie CA, Youssef E, et al. Acute and long-term safety and tolerability of risperidone in children with autism. J Child Adolesc Psychopharmacol. 2007;17(3):367-373.
23. Miral S, Gencer O, Inal-Emiroglu FN, Baykara B, Baykara A, Dirik E . Risperidone versus haloperidol in children and adolescent with AD: A randomized, controlled, double blind trial. Eur Child Adolesc Psychiatry. 2008;17(1):1-8.
24. Hollander E, Wasserman S, Swanson EN, et al. A double-blind, placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. J Child Adolesc Psychopharmacol. 2006;16(5):541-548.
25. Cook S, Auinger P, Li C, Ford ES. Metabolic syndrome rates in United States adolescents, from the National Health and Nutrition Examination Survey, 1999-2002. J Pediatr. 2008;152(2):165-170.
26. D'Adamo E, Santoro N, Caprio S. Metabolic syndrome in pediatrics: old concepts revised, new concepts discussed. Pediatr Clin North Am. Oct 2011;58(5):1241-1255.
27. Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol. 2011;21(6):517-535.
28. Steinberger J, Daniels SR, Eckel RH, et al. Progress and challenges in metabolic syndrome in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular Nursing; and Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2009;119(4):628-647.
29. Jerrell JM, McIntyre RS. Adverse events in children and adolescents treated with antipsychotic medications. Hum Psychopharmacol. 2008;23(4):283-290.
30. Stahl SM, Mignon L, Meyer JM. Which comes first: atypical antipsychotic treatment or cardiometabolic risk? Acta Psychiatr Scand. 2009;119(3):171-179.
31. Yood MU, DeLOrenze GN, Quesenberry CP, et al. Association between second-generation antipsychotics and newly diagnosed treated diabetes mellitus: does the effect differ by dose? BMC Psychiatry. 2011;11:197.
32. Holt RIG, Peveler RC. Obesity, serious mental illness and antipsychotic drugs. Diabetes Obes Metab. 2009;11(7):665-679.
33. Starrenburg FCJ, Bogers JP. How can antipsychotics cause diabetes mellitus? Insights based on receptor-binding profiles, humoral factors and transporter proteins. Eur Psychiatry. 2009;24(3):164-170.
34. McIntyre RS, Jerrell JM. Metabolic and Cardiovascular Adverse Events Associated with Antipsychotic Treatment in Children and Adolescents. Arch Ped Adolesc Medicine. 2008;162(10):929-935.
35. Simon V, van Winkel R, DeHert M. Are Weight Gain and Metabolic Side Effects of Atypical Antipsychotics Dose Dependent? A literature Review. J Clin Psychiatry. 2009;70(7)1041:1050.
36. Zemrak WR, Kenna GA. Association of antipsychotic and antidepressant drugs with Q-T interval prolongation. Am J Health Syst Pharm. 2008;65(11):1029-1038.
37. Cysneiros RM, Terra VC, Machado HR, et al. May the best friend be an enemy if not recognized early. The possible role of omega-3 against cardiovascular abnormalities due antipsychotic treatment of autism. Arq Neuropsiquiatr. 2009(3-B):922-926.
38. Hasnain M, Vieweg WVR, Fredrickson SK. Metformin for atypical antipsychotic induced weight gain and glucose metabolism dysregulation. CNS Drugs. 2010;24(3):193-206.