Introduction

Weight Gain and Glucose Regulation During Antipsychotic Drug Treatment

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Excessive increases in body weight as a treatment-emergent effect of atypical antipsychotic drugs has become the focal point of clinical and research interest. Weight gain has long been recognized as a potential side effect of treatment with conventional antipsychotic agents. The lack of demonstrable differences among these older compounds with respect to the incidence and degree of increased body weight made the issue largely irrelevant from a drug selection perspective. After all, not much could be done to avoid the problem.

The current situation is different. Differences have been discovered among the newer atypical agents with respect to their weight gain liability. If clinicians wish to minimize the risk of weight gain and its attendant comorbidities, they now have choices. In the same way that they elect to avoid an antipsychotic agent because of potential extrapyramidal side effects, sexual dysfunction, or effects on cardiac conduction, clinicians can prescribe an atypical antipsychotic because it is less likely to make patients obese. It thus becomes important to have an accurate understanding of the real differences among the atypical medications. The task of forming a clear perspective is clouded by the way in which data are collected and analyzed. How are we as clinicians to exclude the possibility that the risks of weight gain with one or more drugs are being exaggerated for commercial purposes in an attempt to achieve some competitive advantage? On the other hand, how do we know if potentially damaging findings are being minimized to prevent them from adversely influencing prescribing decisions?

In an attempt to address these complex questions about the nature of antipsychotic-associated weight gain, as well as the related issues of glucose and triglyceride regulation, a symposium was held in December 2000 at the New York University School of Medicine. Experts from the United States and Canada were asked to review the available evidence and to comment on their research and clinical experience. They were also asked to discuss their conclusions and recommendations. This supplement contains information from the presentations from this symposium.

In my overview of the evidence of weight changes associated with the treatment of schizophrenia, I mention that some degree of weight gain may occur with any agent, particularly early in treatment. However, considering the chronic nature of schizophrenia, it is the long-term rather than transient effects on body weight that are most significant clinically. Published data should include both short-term and long-term findings. Furthermore, they should describe the relationship of changes in body weight to the pretreatment body mass index (BMI) and the relationship of dose to weight changes and should contain both intent-to-treat and completer analyses. Both the mean and median changes in weight should be presented to provide a more accurate picture of the findings. Finally, whether study subjects are chronically ill, institutionalized, or outpatients should also be considered.

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Louis J. Aronne, M.D., notes that overweight and obesity represent global epidemics, with the most pronounced prevalence in the United States. Obesity and overweight are serious and potentially life-threatening conditions. He also points out that these problems may, in fact, be more prevalent in patients with schizophrenia, because of unhealthy lifestyle habits or the propensity for significant weight gain associated with antipsychotic drugs, or both.

Roger S. McIntyre, M.D., and colleagues provide an overview of why patients may gain weight. They review the potential mechanisms of antipsychotic-induced weight gain as well as other variables potentially associated with weight gain such as inactivity, negative symptoms, poor access to exercise venues, socioeconomic status, and increased exposure to obesity-promoting environments such as hospitalization. They confirm that the weight gain noted with some of the newer atypical antipsychotics does tend to exceed that produced by the older conventional antipsychotics and that weight gain induced by novel antipsychotics increases the risk of obesity-related morbidity.

Jean-Pierre Lindenmayer, M.D., and colleagues address the various factors that combine to increase the risk of diabetes mellitus in patients with schizophrenia who are taking atypical antipsychotic medication. They note that, among the atypical medications, treatment with clozapine and olanzapine appears to increase the risk for diabetes mellitus. They recommend that the patient's fasting plasma glucose level should be measured if hyperglycemia develops during treatment with atypical medications. If the results are questionable, a glucose tolerance test should be performed and the risk-benefit factors reassessed. Cholesterol and triglyceride levels should also be monitored, and a weight-reduction program should be implemented. In these high-risk individuals, they observe, an increase in body weight of just 5% would result in corresponding increases in morbidity and the risk of early mortality.

David C. Henderson, M.D., details his clinical experience with weight gain and diabetes mellitus associated with clozapine treatment. He emphasizes the importance of obtaining regular fasting plasma glucose values, but notes that these tests may be difficult to perform in some patients. He nevertheless recommends monitoring for weight change, educating patients, and considering weight loss and exercise programs. Psychiatrists, in his view, need to be proactive regarding the potential side effects and medical morbidities of therapies for schizophrenia. Careful drug selection, early patient education, and other interventions, including add-on therapy, may prevent weight gain or the development of diabetes mellitus.

Vincenzo S. Basile and colleagues review the genetic factors that influence a patient's clinical responses to drug treatment and his or her propensity to develop a side effect. Their research has found that genetic variation may account for some of the differences seen among patients in terms of both the efficacy of antipsychotics to alleviate psychosis and the propensity of patients to develop antipsychotic-induced side effects.

Brown et al.[1] followed a cohort of patients with schizophrenia to determine the most common causes of death. Epilepsy was the most prevalent, and diabetes was the second most common, followed by cerebrovascular disease and cardiovascular disease, thus proving that diabetes and weight gain clearly have implications on longevity in this patient population. The authors concluded that some of the excess mortality seen in patients with schizophrenia could be reduced by decreasing patients' smoking and exposure to other environmental risk factors and by improving the management of medical disease, mood disturbance, and psychosis. As clinicians, we must understand the issues surrounding weight gain and glucose dysregulation associated with the use of atypical antipsychotics so we can better control the side effects associated with treatment and choose the most effective and tolerable medication overall.

REFERENCE

1. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. Br J Psychiatry 2000;177:212–217