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Weight Gain from Novel Antipsychotic Drugs: Need for Action

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Abstract: *Obesity is common in schizophrenia, and people with schizophrenia appear to be at increased risk for certain obesity-related conditions, such as type 2 diabetes and cardiovascular disease. Antipsychotic drugs, used chronically to control symptoms of schizophrenia, are associated with often-substantial weight gain, a side effect that is a special concern with the latest generation of highly effective "novel" agents. That the most effective (e.g., novel) antipsychotic medications lead to substantial weight gain presents the field with a critical public health problem. Although preliminary data have been reported regarding the beneficial use of behavior therapy programs for short-term weight control in patients with schizophrenia, the available data are quite limited, and there are no data regarding the long-term beneficial effects of these programs in this population. The obesity field recently has developed programs emphasizing "lifestyle changes" (e.g., diet, exercise, and problem-solving skills) to successfully manage weight in patients without schizophrenia. Such programs can be adapted for patients with schizophrenia through the use of highly structured and operationalized modules emphasizing medication compliance, social skills development, and participation in outpatient programs. Moreover, these programs can potentially be combined with the use of adjunctive pharmacotherapy to maximize and maintain weight loss. The field must solve the paradox that some of our most effective medications for schizophrenia produce substantial weight gain and its associated troubling health risks.* © *2000 Elsevier Science Inc.*

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Introduction

Schizophrenia is a tragic and devastating mental illness that usually manifests in young people on the threshold of adulthood [1]. The disease, which has a lifetime prevalence of 1% worldwide, extracts a high toll in morbidity (60% of patients receive disability benefits within the first year after onset) [2] and mortality (the suicide rate is 10%) [3,4]. Antipsychotic medications are an integral part of the therapeutic program for most individuals with schizophrenia, and the new generation of "novel" antipsychotics are particularly helpful for many patients with this and other psychotic disorders. To derive maximum benefit from these antipsychotic agents, however, patients must be able to tolerate their side effects and take them as prescribed.

One untoward side effect of many antipsychotic drugs, especially the newer "novel" or "atypical" antipsychotics, is often-substantial weight gain [5–9]. Studies suggest that 40% to 80% of patients taking antipsychotic medication experience weight gain that exceeds ideal body weight by 20% or greater [10,11]. This noticeable and unwanted side effect may undermine compliance and thus predispose patients to relapse, in addition to increasing obesity-related comorbidities and health risks [5,11–13].

That the most effective (e.g., novel) antipsychotic medications lead to substantial weight gain presents the field with a critical public health problem. This article will initially provide an overview of the topic of weight gain in patients treated with the novel antipsychotic agents. Then, after reviewing the limited data regarding approaches to the prevention of such weight gain, we will present one possible strategy for an approach to treatment in this area.

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Schizophrenia

Schizophrenia is considered a disease of neural connectivity caused by multiple factors that affect brain development [14–16]. Symptom onset typically is seen during the late teens and early 20s, when brain maturation is reaching completion [17]. Its course is characterized by florid symptoms and frequent exacerbations early in the illness, followed by a chronic and often downhill progression over time that leads to severe social disability [18,19]. Patients with schizophrenia also have impairments in neurocognition, with deficits in memory, attention, and executive function [20–22], which are thought to be key components of the functional disability caused by the illness [23,24]. Nearly 50% of patients suffer from comorbid substance abuse, leading to poor outcomes in these individuals [25,26]. People with schizophrenia have an overall mortality rate of about twice that of the general population, a rate comparable to that of individuals with diabetes mellitus [27]. The rate of completed suicide, most often seen in the early years of the illness, is 10%—comparable to that for depression [28,29].

Treatment of Schizophrenia

Treatment of schizophrenia usually involves the use of antipsychotic medications, first introduced in the 1950s, which are prescribed in the context of an overall psychotherapeutic program. The availability of the standard or "typical" antipsychotic agents (e.g., chlorpromazine and haloperidol), all potent antagonists at dopamine D_2 receptors, heralded a major therapeutic advance [30] and allowed many patients with schizophrenia to be discharged from hospital settings [31]. Although these drugs control positive symptoms of schizophrenia, they offer no "cure," and have many shortcomings. Only some patients respond symptomatically to treatment, whereas others respond poorly if at all. Some patients improve but quickly relapse, while others, who might show improvement, cannot tolerate the drugs because of severe neurologic side effects (e.g., dystonia, Parkinsonism, akathesia, or tardive dyskinesia) [32–34].

