Metformin for the Treatment of Atypical Antipsychotic Mediated Weight Gain

Objectives:
1. Identify the potential for weight gain given an atypical antipsychotic.
2. Describe the mechanism of action of atypical antipsychotics and metformin.
3. Compare and contrast the available evidence for the treatment of atypical antipsychotic mediated weight gain with metformin.
I. Introduction\textsuperscript{1-2}
   a. Approximately 1.5-2 times higher prevalence of obesity in patients with schizophrenia and affective disorders as compared to the general population
      i. Few studies conducted in drug-naive subjects
      ii. Effects of psychiatric illness versus medication effects are difficult to evaluate
   b. Treatment with atypical antipsychotics can cause rapid weight gain within the first few months of treatment and weight may continue to increase for more than one year
      i. After 10 weeks of therapy, average increase in weight ranges from 0.5-5kg
      ii. Some patients will not experience a plateau in weight gain

II. Atypical Antipsychotics\textsuperscript{1-6}
   a. Mechanism of Action
      i. Moderate to high D\textsubscript{2} antagonism
         1. 60-65\% occupation of D\textsubscript{2} receptors is necessary to decrease positive psychotic symptoms
         2. Blockade of >77\% of D\textsubscript{2} receptors associated with extrapyramidal symptoms
         3. Transient blockade of D\textsubscript{2} receptors can be adequate to produce antipsychotic effect
         4. Rapid rate at which the antipsychotic dissociates from the D\textsubscript{2} receptor is associated with “atypicality”
      ii. High 5-HT\textsubscript{2A} antagonism
         1. 5-HT\textsubscript{2A} antagonism in combination with D\textsubscript{2} blockade causes release of dopamine in the prefrontal cortex
         2. Produces a decrease in negative symptoms and improves cognitive function

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>D\textsubscript{2}</td>
<td>EPS, prolactin elevation</td>
</tr>
<tr>
<td>M\textsubscript{1}</td>
<td>Cognitive deficits, dry mouth, constipation, increased heart rate, urinary retention, blurred vision</td>
</tr>
<tr>
<td>H\textsubscript{1}</td>
<td>Sedation, weight gain, dizziness</td>
</tr>
<tr>
<td>(\alpha\textsubscript{1})</td>
<td>Hypotension</td>
</tr>
<tr>
<td>5-HT\textsubscript{2A}</td>
<td>Anti-EPS (?)</td>
</tr>
<tr>
<td>5-HT\textsubscript{2C}</td>
<td>Satiety blockade</td>
</tr>
</tbody>
</table>

D=dopamine, EPS=extrapyramidal symptoms; M=muscarine; H=histamine; 5-HT=serotonin.

b. Comparison of Weight Gain Among Atypical Antipsychotic Agents
   i. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Schizophrenia Trial
      1. Designed to assess efficacy of second-generation antipsychotic agents
      2. Compared olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
<th>Ziprasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of patients gaining &gt;7% of body weight (%SWG)</strong></td>
<td>30%</td>
<td>14%</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td><strong>Weight change, mean (SE), lb/month</strong></td>
<td>9.4 (0.9)</td>
<td>0.8 (0.9)</td>
<td>1.1 (0.9)</td>
<td>-1.6 (1.1)</td>
</tr>
</tbody>
</table>

**CATIE Phase II (from baseline)**

<table>
<thead>
<tr>
<th></th>
<th>27%</th>
<th>13%</th>
<th>13%</th>
<th>6%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%SWG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight change, lb/month</strong></td>
<td>1.3 (1.1)</td>
<td>-0.2 (0.1)</td>
<td>0.1 (0)</td>
<td>-1.7 (-1.5)</td>
</tr>
</tbody>
</table>

**CATIE Phase III (from Phase III baseline to last observation)**

<table>
<thead>
<tr>
<th></th>
<th>23%</th>
<th>14%</th>
<th>16%</th>
<th>7%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%SWG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight change, mean (SD), lb/month</strong></td>
<td>1.0 (1.3)</td>
<td>-0.1 (2.2)</td>
<td>-0.4 (2.5)</td>
<td>-1.3 (2.6)</td>
</tr>
</tbody>
</table>

ii. Comparison of Atypicals in First Episode Psychosis (CAFE) study
   1. Analyzed metabolic side effects of patients randomized to receive olanzapine, quetiapine, or risperidone over 52 weeks
   2. Mean weight gain was significantly higher in patients receiving olanzapine (24.2 ± 1.9 lb) versus risperidone (14.0 ± 1.9 lb) and quetiapine (12.1 ± 1.8 lb), P <0.001

iii. Effect of Second Generation Antipsychotics on Weight Gain

| Relative Effect of Second Generation Antipsychotics on Weight Gain |
|-------------------------|------------------|-----------------|----------------|----------------|
|                         | Generic (Trade Name) | Weight Gain     |                |                |
|                         | Olanzapine (Zyprexa) | High            |                |                |
|                         | Clozapine (Clozaril) | High            |                |                |
|                         | Risperidone (Risperdal) | Moderate     |                |                |
|                         | Quetiapine (Seroquel) | Moderate       |                |                |
|                         | Asenapine (Saphris) | Low to Moderate |                |                |
|                         | Iloperidone (Fanapt) | Low to Moderate |                |                |
|                         | Ziprasidone (Geodon) | Low            |                |                |
|                         | Aripiprazole (Abilify) | Low           |                |                |
|                         | Paliperidone (Invega) | Low           |                |                |

