

# Dopamine, Striatum, Antipsychotics, and Questions About Weight Gain

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**For decades, psychiatrists worried** about the adverse motor effects of antipsychotics and tried to understand what caused them and why some patients developed them and others did not. In the late 1990s, the game changed. The new atypical antipsychotics caused fewer adverse motor effects but caused more weight gain. At present, a large number of patients with schizophrenia experience a clinically important (>7%) weight increase after starting therapy with an antipsychotic. This weight gain contributes to type 2 diabetes mellitus, dyslipidemia, and hypertension, which increase the risk for cardiovascular events. What causes this weight gain? Why do some patients gain weight and others not?



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Some drugs clearly are more likely to induce weight gain (eg, olanzapine, quetiapine fumarate, and clozapine) than others (eg, ziprasidone and lurasidone hydrochloride).<sup>1</sup> The reason for these differences is not known for certain, but the serotonin<sub>2C</sub> receptors and the H<sub>1</sub> receptors are often implicated.<sup>2</sup> However, no drug is completely free of a weight gain effect, and none causes weight gain in every patient. Why some patients are more susceptible than others remains largely unexplained. Previous studies have explored the genetic reasons for individual susceptibility,<sup>3</sup> and others have explored diet and lifestyle predictors. In this issue of *JAMA Psychiatry*, Nielsen and colleagues<sup>4</sup> report on a study exploring the association between brain activity in the striatum during reward anticipation and antipsychotic-induced weight gain.

Dopamine is known to be one of the key agents for food reward and control of food intake.<sup>5</sup> Dopamine is also central to schizophrenia and to antipsychotic action. Furthermore, in a healthy population, a reduction in the dopaminergic striatal response has been shown to be an important contributor to weight increase and obesity<sup>6</sup> and is one of the pillars of the reward-deficiency hypothesis of obesity. Therefore, we may hypothesize that differences in baseline function related to dopamine and striatal activity account for the variability in antipsychotic-induced obesity.

Nielsen and colleagues<sup>4</sup> report on an important study in this direction. They recruited patients with first-episode schizophrenia who were antipsychotic naive and treated them with amisulpride for 6 weeks. Amisulpride is a relatively selective dopamine D<sub>2</sub> receptor antagonist antipsychotic used widely in Europe (although not available in the United States). Amisulpride is relatively selective for dopamine D<sub>2</sub> receptor, unlike the other atypical antipsychotics (eg, risperidone, olanzapine, and quetiapine); therefore, the weight gain as a conse-

quence of amisulpride helps rule out the contribution of other neurotransmitter systems (serotonin and histamine) conventionally associated with weight gain. To measure striatal activity, the investigators asked the patients to perform a reward task while undergoing functional magnetic resonance imaging. The task required the patient to react to a visual stimulus to win or to avoid losing a monetary reward. This paradigm allows a detailed examination of the different stages of reward processing, such as the reward anticipation and consumption. Although the task was not specifically designed to assess the striatal response to food, it provides a general measure of striatal response to a rewarding stimulus. The authors were able to assess the relationship of antipsychotic-related weight gain with the baseline (before treatment) level of striatal activity and its change during the 6 weeks of treatment.

The authors found a significant association between baseline striatal activity and subsequent weight gain during antipsychotic treatment. Patients with lower baseline reward activity in the right-sided putamen had the most pronounced weight gain. After 6 weeks of amisulpride treatment, those patients with the most weight gain showed the greatest change (increase) in right-sided putamen striatal activity.

At first glance, the results are straightforward. Those with low baseline striatal activity (and hence putative reward deficiency) gained more weight when treated with an antipsychotic; this result is associated with the subsequent normalization of their striatal signaling. However, on closer inspection, the implications are more complicated. If baseline reward deficiency is what drives the weight gain, one would assume that this deficiency should have existed before the first functional magnetic resonance imaging investigation. One must wonder why those patients had not put on weight already. One could argue that the antipsychotic (a dopamine antagonist) served as a trigger to weight gain, but reconciling that argument with the well-described finding of weight increase after dopaminergic agonist medication therapy, such as that seen in patients with Parkinson disease, is difficult.<sup>7</sup>

Other complex factors are likely at play. Recent data suggested that antipsychotic-induced weight gain has a high genetic contribution,<sup>3</sup> although none of the single-nucleotide polymorphisms identified in genome-wide association studies have implicated the dopaminergic pathway, which suggests that alternative biological mechanisms are involved. Furthermore, in this study, the weight gain was induced by amisulpride, a dopamine-selective antipsychotic. How this finding translates to antipsychotics, which act on multiple transmitters, has not been determined. Finally, antipsychot-

ics act on neurotransmitters but are known to affect the neuroendocrine network that controls food intake, such as insulin, ghrelin, and orexin. The complex relationship among genes, neurotransmitters, hormones, neuropeptides, and lifestyle habits is largely unknown and is likely the basis of the inter-individual variability.

In summary, this interesting new study reports an index of striatal function that correlates with weight gain after the

use of a relatively selective dopamine blocker. The study is to be commended for its ability to find antipsychotic-naïve participants, provide longitudinal follow-up, and use a selective antipsychotic. Although the effect size is too small for the findings to be used for individual prediction in the clinic, the link to the reward-deficiency hypothesis of obesity provides a central piece of what is likely a rather complex puzzle.

#### ARTICLE INFORMATION

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