Within the past 10 years, a new generation of "atypical" or "novel" antipsychotic drugs (e.g., clozapine, risperidone, olanzapine, quetiapine) has been introduced into clinical practice [35–38]. These new medications have important advantages over the older "typical" agents and are gradually supplanting them in clinical use. Whereas "typical" antipsychotics are primarily dopamine D_2 antagonists, the "novel" drugs have more broad-spectrum pharmacological activity at other receptor sites, including dopamine D_1 and D_4, adrenergic $alpha_1$ and $alpha_2$, serotonin $5HT_{2a}$ and $5HT_{2c}$, and histaminic and muscarinic receptors [36,39].

From a clinical perspective, these new agents appear to be more effective than the older ones for control of positive and (at least some) negative symptoms of schizophrenia [32,40]. They may also prevent relapses [41], improve some cognitive deficits [42,43], and produce a higher level of functioning of patients with schizophrenia in the community [44,45]. One of the newer agents, clozapine, also appears to limit comorbid substance abuse [46,47] and suicidality [29] in patients with schizophrenia. In addition to these beneficial effects, novel agents are less likely to produce severe neurological side effects [48], and are, in general, more acceptable to patients than the older, "typical" antipsychotics [49,50]. The availability of these novel antipsychotics has ushered in a new era of optimism in the field, including considerable work on preventive intervention strategies to dramatically improve the outcome of patients with schizophrenia [51].

Antipsychotics and Weight Gain

Weight fluctuations in patients with schizophrenia were well documented in the pre-antipsychotic drug era [52]. Since the advent of antipsychotic medications, however, weight gain has become an enduring health concern [6,8,53–55]. Data from the mental health supplement of the 1989 National Health Interview Survey (NHIS) [56] indicate that body mass index (BMI) distributions of individuals with schizophrenia are generally similar to or higher than the general population and, thus, a substantial proportion were obese even before the widespread use of novel antipsychotic drugs [6]. The reported prevalence of overweight and obesity in patients with schizophrenia has been found to range from 40% to 62% [6,57–60], and may be especially high for women with schizophrenia. Obesity is a complicating factor in many medical illnesses commonly seen in patients with schizophrenia, e.g., type 2 diabetes, hypertension, dyslipidemia, sleep apnea, and osteoarthritis [11,61].

It appears that novel antipsychotics produce an even greater weight gain than the typical agents [7,9–11,62–66]. A recent meta-analysis of over 80

studies on weight change during antipsychotic treatment showed a mean weight gain after 10 weeks of treatment of 9.8 lb. (4.45 kg) with clozapine, 9.1 lb (4.15 kg) with olanzapine, and 4.6 lb. (2.10 kg) with risperidone compared to 2.4 lb. (1.08 kg) with the typical antipsychotic haloperidol [67]. Patients taking 15 mg/day of olanzapine have been found to gain a mean of 26 lb. (11.8 kg) after a year of treatment [7]. In short-term trials of patients treated with quetiapine, 23% were reported to have had a 7% or more weight gain. In studies involving 1 year of treatment with quetiapine, the mean weight gain was 4.8 lb. (2.2 kg) [68]. Interestingly, some but not all investigators have suggested that weight gain with these novel agents may be related to therapeutic response [10,62,69,70]. While two studies suggest that weight gain may be most dramatic in patients with a low baseline weight [10,65], others have failed to find such an association [62,71]. Weight gain from these agents may be a particular problem for children and adolescents who are treated with them [72,73].

Compliance with antipsychotic therapy, which is often a problem for patients with schizophrenia, may be further undermined by weight gain [11,74]. This is a particularly difficult problem for the treatment of patients with schizophrenia because stopping pharmacological treatment dramatically increases relapse rates for these patients (by as much as 5-fold [75]). Moreover, since there is evidence that relapse and continued psychosis may be biologically "toxic" [41,76,77], such non-compliance with treatment may worsen the outcome of the disorder. Medication side effects are thought to be the cause of non-compliance in up to one-third of patients, and although specific data are not available, a general perception in the field is that weight gain is an important factor determining non-compliance for many patients [11].

Many theories (including increased food intake [66,78]) have been advanced to explain the antipsychotic-induced weight gain in schizophrenia [8,55]. Recently, serotonin (e.g., $5HT_{2c}$), dopamine (D_2), and histamine (H_1) receptor blockade have been implicated [5,71,79]. Some have also suggested that changes in neurohormones and neuropeptides may underlie weight gain.

Obesity

Beyond any possible effect of weight gain from antipsychotic drugs on non-compliance with treatment, weight gain occurs and is associated with a disturbing array of increased health risks in patients with schizophrenia. In some ways, the weight gain from "novel" antipsychotics in patients with schizophrenia mirrors the general population, in which the prevalence of obesity has increased dramatically over the past 10 years. Over 50% of adult Americans are now either overweight (BMI $> 25\ kg/m^2$) or obese (BMI $> 30\ kg/m^2$) [80]. Obese individuals experience numerous adverse health consequences, including increased risk for cardiovascular disease, diabetes, stroke, some cancers, osteoarthritis, sleep apnea, gallbladder disease, and higher mortality rates from all causes compared to normal-weight individuals [81]. The most common comorbidity of obesity, hypertension, affects more than 50 million people [82], and an estimated 33% of the cases of hypertension are obesity related [83].

