New Psychotropics, Serotonin, and Weight Gain: *Looking for Answers*

Norman Sussman, MD  e-mail: ns@mblcommunications.com

One common denominator among most of the new-generation antidepressants and antipsychotics is that they all have significant serotonin activity and also cause weight and metabolic changes. These side effects have become major obstacles to patient adherence to treatment as well as a potential public health problem in the psychiatric patient population. One positive aspect of the widespread use of these agents is that it has propelled research aimed at uncovering the mechanisms underlying these side effects. The result may be improved understanding of the pathophysiology involved in control of body weight, metabolic rate, and lipid regulation. Some recently published studies suggest that this may well be the case.

My curiosity about drug-induced weight gain began with my observations of patients taking fluoxetine. It was originally promoted as being associated with modest weight loss, but I soon began to notice many patients complained of significant increase in body weight. Typically, they lost weight soon after starting treatment, regained that weight over several weeks or months, and then, in some instances, started reporting weight increases of 20–80 pounds over several months of treatment. Most of these patients never had a serious weight problem in the past. It seemed likely that they were gaining weight from the fluoxetine. Moreover, many patients reported that they were not eating more or different food.

At first, those I spoke to were skeptical about my observations, and even more so when I mentioned patients reported weight gain without any change in caloric intake or activity levels. Support for the fact that there might be a metabolic change of some sort that accounted for the increase in weight was suggested by the results of an obscure study published in 1999. This was the first full year of fluoxetine’s availability. This study examined the effects of fluoxetine on food intake, body weight, and mood of obese individuals. It was a 16-week inpatient/outpatient study, where subjects lived in a residential laboratory during three 1-week inpatient periods separated by a 5-week and 8-week outpatient period. As described in the article:

Following an initial 4-day placebo baseline, participants were maintained on fluoxetine (60 mg/day) for the remainder of the study. Food intake parameters, body weight, subjective effects, and task performance were measured several times during the day during inpatient periods; food intake questionnaires were completed daily during the outpatient periods. Fluoxetine significantly reduced daily energy intake derived from fat, carbohydrate, and protein by decreasing the mean number of eating bouts per day throughout the study. No other food intake parameter was affected. Body weight was significantly reduced after 7 weeks, but not after 16 weeks of daily fluoxetine administration. These results indicate that fluoxetine reduced food intake for at least 16 weeks in non-depressed obese individuals without specifically affecting carbohydrate intake.

The other finding was that the weight lost during the first few weeks of daily fluoxetine administration was subsequently regained even though food intake remained reduced. This suggested that a metabolic change did take place.

This study did not address the underlying mechanisms of weight gain or why some patients were more prone to this side effect. My reading of the literature, however, suggested that one of the serotonin (5-HT) receptor subtypes, 5-HT$_{2C}$, was prominently involved in drug-induced weight gain. Animal studies indicated that the drugs most likely to cause weight gain—clozapine and olanzapine—have direct effects on 5-HT$_{2C}$ receptors and on neuropeptide Y-con-

Dr. Sussman is editor of *Primary Psychiatry* as well as professor of psychiatry and interim chairman in the Department of Psychiatry at the New York University School of Medicine in New York City. Dr. Sussman reports no affiliation with or financial interest in any organization that may pose a conflict of interest.
taining neurons of the hypothalamus. These neurons mediate control of food intake. Tecott and colleagues\(^2\) worked with a transgenic mouse line lacking that receptor. These 5-HT\(_{2C}\) knockout mice were noted to develop late-onset obesity, weighing 13% more than their littermate controls at 11–15 weeks of age, and 30% more after 42 weeks. The weight increase was found to be associated mainly with an increase in white adipose tissue. The weight gain in these animals was due to increased feeding. They also exhibited hyperleptinemia (leptin is an anorexigenic hormone) and hyperinsulinemia, and they were completely insensitive to the anorectic action of 5-HT\(_{2C}\) agonist.

Reynolds and colleagues\(^3\) have been studying pharmaco-genetic correlates and have found that a common 5-HT\(_{2C}\) receptor promoter region polymorphism demonstrates strong associations with weight gain during antipsychotic therapy. They also have found an association between antipsychotic drug-induced weight gain with a common and functional polymorphism of the gene for leptin. They reported that along with initial body mass index (BMI), these two pharmacogenetic factors account for ~30% of the variance in drug-induced weight gain. The 5-HT\(_{2C}\) polymorphism determines levels of circulating leptin, providing a potential mechanism underlying the genetic association of the 5-HT\(_{2C}\) receptor with weight gain. The authors’ functional studies of haplotypes of the 5-HT\(_{2C}\) promoter region found the allele associated with protection from weight gain results in reduced promoter activity.

In newer studies using genetic mouse models, scientists have linked serotonin-active compounds with the regulation of feeding behavior and body weight. Xu and colleagues\(^4\) have identified a specific group of brain cells that mediate energy balance. The 5-HT\(_{2C}\) receptor subtype was identified years ago as being involved in the regulation of energy homeostasis. Animals bred to be 5-HT\(_{2C}\) deficient eat excessively and become obese. The new-generation antipsychotics that produce the greatest amount of weight gain, olanzapine and clozapine, are potent blockers of the 5-HT\(_{2C}\) receptors. Drugs that stimulate these receptors, most notably d-fenfluramine, are powerful appetite suppressants. Unfortunately, d-fenfluramine was withdrawn from the market because of adverse cardiac effects.

It is known that pro-opiomelanocortin (POMC) neurons in the hypothalamus of the brain release neuropeptides that activate the central melanocortin receptors. These receptors are crucial to maintaining food intake, body weight, and glucose homeostasis. Xu and colleagues\(^5\) used 5-HT\(_{2C}\) knockout mice in a complex procedure and observed that the knockout mice, as expected, exhibited excessive eating, hyperactivity, and obesity, and showed reduced responses to 5-HT drugs known to suppress appetite. However, these deficiencies can be completely restored when the expression of 5-HT\(_{2C}\) receptors solely on POMC neurons is restored.

I wonder how any of this will tie into the recent report that there are two different types of body fat—each of which seems to provide metabolic energy at different rates under different temperature conditions. A study in the New England Journal of Medicine\(^6\) followed 24 healthy men—10 who were lean and 14 who were overweight or obese—under thermoneutral conditions (22°C) and during mild cold exposure (16°C). So-called brown-adipose-tissue activity was determined and body composition and energy expenditure were measured. According to the authors:

Brown-adipose-tissue activity was observed in 23 of the 24 subjects (96%) during cold exposure but not under thermoneutral conditions. The activity was significantly lower in the overweight or obese subjects than in the lean subjects (\(P=0.007\)). BMI and percentage of body fat both had significant negative correlations with brown adipose tissue, whereas resting metabolic rate had a significant positive correlation.

They concluded that “the percentage of young men with brown adipose tissue is high, but its activity is reduced in men who are overweight or obese. Brown adipose tissue may be metabolically important in men, and the fact that it is reduced yet present in most overweight or obese subjects may make it a target for the treatment of obesity.” I would be very interested in knowing whether the effects of psychotropic agents on body weight, especially when patients do not report significant increases in the amount and composition of food intake, may be mediated by some mechanism involving a shift in the activity of adipose tissue type.

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REFERENCES