III. Possible Mechanisms of Atypical Antipsychotic Mediated Weight Gain\textsuperscript{1,3,7-10}

a. Weight regulation is a complex balance of energy intake, expenditure, and storage driven by both central nervous system and endocrine mechanisms

i. Central Nervous System Drives
   1. Satiety – desire to limit further food intake after completing a satisfying meal
   2. Appetite – desire for food or drink
   3. Craving – an intense desire or longing

ii. Endocrine Actions
   1. Metabolism
   2. Energy utilization

iii. When energy ingestion is greater than energy expenditure, the imbalance leads to weight gain

b. Receptor Mediation of Neurotransmitters and Hormones

i. 5-HT\textsubscript{2C} Receptor
   1. Key regulator of appetite
   2. Increased serotonin (5-HT) in the synaptic cleft or direct activation of 5-HT\textsubscript{2C} receptors decreases food consumption
   3. Antagonism of 5-HT\textsubscript{2C} receptors induces the opposite effect

ii. Histamine-I (H\textsubscript{1}) Receptor
   1. Regulates arousal and appetite
   2. Antagonist of H\textsubscript{1} cause increased appetite and weight gain in humans and animals
   3. Binding studies show that sedation and weight gain in humans is proportional to an agent’s ability to block H\textsubscript{1} receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Ziprasidone</th>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Quetiapine</th>
<th>Clozapine</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>D\textsubscript{2}</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>5-HT\textsubscript{2A}</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>5-HT\textsubscript{2C}</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>5-HT\textsubscript{1A}</td>
<td>++++\textsuperscript{t}</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>++++\textsuperscript{t}</td>
</tr>
<tr>
<td>5-HT\textsubscript{1D}</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>\alpha\textsubscript{1}-adrenergic</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>M\textsubscript{1}-muscarnic</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>H\textsubscript{1}-histaminergic</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>5-HT/NE reuptake\textsuperscript{t}</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-5-HT\textsubscript{NE}</td>
<td>-5-HT\textsubscript{NE}</td>
<td>++ 5-HT\textsubscript{NE}</td>
</tr>
</tbody>
</table>

+++ = very high; +++ = high; ++ = moderate; + = low; = negligible; 5-HT = serotonin; NE = norepinephrine.
* Bovine binding affinity. \textsuperscript{t} Rat synaptosomes; all other affinities human. \textsuperscript{t} Partial agonist.

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iii. Leptin
   1. Member of the IL-6 cytokine family
   2. Secreted by white adipose cells
   3. Highly correlated with body fat mass and size of fat cells
   4. Regulates insulin secretion
   5. Regulates energy metabolism in fat cells and skeletal muscle
      a. Ensures the maintenance of adequate energy stores
      b. Guards against starvation
   6. Leptin deficiency in humans associated with early-onset obesity
   7. Obesity may be associated with malfunctioning leptin receptors termed *leptin resistance* because leptin is unable to generate an adequate response with receptor occupation

c. Poor Self Care
d. Sedentary Lifestyles
e. Unhealthy Dietary Habits

IV. Clinical Significance of Weight Gain

a. Mortality
   i. In a study of 1.46 million white adults with a follow-up period of 10 years, overweight and obesity were associated with increased all-cause mortality
   ii. Increased BMI is associated with increased all-cause mortality and death from cardiovascular disease
   iii. Annual number of excess deaths attributable to obesity may range from 111,909 to 365,000
   iv. In the upper BMI range (25-50 kg/m²), each 5 kg/m² increase in BMI was associated with a significant increase in mortality from ischemic heart disease, diabetes, non-neoplastic chronic kidney disease, neoplastic disease, and respiratory diseases
   v. Baseline risk of cardiovascular related mortality is increased in schizophrenic patients

b. Morbidity
   i. Obese and overweight individuals have a higher relative risk of hypertension, hypercholesterolemia, and diabetes mellitus compared with normal weight individuals
   ii. Higher prevalence of diabetes mellitus in schizophrenic patients as compared to non-schizophrenic patients

c. May lead to poor medication adherence

V. Metformin

a. Biguanide medication for type II diabetes mellitus
b. Mechanism of Action
   i. Reduces hepatic glucose production
   ii. Reduces intestinal glucose absorption
   iii. Increases insulin sensitivity
      1. Improved peripheral glucose uptake and regulation
   iv. Does not increase insulin secretion
Metformin for the Treatment of Antipsychotic Mediated Weight Gain  