As noted above, obesity is a common concomitant of schizophrenia [6], and schizophrenic individuals appear to be at increased risk for certain obesity-related conditions, such as type 2 diabetes and cardiovascular disease [84–87]. Epidemiological studies show that specific stages of life, including early adulthood (the time of onset of schizophrenic symptoms), confer high risk for the development of obesity in susceptible individuals [88]. This risk will only be further increased when patients with schizophrenia are treated with antipsychotic drugs [89].

The NIH's recently released clinical guidelines on obesity [81] cite research showing significant increases in morbidity beyond a BMI of $25\ kg/m^2$ and mortality beyond a BMI of $30\ kg/m^2$ [12,90,91], and rising incidences of diabetes, coronary heart disease, and hypertension well before that point [92,93]. Numerous studies consistently have shown that short-term reduction in body weight improves obesity-related insulin resistance and cardiovascular risk factors—hyperglycemia, hyperlipidemia, hypertension, and hyperinsulinemia [94,95]. Clinical and laboratory evidence also show that weight losses as low as 5% to 10% of body weight reduce obesity-related disorders [96,97] and improve serum glucose levels, glucose tolerance, and blood pressure [92,98]. These findings, coupled with the well-documented adverse health effects of weight gain and obesity, indicate that the often-substantial weight gain observed with antipsychotic medications [67] is an important clinical as well as a public health concern [6].

Obesity, Insulin Resistance, Cardiovascular, and Neurological Risk Factors

Fifty percent of obese individuals (compared to 10% of non-obese individuals) [99–101] develop Syndrome X (also known as the metabolic or primary insulin resistance syndrome) that includes a cluster of coexisting clinical conditions: glucose intolerance or diabetes; hypertension; and hyperlipidemia with hyperinsulinemia and insulin resistance. Other laboratory abnormalities commonly found with Syndrome X include microalbuminuria, hyperuricemia, elevated free fatty acids, and the presence of Factor VII (with increased levels of fibrinogen and/or PAI 1 [plasminogen activator inhibitor 1], and thus with defective fibrinolysis and increased blood viscosity) [94,102].

A recent epidemiological study shows that clinically significant weight gain from early adulthood to middle age is strongly associated with increased risk for developing the metabolic risk factors of Syndrome X [103]. In fact, each 5% increase in body weight—independent of age, height, smoking, physical activity, education, and family history—is associated with a 200% greater risk of developing the insulin resistance syndrome by middle age [103]. The cluster of metabolic risk factors associated with both insulin resistance and obesity may also underlie the well-documented increase in cardiovascular-related mortality found in type 2 diabetics (a rate that is similar to that found in nondiabetic subjects with prior myocardial infarctions) [104].

According to the NIH Guidelines for the treatment of obesity [81], weight loss is recommended in overweight and obese people with dyslipidemia to raise low levels of high-density lipoprotein (HDL) cholesterol and to lower elevated levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. This recommendation is based on randomized control trial data showing that 5% to 13% reductions in body weight produced impressive improvements in lipid profiles [81]. In response to the mounting evidence about the relationship of adiposity to coronary heart disease (CHD), the American Heart Association recently classified obesity as a major, modifiable risk factor for CHD and issued a nine-point "call to action" that urged legislators, insurers, health care providers, and the public to sharply escalate the war against obesity [105].

Relevant to schizophrenia, a recent report [106] suggests that hyperinsulinemia and hyperglycemia associated with insulin resistance in patients treated with antipsychotic drugs are related to the severity of abnormal involuntary movements secondary to the use of these drugs. Weight gain from novel antipsychotic drugs only makes this condition worse.

Efficacy of Weight Loss Programs Emphasizing Lifestyle Change

Obesity research has yet to develop completely successful methods for achieving long-term weight loss, but a recent review of maintenance strategies (none of which was designed for patients with psychosis) shows that some approaches are more promising than others [107]. A weight-focus "lifestyle" orientation, where individuals learn diet, exercise, and problem-solving skills in weekly intensive intervention sessions for a number of months, followed by monthly maintenance treatment meetings [108], is one such method (with demonstrated losses of 5%–13% of body weight [81]). The use of formula diet preparations, such as commercial weight loss beverages that supplement a portion of daily energy intake, is another [109].

