Introduction

Metabolic Disturbances Associated With Antipsychotic Use

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Newer antipsychotic medications are now widely used in the management of psychotic disorders such as schizophrenia. These so-called atypical antipsychotics offer several important advantages over typical antipsychotic drugs, including their characteristic lower risk of extrapyramidal symptoms (EPS) (e.g., parkinsonism) in comparison with typical medications at clinically relevant doses. Newer antipsychotics may offer improved treatment of various symptoms, including cognitive impairments associated with the illness, and improvements in relapse prevention. Treatment successes have contributed to the increased use of newer antipsychotics and have also allowed psychiatrists to expand clinical expectations. Recently, the important goals of response to acute treatment of positive symptoms, medication compliance, and relapse prevention have been supplemented with longer-term considerations of quality of life, reintegration into the community and workplace, and the quality of overall health outcome.

The World Health Organization, the Centers for Disease Control and Prevention (CDC), the American Diabetes Association, and the United States Public Health Service, among other organizations, maintain ongoing efforts concerning the primary prevention of diabetes mellitus and cardiovascular disease. These efforts have increased recently as various groups, including the CDC, have expressed concern about a growing epidemic of type 2 diabetes mellitus. Diabetes mellitus and impaired fasting glucose are associated with microvascular disease, including retinopathy, nephropathy, and autonomic and peripheral neuropathies. Microvascular disease produces considerable morbidity, accounting, for example, for approximately 25% of the end-stage renal failure in the United States.[1] Diabetes mellitus, as well as increases in plasma glucose below the threshold for diabetes, can cause or contribute to increases in macrovascular disease, or atherosclerosis. Atherosclerosis increases risk for cardiovascular and cerebrovascular events such as myocardial infarction and stroke, accounting for considerable mortality as well as morbidity. Diabetes mellitus is also associated with serious acute adverse events such as diabetic ketoacidosis (DKA). DKA is a severe metabolic complication of type 1 and type 2 diabetes mellitus, associated with a mortality rate of 2% to 5%, with higher mortality in the elderly or when insulin therapy is delayed.[2]

A major risk factor for diabetes mellitus is increased adiposity, largely modulated by the relationship between abdominal adiposity and insulin resistance. Rising rates of obesity in the United States and other urbanized settings, along with dietary changes and decreased activity levels, have largely been blamed for the epidemic rise in the prevalence of type 2 diabetes mellitus. While increased adiposity predictably increases one's risk of diabetes mellitus, obesity is also independently associated with increased risk for hypertension, dyslipidemia, and cardiovascular disease. In the field of psychiatry, there is growing concern with the underrecognized problem of iatrogenic, psychotropic drug–induced weight gain, along with associated disturbances in glucose and lipid metabolism. These antipsychotic treatment–related disturbances have included new-onset cases of type 2 diabetes, exacerbations of existing type 1 and type 2 diabetes, and diabetic complications, including DKA and DKA-related mortality. The concern about these adverse events is driven in part by the serious cardiovascular complications of obesity, diabetes mellitus, and dyslipidemia, as well as by the other important adverse health consequences of these conditions. Clinicians also recognize the adverse effect of weight gain on patient self-esteem, andthey are increasingly aware of the deleterious effect of adverse treatment events on patient compliance with prescribed medication. On the basis of the combined effects of lifestyle, family history, psychiatric disease–related effects, and treatment-related adverse events, many patients currently carry the burden of multiple cardiovascular risk factors, including smoking, obesity, hyperglycemia, and hypertriglyceridemia.