<table>
<thead>
<tr>
<th>Purpose</th>
<th>To assess the efficacy of metformin in preventing olanzapine-induced weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, double-blind, placebo controlled trial</td>
</tr>
</tbody>
</table>
| Enrollment | • Patients 18-50 in their first psychotic episode of schizophrenia as diagnosed by DSM-IV  
   • All patients were hospitalized and remained so throughout the trial  
   • All patients were free of other antipsychotics or recreational drugs for 3 months prior to enrollment |
| Methods | • Participants randomly assigned to 12 weeks of therapy  
   o Olanzapine 15 mg/day + metformin 750 mg/day  
   o Olanzapine 15 mg/day + placebo  
   • Oral trihexyphenidyl for EPS or lorazepam for insomnia or agitation allowed as needed  
   • Assessments  
     o Baseline: demographics, medical history, physical examination, anthropometric measurements, lab work  
     o Scale for the Assessment of Positive Symptoms (SAPS)  
     o Scale for the Assessment of Negative Symptoms (SANS)  
     o Treatment Emergent Symptom Scale  
   • Follow-up visits at weeks 2, 4, 8, and 12 after randomization  
     o All baseline evaluations repeated at each visit  
     o SAPS and SANS repeated at week 12  
     o Lab work reevaluated at weeks 4, 8, and 12 |
| Outcomes | • Primary outcomes: changes of weight, BMI, WC, waist-to-hip ratio, fasting glucose, fasting insulin, proportion of patients who gained >7% of their baseline body weight at 3 months, and insulin resistance index  
   • Secondary outcomes: changes in SAPS and SANS scores and adverse effects |
| Statistics | • Means and standard deviation for continuous variables  
   • Frequencies and percentages for categorical variables  
   • Student’s t test and chi square analysis to evaluate between-group differences  
   • Analysis of covariance (ANCOVA) with repeated measurements  
   • Pearson’s correlation used to evaluate the relationship between initial BMI and body weight changes at 12 weeks  
   • Significance was accepted at p ≤ 0.05 |
| Results | • Forty patients entered the trial  
   o Three withdrew within the first 4 weeks due to lack of response  
   o Thirty-seven patients included in the study  
   o Treatment groups did not differ significantly between the groups  
     ▪ Patients approximately 25 YOA with a 7 year duration of illness  
     ▪ BMIs all within the normal range  
   • Mean weight and BMI values increased significantly between the two groups during weeks 2, 4, 8, and 12 |
Metformin for the Treatment of Antipsychotic Mediated Weight Gain

● Increases in weight and BMI in the olanzapine + placebo group were significantly greater relative to the olanzapine + metformin group.
● Significantly fewer patients in the metformin group (16.7%) compared with the placebo group (63.16%) increased their initial body weight by >7%.
● ANCOVA for all assessments found a significant group effect, including weight and BMI.
● Significant decrease in SAPS and SANS scores within each group from baseline to week 12.
● No between-group differences were found in changes from baseline in SAPS or SANS.
● Metformin was well-tolerated; nausea reported at similar rates in both groups.

Conclusions
● Statistically significant weight increases in the mean weight and BMI within the study groups at each follow-up visit.
● Increase in weight and BMI significantly less in the olanzapine + metformin group as compared to the olanzapine + placebo group.
● Significantly fewer patients in the olanzapine + metformin group increased baseline weight by >7% than the olanzapine + placebo group.
● Olanzapine was associated with substantial weight gain in schizophrenia patients beginning in the second week of treatment, and the addition of metformin was effective in lessening the olanzapine-induced weight gain in drug-naïve first-episode schizophrenia patients.
● The addition of metformin had no effect on the SAPS or SANS scores.

Strengths
● Randomized, blinded, and placebo controlled.
● Evaluated an strategy to attenuate weight gain rather than a reactive intervention.

Limitations
● Short study duration of only 12 weeks.
● No behavioral or nutrition interventions attempted.
● Patients were treated in an inpatient facility and received a standardized diet.
● No examination of olanzapine-metformin pharmacokinetic interactions.
● Metformin dosed TID which may not be beneficial for compliance.

### TABLE 2. Change in Weight and Body Mass Index in Patients With First-Episode Schizophrenia Randomly Assigned to 12 Weeks of Double-Blind Treatment With Olanzapine Plus Metformin or Olanzapine Plus Placebo

