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Implications of Marked Weight Gain Associated With Atypical Antipsychotic Medications in Children and Adolescents

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THE FINDINGS REPORTED BY CORRELL AND COLLEAGUES¹ in this issue of *JAMA* are both timely and sobering. Prior treatment-naive youth (N=272), aged 4 to 19 years, gained substantial weight during a 12-week period of clinician's choice treatment with atypical antipsychotic medications aripiprazole, olanzapine, quetiapine, or risperidone. The mean weight gain across treatment groups ranged from 8.5 kg with olanzapine to 4.4 kg with aripiprazole. More than half gained more than 7% of their total body weight. Significant abnormalities in lipid profiles and other metabolic parameters were also noted, especially with olanzapine. Comparison patients had minimal changes in body weight and lipid levels over the same period.

These data confirm prior findings that children and adolescents are highly vulnerable to antipsychotic medication-induced weight gain and metabolic adverse effects.²⁻⁴ The magnitude of weight gain is particularly concerning, as is the implication that metabolic adverse events may be underestimated in studies in which participants have had prior atypical antipsychotic medication exposure. Furthermore, the development of clinically significant hyperlipidemias and insulin resistance after only 12 weeks of treatment portends severe long-term metabolic and cardiovascular sequelae. These results challenge the widespread use of atypical antipsychotic medications in youth.

During the past decade, the use of antipsychotic medications in children and adolescents increased substantially in the United States.² From 2003 to 2004, approximately 1% of outpatient pediatric visits resulted in the prescription of an atypical antipsychotic medication.^{2,3,5} All the atypical antipsychotic medications, with the exception of clozapine, are commonly prescribed to youth for a variety of problems. Only 2 have current approval from the US Food and Drug Administration (FDA) for pediatric use: risperidone for irritability associated with autistic disorder, schizophrenia, and bipolar disorder; and aripiprazole for schizophrenia and bipolar disorder. In June 2009, the FDA Psychopharmacologic Drugs Advisory Committee voted to

approve quetiapine, ziprasidone, and olanzapine for schizophrenia and/or bipolar mania, but no formal action has been taken yet. Studies support the use of these medications for autism, schizophrenia, bipolar disorder, aggression, and tics.⁶⁻¹⁰ However, most of the trials in children and adolescents are short-term and have methodological limitations.

Schizophrenia is the best-supported indication for use of atypical antipsychotic medications. Atypical antipsychotic medications have been widely viewed as superior to traditional agents and are now almost universally used as antipsychotic medications of first choice. Yet, recent research challenges these assumptions. Large clinical trials in adults¹¹⁻¹³ do not support the superiority of atypical antipsychotic agents over traditional neuroleptics for schizophrenia. Moreover, regardless of medication choice, many patients do not continue the same treatment long-term due lack of efficacy, adverse effects, or nonadherence.

In the Treatment of Early-Onset Schizophrenia Spectrum Disorder (TEOSS) study⁷ risperidone and olanzapine were not superior to molindone, a traditional neuroleptic, in the acute treatment (8 weeks) of youth with schizophrenia spectrum disorders (N=119). Overall, less than 50% of participants achieved an adequate response to treatment. Weight gain was significantly greater with the atypical antipsychotic agents, so much so that the study's safety monitoring board stopped the olanzapine treatment group (mean [SD] weight gain, 6.1 [3.6] kg).

The sharp increase in atypical antipsychotic medication prescriptions coincides with the controversial increase in the number of children and adolescents diagnosed with bipolar disorder, including children younger than 5 years old.¹⁴ Atypical antipsychotic medication use in pediatric bipolar disorder is justified primarily based on the adult literature. However, the continuity between childhood and adolescent forms and adult-onset forms has not been established, especially for younger children.¹⁴ Pediatric mania overlaps significantly with disruptive behavior disorders. Medication treatment of bipolar disorder in youth often targets aggression and explosive behavior, raising questions of speci-

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See also p 1765.

ficity and the relative prioritizing of medications vs psychosocial interventions.

When first introduced, the atypical antipsychotic medications were widely touted as being more effective and safer than older neuroleptic agents. This perception undoubtedly eased physician reticence toward prescribing these medications for young patients. Prior to this time, traditional antipsychotic medications were much less commonly prescribed for disruptive behavior disorders.

These medications can be lifesaving for youth with serious psychiatric illnesses such as schizophrenia, classically defined bipolar disorder, or severe aggression associated with autism. However, given the risk for weight gain and long-term risk for cardiovascular and metabolic problems, the widespread and increasing use of atypical antipsychotic medications in children and adolescents should be reconsidered.

Pronounced weight gain early in life and significant changes in lipid profiles have ominous long-term health implications. Children and adolescents with mental health problems often have multiple risk factors, including poor nutrition, inadequate exercise, substance abuse, and lack of adequate health care monitoring. Consensus guidelines have been developed as to how patients should be monitored for the development of cardiometabolic adverse effects.¹⁵ To date, there are no data as to whether clinicians who prescribe these medications to children and adolescents regularly adhere to these guidelines or that fidelity to the monitoring recommendations lessens risk. Research is needed to establish whether dietary interventions or the addition of medications targeting obesity or glucose regulation (eg, metformin) mitigate metabolic adverse effects. A careful cost-benefit analysis needs to accurately gauge both short-term and long-term risks. Anticipating these risks is necessary because longitudinal data will not be available until a generation of children and adolescents who are exposed to these medications potentially experiences the metabolic consequences of their treatment.

Finally, much of the support for atypical antipsychotic agents is provided by industry-sponsored investigations. Recent congressional investigations and media scrutiny have raised concerns over the pharmaceutical industry's influence on prescribing practices. Medical treatment should be dictated by empirical data rather than by anecdote, assumptions, or marketing strategies. It is critical

that large-scale independently funded investigations be conducted to establish the long-term safety and benefit of atypical antipsychotic medications in children and adolescents. Until those data are available, consideration of less risky treatment interventions and scrupulous attention to metabolic parameters in children and adolescents who receive atypical antipsychotic medications are essential.

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