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Samuel B. Guze, M.D., an internist as well as a psychiatrist by training and a leader in psychiatry for many years, reminded many of us that psychiatry is a branch of medicine.[3] During his life, he worked to advance a medical model of mental illness. Consistent with the wide acceptance of the medical model of psychiatric diseases, psychiatrists recognize the importance of preexisting and intercurrent medical conditions for the correct diagnosis and treatment of psychiatric patients. Psychiatrists also increasingly appreciate their role in the primary prevention of nonpsychiatric medical illnesses. For a variety of reasons, psychiatrists are motivated to monitor risk factors and adjust treatment decisions to assist in the prevention of medical diseases, even when these diseases are not the traditional concern of psychiatry. Some of these conditions (e.g., cardiovascular disease) can directly and indirectly impact behavior, for example, decreasing treatment compliance and increasing the risk of depression. Diabetes mellitus and cardiovascular disease, noted above, can alter quality of life in the critical sense of medical morbidity and ultimately mortality. Patient- and schizophrenia-related variables such as alterations in diet and activity levels, elevated rates of smoking, and possible pretreatment disturbances in weight regulation and glucose metabolism provide important reasons to monitor and otherwise address risk factors for diabetes mellitus and cardiovascular disease. Evidence that psychotropic treatments may further disturb weight regulation as well as glucose and lipid metabolism suggests additional reasons for clinicians to monitor parameters such as plasma glucose, lipids, and weight. The goal of pharmacotherapy is to maximize benefits while minimizing adverse events. The task of preventing adverse events may prove easier and more effective than treating these events once they occur. There are currently few data addressing the effectiveness of diabetes management, including diet, exercise, and glucose monitoring, in patients with psychotic disorders, but we can assume this will be challenging to implement and difficult to maintain compliance with.

In addition to important clinical considerations that underlie the increased interest in this area, marketing efforts by various manufacturers have increasingly focused on differences in adverse events across individual medications. This can be a healthy competitive process, but it requires clinicians to carefully weigh evidence, distinguish between theoretical and well-established risks, and identify adverse effects associated with morbidity versus adverse events associated with mortality. Marketing can sometimes educate, but it can often make it harder for clinicians to distinguish between those adverse events that are given life largely through marketing and those adverse events (e.g., weight gain) that are related to important public concerns targeted by various independent agencies. One of the important legacies of atypical antipsychotics may turn out to be that they facilitated discussion of adverse events that have always been a part of antipsychotic therapy, allowing clinicians to better address risk factors for medical comorbidity and mortality in this population.

In this supplement, the interrelated problems of weight gain, hyperglycemia, and dyslipidemia in patients treated with antipsychotic medications will be reviewed. Harold E. Lebovitz, M.D., reviews the physiology of glucose metabolism and provides an overview of the American Diabetes Association's new criteria for the diagnosis and classification of diabetes mellitus. Dan W. Haupt, M.D., and I provide a review of the associations between type 2 diabetes, schizophrenia, and antipsychotic medications. David C. Henderson, M.D., reports on further clinical experiences with impaired glucose metabolism during antipsychotic treatment. Jonathan M. Meyer, M.D., focuses on the interrelated effects of antipsychotic medications on body weight and lipid metabolism. Finally, Herbert Y. Meltzer, M.D., provides an important discussion of the risks and benefits associated with atypical antipsychotic treatment. His discussion deserves special emphasis. He appropriately cautions that the data do not suggest that atypical antipsychotics should be abandoned due to their adverse metabolic side effects. While all antipsychotics can induce some degree of weight gain, and virtually all have been associated with disturbances in glucose and lipid metabolism, it remains a clinical imperative to treat psychosis, and the newer agents offer a number of advantages. This debate is not about whether or not to treat psychosis, but whether the adverse event profile can be optimized. There is ample evidence of clinically significant differences in the magnitude of weight gain caused by different older and newer antipsychotics, just as there is interpatient variability in the weight gain observed during treatment with any given drug. We would argue that clinicians should be aware of these potential adverse effects and monitor patients taking antipsychotic medications for the appearance of these problems. Significant disturbances in weight regulation or glucose or lipid metabolism should lead to early interventions to reduce the adverse metabolic effects while maintaining clinical benefits. It is our hope that clinicians will be stimulated to view weight gain and related metabolic disturbances as an undesirable consequence of treatment that should be avoided whenever possible.

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