<table>
<thead>
<tr>
<th>Variable and Week</th>
<th>Olanzapine Plus Metformin (N=18)</th>
<th>Olanzapine Plus Placebo (N=19)</th>
<th>Between-Group Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (kg)</td>
<td>Mean (kg)</td>
<td>t</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>1.37±</td>
<td>1.49±</td>
<td>-0.122</td>
</tr>
<tr>
<td>Week 4</td>
<td>1.86±</td>
<td>2.13±</td>
<td>-0.216</td>
</tr>
<tr>
<td>Week 8</td>
<td>1.67±</td>
<td>5.14±</td>
<td>-2.573</td>
</tr>
<tr>
<td>Week 12</td>
<td>1.90±</td>
<td>6.87±</td>
<td>-2.861</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>0.41±</td>
<td>0.45±</td>
<td>-0.17</td>
</tr>
<tr>
<td>Week 4</td>
<td>0.53±</td>
<td>0.59±</td>
<td>-0.223</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.53±</td>
<td>1.92±</td>
<td>-2.882</td>
</tr>
<tr>
<td>Week 12</td>
<td>0.54±</td>
<td>2.26±</td>
<td>-3.063</td>
</tr>
</tbody>
</table>

*p<0.05.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>To assess prevention of body weight gain and metabolic dysfunction in schizophrenic patients treated with olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
</tr>
</tbody>
</table>
| Enrollment       | • Clinically stable inpatients with severe schizophrenia or schizoaffective disorders who were switching from conventional to atypical antipsychotics  
                    • Patients were free of other chronic diseases and hormone replacement therapy  
                    • Previous treatment with depot antipsychotics and conventional antipsychotics |
| Methods          | • Treatment Groups                                                                                             |
|                  |   • Olanzapine 10mg/day + metformin 850mg-1750mg/day                                                           |
|                  |   • Olanzapine 10mg/day + placebo                                                                              |
|                  |   • Depot antipsychotics maintained throughout the trial                                                        |
|                  |   • Balanced diet provided, but tobacco use, snacks, and physical exercise not controlled                      |
|                  | • Assessments                                                                                                  |
|                  |   • Reported at baseline and at weeks 7 and 14 under fasting conditions: body weight, BMI, WC, glucose, BPRS |
|                  |   • Reported at baseline and week 14: lipids, postload glucose levels, HOMA-IR                                    |
| Outcomes         | • Primary outcome: body weight gain                                                                            |
| Statistics       | • Two-tailed t tests for unpaired and paired samples for between- and within-group comparisons, respectively   |
|                  |   • Bivariate correlations calculated between BPRS scores, anthropometric variables, and chemical variables  |
|                  |   • Significance was accepted at p ≤ 0.05                                                                      |
| Results          | • 37 subjects completed the study                                                                             |
|                  |   • Average age was approximately 47 years and average length of treatment was approximately 30 years          |
|                  |   • Groups were similar at baseline and did not differ significantly on any variable                           |
|                  |   • Mild gastrointestinal discomfort was the main side effect of metformin; however, the highest dosage was well-tolerated by all patients |
|                  |   • Body weight increased similarly in the metformin group and the placebo group                               |
|                  |   • At week 14, the mean body weight gain increase was 5.5±3.3 kg in the metformin group and 6.3±2.3 kg in the placebo group, which was not significantly different between groups |
|                  |   • BMI and WC increased significantly within both groups but there were no between-group differences        |
| Conclusions      | • Metformin did not prevent increases in body weight gain or waist circumference                               |
|                  | • Metformin displayed a positive metabolic effect that appears dissociated from its ability to prevent body weight gain |
|                  | • Metformin was well tolerated and did not interfere with clinical improvement                                 |
## Metformin for the Treatment of Antipsychotic Mediated Weight Gain

### Strengths
- First double-blind, placebo-controlled study of metformin for this indication

### Limitations
- Patients received a relatively low dose of olanzapine
- Short study period of only 14 weeks
- No description of dose titration or adverse effects
- Sample may not represent most patients with schizophrenia who are taking atypical antipsychotic drugs

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### Purpose
To evaluate the effectiveness of metformin in managing weight gain in children and adolescents who had experienced weight gain with an atypical antipsychotic

### Design
Randomized, double-blind, placebo controlled trial

### Enrollment
- Patients were aged 10-17 years who had gained >10% of their predrug weight during treatment with olanzapine, risperidone, or quetiapine

### Methods
- Treatment
  - Given 500mg capsule containing metformin or placebo at the evening meal for 1 week
  - Second metformin/placebo dose added before breakfast
  - Dose increased to 850mg given with breakfast and supper after the second week and continuing through week 14
- Assessments
  - Performed at baseline and weeks 4, 8, 12, and 16
  - Anthropometric measurements and reports of side effects or adverse events collected at each visit
- Nutrition counseling provided by a registered dietitian at weeks 4, 8, and 12

### Outcomes
- Primary outcome: prevention of further weight accumulation from atypical antipsychotics with metformin

### Statistics
- For a power of 0.90 and alpha of 0.05, 9 children would need to be enrolled in each treatment modality
- Chi-square test with 1 degree of freedom utilized for categorical variables
- Continuous variables assessed with analysis of variance with least squares means
- Student’s t tests used to detect differences in anthropometric measurements
- Significance was accepted at p ≤ 0.05