Whatever the method used for weight loss exercise is an essential component for maintenance [110]. Jeffery and colleagues [111] describe an intensive exercise intervention that increases cues for activity, makes use of a personal trainer, and reinforces attendance at exercise sessions with small financial incentives. In that study, subjects who exercised at a level that increased energy output to 2,500 kcal/week demonstrated substantial long-term weight loss.

Weight loss programs that aim to change lifestyle must be appropriate for the population being treated. For example, Blackburn and colleagues [112] recently have described a multifaceted, culturally sensitive weight loss intervention that they designed for use with obese African-American women (adapting the intervention for this population from existing lifestyle interventions) specifically emphasizing the development of new skills in four main areas, each of which support healthy lifestyles, that were deemed relevant to this population [113–115]: cognitive/behavioral techniques; exercise; nutrition/education; and gender/ethnic issues.

Lifestyle Intervention in Schizophrenia

It is reasonable to presume that lifestyle interventions for individuals with schizophrenia must be adapted to be effective in this population. Many patients with schizophrenia have cognitive deficits [21,43], including attention [22], executive function, learning, memory, verbal intelligence, and language function skills [20] that may prevent the acquisition of social skills [24]. Nonetheless, programs that use concrete models, simple directions, and reinforcement (to compensate for the cognitive deficits) appear to facilitate participation of patients with cognitive difficulties and psychosis in weight loss programs [116]. Treating patients with schizophrenia living in a residential program, Rotatori et al. [116] assessed a modified behavioral self-control 14-week weight loss program involving 14 patients; those in the active program (n=7) had a mean weight loss of 7.28 lbs while those in the control group (n=7) had a mean weight gain of 5.6 lbs. In this program, however, on follow-up 16 weeks after the completion of treatment, those available from the active program (n=4) had a mean weight loss of 1.81 lbs while in the controls (n=5) the average weight gained was 2.8 lbs. While these results are encouraging, the long-term outcome remains unclear. Other reports of weight loss in carefully controlled small programs for inpatients with schizophrenia (or in individual case reports) have also been published [117–120]. Taken together, the existing data suggest that short-term weight loss is achievable in this population, but that careful attention to design of the program is essential, and new innovative approaches to achieve long-term weight loss are necessary.

The experience of a number of investigators over the past 15 years (e.g., [121–125]) has demonstrated that highly structured and operationalized "module" programs (e.g., [126,127]) lead to improvement in medication compliance, social skills development, and participation with outpatient programs, and they potentiate the functional gains that patients with schizophrenia obtain from the use of novel antipsychotics alone [124]. These programs emphasize skill acquisition, use of social reinforcements, incremental approaches to complex behavioral change, and redundancy of presentation using multiple educational modalities [128]. Hence, they represent a more sophisticated application of the same principles used in the simpler, early behavioral interventions described above. Any weight loss lifestyle intervention designed for patients with schizophrenia should follow the same principles of these "module" programs to help the patients acquire, strengthen and generalize knowledge and skills in the areas of nutrition and lifestyle modification.

Effect of Physical Activity on Glucose Intolerance in Obesity

Epidemiological data show that exercise, and exercise combined with weight loss intervention, can prevent and/or slow the transition from impaired glucose tolerance to type 2 diabetes [82,129]. Intervention-based randomized controlled trials also consistently indicate that physical activity improves insulin action in obesity. Findings in overweight patients with type 2 diabetes, though more ambiguous, indicate a positive effect on insulin sensitivity [130], which does not always translate, however, into improved glucose control. This lack of effect on glucose control reflects, in part, the inability of many patients with type 2 diabetes to engage in regular high-intensity exercise, as well as the strong and persistent nature of insulin secretory defects. Data on the physiological effects of exercise on insulin sensitivity and glucose tolerance consistently indicate that the positive effects are relatively short-lived, lasting 2 to 3 days after each exercise session—a finding that underscores the need for a regular program of exercise to sustain health benefits [131]. Thus, any lifestyle program aimed at weight control for patients with schizophrenia should include a moderate-level exercise program. Fortunately, this type of program should be appropriate to the capabilities and dispositions of individuals with schizophrenia [132,133]. Indeed, above and beyond weight loss, exercise may have beneficial effects in this population [134].

The Potential Role of Adjunctive Pharmacotherapy

The effect of pharmacotherapy on weight loss has been evaluated in over 41 randomized controlled trials (none of which have been performed in patients with schizophrenia) [135]. Studies of single-drug and combination therapy have shown that, although mean weight losses with pharmacotherapy are modest (2–10 kg), those who take the active drug are more likely to achieve a clinically significant weight loss (5%–10% of initial body weight) [96,136] than those who take placebo [135,137,138].

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