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## Weighty Issues in 2007

*Researchers examined weight gain: psychiatric patients' propensities, molecular mechanisms, and potential treatments.*

The U.S. epidemic of obesity and diabetes holds special meaning for psychiatrists because their patients seem particularly at risk and because many psychotropic medications have metabolic effects. In October, the Food and Drug Administration mandated changes to the label for olanzapine to warn of its associations with increased levels of glucose, cholesterol, and triglyceride levels. This past year saw several studies clarifying these issues.

[One research group](#) followed weight gain in 98 patients with first-episode schizophrenic or affective psychosis (91 were initiating antipsychotic treatment). A significantly higher percentage of atypical-antipsychotic recipients than of older-neuroleptic recipients experienced at least 7% weight gain at 1 year (mean weight gain: olanzapine, 37 lb; risperidone, 17 lb; haloperidol, 9 lb; perphenazine, 3 lb).

Some weight-related research might augur psychiatric pharmacogenomics, allowing clinicians to identify patients who are likely to gain weight when taking certain medications. In an [animal study](#), the binding of antipsychotic drugs to histamine H<sub>1</sub> receptors paralleled their likelihood of increasing appetite. Clozapine and olanzapine, both strongly associated with weight gain, increased hypothalamic AMP-kinase, which regulates food intake through H<sub>1</sub> receptors. Atypical antipsychotics might increase appetite and therefore weight gain through this mechanism, which could become a target for treatment. Other receptors might be involved in antipsychotic-induced weight gain. Increased waist circumference, a core component of the metabolic syndrome, was associated with [three polymorphisms of the serotonin 2C receptor gene](#).

Eating more, especially foods that pack a lot of calories into a small volume, is undoubtedly one mechanism of medication-associated weight gain. [Animals given high-fat foods](#) showed increased expression of striatal FosB, an early gene product involved in reward signaling. After withdrawal of high-fat or high-carbohydrate foods, animals showed stress responses mimicking those seen after withdrawal from substances that cause physical dependence. Animals also endured an aversive environment to obtain high-fat foods. Any strategy to prevent or treat weight gain must involve an appreciation of the potent effect of food on reward mechanisms.

How obesity and diet contribute to glucose intolerance and hyperlipidemia was also examined in 2007. In an [animal study](#), a sensory neuron altered insulin sensitivity through actions on inflammatory cells that attack pancreatic  $\beta$  cells. Other researchers identified an obesity pathway in mice; chronic stress and a palatable high-fat diet, mediated through the glucocorticoid system, increased levels of the sympathetic neurotransmitter neuropeptide Y to promote growth of adipose tissue and consequently obesity and the metabolic syndrome ([Nat Med Jul 13; 13:803](#)). Pharmacologic and, possibly, behavioral approaches to diabetes might eventually aim at the initial inflammatory response.

Metformin, used to treat type 2 diabetes, has been advocated as a potential adjunct to reduce medication-associated weight gain and glucose intolerance. [In a 16-week, randomized, controlled trial](#) in 38 juvenile patients who had gained at least 10% of their weight in less than a year of atypical-antipsychotic treatment, weight was stable or decreased with metformin but increased with placebo (glucose tolerance did not differ between

groups). However, in a [12-week study](#) of 80 adult patients being treated with olanzapine, metformin was not significantly better than placebo in promoting weight loss (or reducing insulin resistance). Metformin was well tolerated in both of these short-term studies, but it has serious potential risks. It might be safer to address diet and activity before starting a drug that is likely to cause weight gain rather than to try treating the problem once it occurs.

Rimonabant, a cannabinoid type 1 receptor antagonist that promotes weight loss, would seem to be a useful adjunctive medication when weight gain complicates an otherwise effective treatment. In a [meta-analysis](#) of four placebo-controlled trials in 4105 obese patients without a psychiatric history, rimonabant recipients did achieve weight loss but also had elevated anxiety and drop-out rates because of treatment-emergent depression and anxiety. Although these effects were not severe, they would be important in psychiatric patients who are already anxious or depressed.

Until cost-effective tests are developed for factors that increase the risk for weight gain and metabolic changes, and until well-tolerated, reliable treatments are available for this major side effect, all patients taking antipsychotic drugs should be warned of the risk, and dietary interventions should be instituted before, rather than after, weight gain begins.

— [Steven Dubovsky, MD](#)

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