### Results
- 39 subjects enrolled in the trial; 38 subjects randomized to treatment
  - Higher proportion of African Americans in the placebo group
  - Patients were approximately 13 YOA and of Caucasian race
  - Mean weight gain after initiation of atypical antipsychotic therapy prior to study entry was 9.4±7.5 kg in the metformin group and 10.8±6.8 kg in the placebo group
- Study discontinuation
  - Three dropouts in the metformin group; five dropouts in the placebo group
<table>
<thead>
<tr>
<th>Conclusions</th>
<th>Strengthened</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statistically significant difference in the number of dropouts between</td>
<td>Adequately powered to detect</td>
<td>Small sample size</td>
</tr>
<tr>
<td>groups</td>
<td>a statistical difference</td>
<td></td>
</tr>
<tr>
<td>No serious adverse events resulted from metformin treatment</td>
<td>Randomized, double-blind,</td>
<td>Short study duration</td>
</tr>
<tr>
<td>Percentage of subjects reporting adverse events did not differ significantly</td>
<td>and placebo controlled</td>
<td>Variety of diagnoses included</td>
</tr>
<tr>
<td>The number of adverse events reported by the metformin group and placebo</td>
<td></td>
<td>Single dose of metformin utilized in patients with varied body composition</td>
</tr>
<tr>
<td>Weight Change</td>
<td></td>
<td>Difficulty with compliance for study subjects</td>
</tr>
<tr>
<td>Placebo subjects continued to gain weight (4.01±6.23 kg) while patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in the metformin group experienced little change over the treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>period (-0.13±2.88 kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differences between the mean values were significant at all follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>visits</td>
<td></td>
<td></td>
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<tr>
<td>The mean BMI decreased by 0.43±1.07 in the treatment group versus an increase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of 1.12±2.02 in the placebo group which was statistically significant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**

- Children treated with placebo continued to gain weight despite family dietary counseling
- Weight stabilization was associated with metformin content
- Medication therapy with metformin results in decreased weight accretion and insulin resistance in patients receiving atypical antipsychotics
- Metformin treatment is well tolerated in children and adolescents

**Strengths**

- Adequately powered to detect a statistical difference
- Randomized, double-blind, and placebo controlled

**Limitations**

- Small sample size
- Short study duration
- Variety of diagnoses included
- Single dose of metformin utilized in patients with varied body composition
- Difficulty with compliance for study subjects
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Purpose</strong></td>
</tr>
<tr>
<td><strong>Design</strong></td>
</tr>
</tbody>
</table>
| **Enrollment** | - Adult inpatients and outpatients that were informed about the risk of excessive body weight gain and metabolic dysfunction during olanzapine administration  
- Free of chronic medical disease besides the mental disorder and free from hormone replacement therapy  
- Patients under olanzapine monotherapy for >4 months and willing to lose weight or prevent excessive weight gain |
| **Methods** | - Patients randomly assigned to metformin or placebo treatment  
  - Metformin dose range was 850mg – 2250mg per day based on individual tolerance to gastrointestinal discomfort  
  - Each patient provided with a 2-week supply of medication and was contacted weekly via telephone to assess for side effects  
  - Assessments at baseline and week 12: BPRS, body weight, BMI, WC, glucose, insulin, lipids, leptin, cortisol, growth hormone, fibrinogen, c-reactive protein, and glycated hemoglobin |
| **Outcomes** | - Primary outcome: weight loss (body weight, BMI, WC)  
  - Secondary outcomes: glucose, insulin, lipids, leptin, cortisol, growth hormone, fibrinogen, c-reactive protein, glycated hemoglobin, and HOMA-IR |
| **Statistics** | - Data normality estimated with one-sample Kolmogorov-Smirnov test and Levene’s test for the equality of variances  
  - Within- and between-group comparisons conducted with two-tailed t tests for related and unrelated samples, respectively  
  - Bivariate correlation analysis conducted with the Pearson and Spearman coefficients  
  - Frequencies analyzed with a chi square test  
  - Significance was accepted at p ≤ 0.05 |
| **Results** | - Mild gastrointestinal discomfort was the only notable side effect with metformin and was managed with dose reduction  
  - Seventy two of eighty subjects competed the study  
  - Anthropometric Variables  
   - The metformin lost 1.40±3.2 kg (p=0.01) after 12 weeks of therapy while the placebo group lost 0.18±2.8 kg (p=0.7)  
   - The comparison of weight loss between the placebo group and the metformin group was not significant (p=0.09)  
   - A significant decrease in BMI was demonstrated with metformin (p=0.01) but not with placebo (p=0.6)  
   - There was no significant between group difference in BMI (p=0.1)  
  - Biochemical Variables  
   - Leptin levels decreased after metformin (p=0.09) but remained stable after placebo (p=0.5) |
Cortisol levels tended to increase in both groups (metformin, p=0.051, placebo, p=0.1)  
Growth hormone levels assessed at the end of the study did not differ between groups (p=0.4)  
Intergroup analysis reached marginal significance for lepton (p=0.07), but between group comparisons were non-significant for cortisol levels (p=0.3)

