

## Largest Study of Antipsychotic Use in Youth Shows Impact on Weight and Metabolic Outcomes Even at Low Doses

The following is an extract of:

Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA*. 2009;302(16):1765-1773.

Corresponding author: Christopher Correll

### Bottom Line:

- Largest study to date to examine the metabolic impact of four second generation antipsychotics (olanzapine, quetiapine, risperidone and aripiprazole) in youth naïve to antipsychotic medication.
- Outcome measures included:
  - 8 weight metrics: weight (kg, % of baseline), fat mass, BMI (BMI, BMI% of baseline, BMI z score, BMI percentile), waist circumference
  - 6 lipid measures: ratio of triglycerides to HDL, total cholesterol, LDL, HDL, triglycerides, non-HDL cholesterol
  - 3 glucose measures: glucose, insulin, HOMA-IR
- Weight related outcomes: all were associated with significant increases, which were greatest for olanzapine, followed by quetiapine, risperidone and aripiprazole.
- Lipid related outcomes: significant elevations were more numerous for olanzapine (5 of 6 measures), and quetiapine (4 of 6 measures), but were less for risperidone (1 of 6 measures). Aripiprazole had no significant elevations of metabolic parameters (0 of 6 measures).
- Glucose related outcomes: Only olanzapine demonstrated significant changes (3 of 3 measures).
- Dosage analyses showed little to no difference in outcomes for lower vs. higher doses.
  - Olanzapine  $\leq 10$ mg: no difference in weight measures; less lipid elevation than  $>10$  mg/d.
  - Quetiapine: no difference in weight or lipid measures for lower vs. higher doses
- Risperidone  $\leq 1.5$ mg/d: less weight gain and lipid elevation than  $>1.5$ mg/d
- Aripiprazole: no difference in weight or lipid measures for lower vs. higher doses

This study looked at changes in weight-related and metabolic measures in youth newly exposed to the four most frequently prescribed second generation antipsychotics (SGAs) in this population. Results showed that first time exposure to antipsychotics, even at low dosages, is associated with significantly worsened weight-related metrics, while metabolic changes vary across medications. Only aripiprazole demonstrated no significant metabolic changes. Overall, lower doses versus higher doses were not protective for weight-related changes. Higher versus lower dose was only associated with weight-related changes for risperidone. Metabolic effects for aripiprazole and quetiapine were not different based on higher versus lower dose.

### Study Background

Weight gain and metabolic abnormalities experienced in youth, to which SGAs can contribute, can predict adult morbidity. Studies have shown youth to be vulnerable to antipsychotic-induced weight gain. Most past studies included subjects with variable prior antipsychotic exposure.

Since past exposure can complicate interpretation of side effect burden, data are needed on patients with no or minimal prior exposure to antipsychotics. The data in this study were collected as part of the Second-Generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth (SATIETY) study undertaken in Queens, New York, between December 2001 and September 2007. The SATIETY study was nonrandomized and looked at antipsychotic usage in pediatric psychotic, mood, or aggressive spectrum disorders.

### **Study Details**

This study lasted 12 weeks and included two groups: those naïve to one of four antipsychotic medications (aripiprazole, olanzapine, quetiapine or risperidone), and a comparison group composed of individuals who stopped antipsychotics within four weeks of starting. Selection of antipsychotic was deferred to the treating clinician. Fasting assessments were strictly reinforced and taken after  $\geq 8$  hours of fasting at baseline, 4, 8 and 12 weeks. Medication adherence was verified with interview and blood levels. Height was measured three times during the study. Outcomes included eight weight related metrics: weight in kg, weight percentage of baseline, fat mass, BMI, BMI percentage of baseline, BMI z scores, BMI percentile and waist circumference. Other outcomes included nine metabolic measures relating to lipid and glucose metrics: six lipid measures looked at ratio of triglycerides to HDL, total cholesterol, LDL, HDL, triglycerides and non-HDL cholesterol; three glucose measures looked at glucose, insulin, and HOMA-IR. Other analyses looked at incidence rates of weight gain of 7% or higher, individual metabolic parameters, dyslipidemia and the metabolic syndrome. Statistical analyses assessed within and across group differences. Due to observed large body weight changes, subsequent analyses were performed for changes in weight and BMI. Effects of age were explored by dichotomizing into post-pubertal vs. pre-pubertal groups. Dosage effects were explored by dichotomizing the median split of the maximum dosage after twelve weeks' treatment.

### **Results and Limitations**

Of 505 eligible subjects, 272 were able to be analyzed, with an untreated comparison group of 15. After a median of 10.8 weeks of treatment, weight increased by 8.5 kg with olanzapine, 6.1 kg with quetiapine, 5.3 kg with risperidone, and 4.4 kg with aripiprazole, with a minimal weight change of 0.2 kg in the comparison group. Each antipsychotic was associated with significantly increased fat mass, BMI, waist circumference and shifts to overweight or obese status. Olanzapine was associated with the widest array of metabolic abnormalities (significant in 5 of 6 lipid related and 3 of 3 glucose related parameters), followed by quetiapine (significant in 4 of 6 lipid related and 0 of 0 glucose related parameters). Risperidone was significantly associated with 1 of 6 lipid related (increased triglycerides) and 0 of 0 glucose related parameters. Aripiprazole was not significantly associated with any abnormal metabolic parameter. Pubertal status was unrelated to metabolic changes in any group.

Dosage was not associated with weight related changes in patients receiving aripiprazole, olanzapine or quetiapine. Risperidone doses  $\geq 1.5$  mg/d were associated with significantly greater increases in weight, waist circumference, fat mass, and changes in BMI. Olanzapine  $\geq 10$  mg/d and risperidone  $\geq 1.5$  mg/d were associated with significant increases in total cholesterol and non-HDL cholesterol. The metabolic effects of aripiprazole or quetiapine did not differ between lower and higher dosage.

Limitations include the nonrandomized and observational nature of the study; baseline differences that precluded rigorous group comparisons; flexible dosing; relatively short treatment duration; small comparison group; and not having a first generation antipsychotic comparator.

### **Clinical Implications**

All antipsychotics studied (aripiprazole, olanzapine, quetiapine and risperidone) were associated with rapid and significant increases in weight related metrics. Metabolic changes were less uniform. Olanzapine had the largest weight effects and significantly worsened 8 of 9 metabolic measures. The results for quetiapine also indicate broad metabolic effects. The fact that all antipsychotics showed significant adverse changes in weight related metrics, but that dosage failed to be associated with change in body composition for aripiprazole, olanzapine or quetiapine, indicates that these antipsychotics, even at lower dosages, can adversely affect body composition. The finding that higher dosage olanzapine was significantly associated with adverse metabolic changes but not adverse weight related metrics, suggests that olanzapine may affect metabolic parameters independent of changes in body composition. The authors emphasize weighing the benefits of antipsychotic medication against their cardiometabolic risks. They stress the importance of carefully considering lower-risk alternatives, especially given evidence of low rates of clinical and laboratory monitoring.

Drs. Correll, Manu, Kane, and Malhotra report being consultants and/or receiving honoraria from various pharmaceutical companies.