**Conclusions**
- The body weight decrease after metformin may be relevant in comparison to the lack of change in the placebo group  
- In a heterogeneous psychiatric population, metformin induced a small but significant body weight loss after 12 weeks

**Strengths**
- Randomized and placebo controlled  
- Clearly defined, objective outcomes

**Limitations**
- Short trial duration of only 12 weeks  
- Heterogeneous population  
- Patients highly motivated to prevent or lose excess weight  
- Few patients with a BMI >30 kg/m²

### Table 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Basal</th>
<th>Week 12</th>
<th>Δ</th>
<th>Within group t test</th>
<th>Between group t test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td>Metformin (n=36)</td>
<td>66.2±14.6</td>
<td>64.8±14.6</td>
<td>−1.40±3.2</td>
<td>2.6, p=0.01</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=36)</td>
<td>65.6±16.9</td>
<td>65.4±17.7</td>
<td>−0.18±2.8</td>
<td>0.4, p=0.7</td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>Metformin (n=36)</td>
<td>89.6±12.2</td>
<td>89.5±11.8</td>
<td>−0.1±5.9</td>
<td>0.1, p=0.9</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=36)</td>
<td>91.3±13.0</td>
<td>91.8±13.3</td>
<td>0.50±5.6</td>
<td>0.4, p=0.6</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td>Metformin (n=36)</td>
<td>25.0±4.9</td>
<td>24.5±4.9</td>
<td>−0.47±1.2</td>
<td>2.5, p=0.01</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=36)</td>
<td>26.1±5.7</td>
<td>26.0±5.7</td>
<td>−0.07±1.1</td>
<td>0.4, p=0.6</td>
</tr>
</tbody>
</table>

*Values represent mean±standard deviation.*

**Wu R, et al. Lifestyle Intervention and Metformin for Treatment of Antipsychotic-Induced Weight Gain: A Randomized Controlled Trial. JAMA 2008; 299: 185-193.**

**Purpose**
To test the efficacy of lifestyle intervention and metformin alone and in combination for antipsychotic-induced weight gain and insulin sensitivity

**Design**
Randomized, placebo controlled trial

**Enrollment**
- Patients 18-45 years of age with a first psychotic episode of schizophrenia as diagnosed by DSM-IV  
- Gained >10% of pre-drug body weight during the first year of antipsychotic treatment (clozapine, olanzapine, risperidone, or sulpiride)  
- Discharged from inpatient units or first seen in the clinic in the 12 months before enrollment to document weight and antipsychotic treatment  
- Stable improvement (total score of the Positive and Negative Symptom Scale [PANSS] ≤ 60)  
- Taking only 1 antipsychotic agent at a stable dose  
- Excluded if evidence of liver or renal dysfunction, cardiovascular disease, diabetes mellitus, currently pregnant or lactating, unable to perform lifestyle modifications, psychiatric diagnosis other than schizophrenia, or history of substance abuse
**Methods**

- All patients under the care of their parents or an adult caregiver to monitor and record food intake, exercise activity, and medication intake
- Patients randomized to treatment group for 12 weeks
  - Metformin (750 mg/day) alone
  - Placebo alone
  - Lifestyle intervention + metformin (750 mg/day)
  - Lifestyle intervention + placebo
- Pharmacological Intervention
  - Participants took 250mg/day with evening meal for 4 days
  - A 250mg dose before breakfast and lunch added for the following 80 days
  - Antipsychotic remained at a fixed dose throughout the trial
  - Adherence to metformin treatment defined as taking >80% of the study drug dosage prescribed for that interval
- Lifestyle Intervention
  - Psychoeducational program focused on weight management through diet and exercise
  - American Heart Association step 2 diet prescribed for dietary intervention and patients maintained a 3-day food record before each follow-up visit
  - Exercise sessions were directed during the first week by an exercise physiologist, after which sessions were home based without investigator supervision
  - Patients and therapists developed individual programs that ranged in the level of intensity from light to vigorous
- Assessments
  - Baseline: demographics, comprehensive medical history, physical examination, anthropometric measurements, PANSS, Treatment Emergent Symptom Scale (TESS), fasting glucose and insulin, lactic acid, liver and renal function, blood counts, and electrocardiogram
  - Follow-up visits: physical examination, anthropometric measurements, laboratory examinations, and TESS
  - PANSS and lipid levels reevaluated at week 12
  - Branching treadmill tests at 4, 8, and 12 weeks compared with baseline

**Outcomes**

- Primary: changes of weight, BMI, waist circumference, fasting glucose, fasting insulin level, and insulin resistance index
- Secondary: change in PANSS total scores and adverse effects

**Statistics**

- Analyses to compare treatments performed separately for patients completing treatment and randomized patients with at least 1 follow-up test using intent-to–treat analysis using last observation carried forward
- Means and 95% confidence intervals used for continuous variables
- Frequencies and percentages used for categorical variables
- ANOVA utilized to compare all continuous variables
- $\chi^2$ used for categorical variables
- Analysis of covariance used for follow-up data with corresponding baseline values as covariates
• Omnibus testing used to compare the difference among the 4 treatment groups, and when analyses revealed statistically significant differences, least-significant-difference procedure was applied post hoc
• Pearson correlation used to assess the relationship between initial body weight and weight loss at 12 weeks
• Significance was accepted at $p \leq 0.05$

**Results**

• There were 128 eligible patients who were assigned randomly to each of the 4 groups; 118 patients completed the 12-week treatment
• Demographic characteristics and baseline measurements did not differ significantly among groups
• There were no group differences in metformin treatment and lifestyle intervention adherence
• Patients in the placebo group continued to gain weight by 4.8% compared with baseline over the 12-week study period (mean 3.1 kg; 95% CI, 2.4-3.8 kg)
• Weight decreased in the treatment groups
  o Lifestyle + metformin by 7.3% (mean 4.7 kg; 95% CI, 3.4-5.7 kg)
  o Metformin alone by 4.9% (mean 3.2 kg; 95% CI, 2.5-3.9 kg)
  o Lifestyle + placebo by 2.2% (1.4 kg; 95% CI, 0.7-2.0 kg)
• BMI increased in the placebo group by a mean of 1.2 (95% CI, 0.9-1.5)
• BMI decreased in the treatment groups
  o Lifestyle + metformin by 1.8 (95% CI, 1.3-2.3)
  o Metformin alone by 1.2 (95% CI, 0.9-1.5)
  o Lifestyle + placebo by 0.5 (95% CI, 0.3-0.8)
• No significant correlations between initial weight and weigh changes at 12 weeks
• Specific pairwise comparisons of the treatments indicate
  o Lifestyle + metformin was significantly superior to metformin alone, lifestyle + placebo, and placebo alone on weight, BMI and waist circumference
  o Metformin alone was significantly superior to lifestyle + placebo and placebo alone on weight, BMI, and waist circumference
  o Lifestyle + placebo was significantly superior to placebo on weight, BMI, and waist circumference
• No significant differences in the frequency and types of adverse effects reported among 4 treatment groups

**Conclusions**

• Lifestyle intervention and metformin alone and in combination can improve the weight gain induced by antipsychotic medications
• Lifestyle intervention + metformin could be most effective in reversing the weight gain induced by antipsychotic agents in patients with schizophrenia while metformin alone has the same effect on insulin sensitivity as lifestyle intervention + metformin
• Metformin treatment is safe and well tolerated in patients with schizophrenia
• Lifestyle intervention, metformin alone, or their combination could be added to attenuate antipsychotic induced weight gain in patients with schizophrenia
Lifestyle intervention + metformin should be considered first for those with weight gain.
If lifestyle intervention is not tolerated or adherence is poor, then metformin alone should be considered.

**Strengths**
- Power calculations provided
- Combination of diet, exercise, and pharmacotherapy for weight gain

**Limitations**
- Short trial duration
- No assessment of the relative contributions of different components of lifestyle intervention
- No measurement of appetite change
- Treatment adherence based on self-report
- Enrolled patients under the care of parents or adult caregivers
- Low doses of antipsychotics
- Fixed dose of metformin does not allow for study of dose effect
- Results may not be generalizable to Western populations
- Patients generally young, early in illness, and not obese
- Exercise intensity variable among patients

<table>
<thead>
<tr>
<th>Assessment Levels</th>
<th>Mean (95% CI)</th>
<th>Lifestyle + Metformin</th>
<th>Metformin</th>
<th>Lifestyle</th>
<th>Placebo</th>
<th>ANCOVA&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Lifestyle vs Metformin</th>
<th>Lifestyle vs Placebo</th>
<th>Metformin vs Placebo</th>
<th>Metformin vs Lifestyle</th>
<th>Metformin vs Placebo</th>
<th>Metformin vs Lifestyle</th>
<th>Metformin vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>-4.7 (-5.7 to -3.4)</td>
<td>-3.2 (-3.9 to -2.5)</td>
<td>-1.4 (2.0 to -0.7)</td>
<td>3.1 (2.4 to 3.8)</td>
<td>p &lt; .001</td>
<td>.02</td>
<td>.01</td>
<td>&lt; .004</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-1.8 (-2.9 to -1.3)</td>
<td>-1.2 (-1.5 to -0.9)</td>
<td>-0.5 (0.8 to -3.3)</td>
<td>1.2 (0.0 to 1.5)</td>
<td>p &lt; .001</td>
<td>.01</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>-2.0 (-2.4 to -1.5)</td>
<td>-1.3 (-1.5 to -1.1)</td>
<td>-0.1 (0.5 to -0.7)</td>
<td>2.2 (1.7 to 2.8)</td>
<td>p &lt; .001</td>
<td>.03</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>-10.9 (-10.6 to -5.4)</td>
<td>-10.8 (-15.2 to -7.2)</td>
<td>-9.0 (-9.9 to -3.9)</td>
<td>1.8 (-1.8 to 3.6)</td>
<td>p &lt; .001</td>
<td>.08</td>
<td>.48</td>
<td>.006</td>
<td>.04</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin, µU/ml</td>
<td>-15.0 (-17.1 to -10.8)</td>
<td>-12.7 (-15.8 to -10.2)</td>
<td>-4.3 (-6.3 to -1.0)</td>
<td>2.7 (1.0 to 3.3)</td>
<td>p &lt; .001</td>
<td>.80</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>-3.6 (-4.5 to -2.7)</td>
<td>-3.5 (-4.4 to -2.7)</td>
<td>-3.5 (-1.5 to -0.5)</td>
<td>0.4 (0.1 to 0.7)</td>
<td>p &lt; .001</td>
<td>.88</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ANCOVA, analysis of covariance. BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; RI, insulin resistance index.

<sup>b</sup> P value for the omnibus analysis: testing for overall difference between the 4 treatment groups on the continuous variables is based primarily on ANCOVA with baseline levels of the variables as covariates. When the overall omnibus analysis P value was significant, then pair-wise comparisons were performed.
VI. Proposed Treatment Guidelines\textsuperscript{1,19}

\textbf{a. Suggested Treatment Algorithm}

\begin{itemize}
\item Discuss risks of atypical antipsychotic therapy to include significant weight gain and metabolic abnormalities
\item Provide nutritional and physical activity counseling for patients overweight or obese at baseline
\item If a patient gains \( \geq 5\% \) of his or her initial body weight at any point during therapy, then consider selection of an alternative atypical antipsychotic with a lower potential for weight gain
\item In situations where selection of an alternative antipsychotic is unacceptable or a patient is reluctant to change
  \begin{itemize}
  \item Nutritional and physical activity counseling should be provided
  \item Referral to health care professionals (e.g. nutritionist, physical therapist, endocrinologist, etc.) or programs with an emphasis in weight management should be considered
  \end{itemize}
\item Evaluate patient for contraindications or precautions to the use of metformin and for current pharmacotherapy that may interact with metformin
\item Metformin appears to be a safe option that may lead to attenuation or reversal of weight gain and may add to the benefits received from healthy lifestyle changes
\end{itemize}

\textbf{e. Point system has been proposed for metformin therapy}

\textbf{i. Group of physicians from Canada and the United States}

1. Reviewed literature with a focus on the effect of metformin on antipsychotic-induced weight gain and glucose/insulin metabolism dysregulation
2. Reviewed the use of metformin for overweight and insulin resistance in the general population

\textbf{ii. Rationale}

1. BMI and WC are the most commonly used surrogate measures of adiposity
2. WC is a superior predictor of diabetes risk compared to BMI
3. Excess WC is a cardiovascular risk factor
4. Hyperglycemia increases the risk for diabetes and atherosclerotic cardiovascular disease
5. Patients with hyperglycemia are considered pre-diabetic
   iii. Patients with a total score of >4 points are considered candidates for a trial of metformin

<table>
<thead>
<tr>
<th>Features</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline features</strong></td>
<td></td>
</tr>
<tr>
<td>Family history of diabetes mellitus or cardiovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Current BMI within normal range (18.5-24.9 kg/m²) but previous history of overweight or obesity</td>
<td>1</td>
</tr>
<tr>
<td>Current overweight (BMI 25.0-29.9 kg/m²)</td>
<td>2</td>
</tr>
<tr>
<td>Current class I obesity (BMI 30.0-34.9 kg/m²) OR current WC ≥ 102 cm form men and ≥ 88 cm form women irrespective of BMI</td>
<td>3</td>
</tr>
<tr>
<td>Current class II/class III obesity (BMI ≥ 35 kg/m²)</td>
<td>4</td>
</tr>
<tr>
<td>Current hyperglycemia OR impaired glucose tolerance</td>
<td>5</td>
</tr>
<tr>
<td><strong>Features developing after initiation of antipsychotic therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Progression from normal BMI at baseline to overweight</td>
<td>2</td>
</tr>
<tr>
<td>Progression from normal BMI or overweight at baseline to class I obesity OR an increase in WC to WC ≥ 102 cm form men and ≥ 88 cm form women irrespective of BMI</td>
<td>3</td>
</tr>
<tr>
<td>Progression from normal BMI or overweight at baseline to class II/class III obesity</td>
<td>4</td>
</tr>
<tr>
<td>New-onset hyperglycemia OR impaired glucose tolerance</td>
<td>5</td>
</tr>
</tbody>
</table>

*Suggested BMI values for Asians are: overweight ≥ 23.0 to 24.9, obesity ≥ 25.0; and for WC are: >90 cm for men and >80 cm for women
*International Diabetes Foundation defines central obesity for European male individuals as WC ≥ 94 cm and ≥ 80 cm for female individuals
References