

Issue: November 2007

The Diabetes-Mental Illness Link: Clinical Applications

[Normal Version](#)

Beyond Atypical Antipsychotics

By Caroline Helwick

Amsterdam, the Netherlands—The relationship between diabetes mellitus and mental illness is an established reality, even though the pathophysiology of this association has not been well defined and its clinical implications not fully realized. At the European Association for the Study of Diabetes, this topic was explored by a number of experts.

For reasons still not fully understood, the prevalence of diabetes among patients with severe mental illness is 2 to 3 times higher than in the general population. Although this disproportionate risk has largely been attributed to treatment with some of the second-generation (atypical) antipsychotic medications, Stephen Gough, MD, professor of medicine at the University of Birmingham, England, said, "I think the link goes well beyond this."

A recent study that involved 200 Dutch patients (*Diabetes Care*. 2006; 29:786-791) showed that the prevalence of diabetes was 14.5% among those with severe mental illness compared with 1.5% in the general population. Based on other published studies, Dr Gough maintained that the association is multifactorial, involving not only antipsychotic agents but also unhealthy lifestyle and biologic factors.

A family history of type 2 diabetes has been found in up to 30% of patients with schizophrenia. There are overlaps in gene regions encoding for diabetes and schizophrenia and overlaps in the regulatory enzymes for glycolysis and schizophrenia. An association has also been shown between psychosis, beta-cell function, and insulin resistance. As psychosis improves, so do beta-cell function and insulin resistance, Dr Gough said, citing a 2003 study (*Diabetes Care*. 2003;26:1462-1467).

Jogin H. Thakore, PhD, of St. Vincent's Hospital, Dublin, Ireland, further noted that persons with newly diagnosed schizophrenia have 3 times as much intraabdominal fat as matched controls. Impaired glucose tolerance is found in 15% of these individuals and in 18% of their first-degree relatives. Patients with schizophrenia also have increased expression of a surface-bound platelet glycoprotein that is critical to platelet aggregation. "This may partly explain the increased predisposition of the severely mentally ill to cardiac events," Dr Thakore said.

Screen Mentally Ill Patients for Glucose Tolerance

Coronary artery disease is the leading cause of death among the severely mentally ill. This population has triple the mortality rate of the general population, with patients dying 10 to 20 years earlier than the general population—possibly because of the prevalence of diabetes and the metabolic syndrome, according to Richard Holt, PhD, MRCP, of the University of Southampton, United Kingdom.

The Clinical Antipsychotic Trials of Intervention Effectiveness study (*Schizophr Res*. 2005;80:19-32) demonstrated that more than 85% of patients with schizophrenia had at least 1 feature of the metabolic syndrome.



**Richard Holt,
PhD, MRCP**

"The management of metabolic predictors in patients with severe mental illness is a neglected area," Dr Holt said. He recommended screening for glucose tolerance before starting antipsychotic therapy.

Treatment can be challenging, he acknowledged. There may be less awareness of symptoms related to

reliably measuring cardiovascular risk factors and treating these patients as you would treat the general public would be a great leap forward," he said.

Atypical Antipsychotics and New-Onset Diabetes

The role of the second-generation antipsychotics in the development of new-onset type 2 diabetes in patients with schizophrenia has been recently actively explored. A new study quantified the potential risk of treatment-emergent diabetes in 15 pharmacoepidemiologic studies (*Ann Pharmacother.* 2007;41:1593-1603). Lead author Leslie Citrome, MD, MPH, of the New York University School of Medicine, presented the results at the meeting.

Attributable risk was determined by calculating the number needed to treat to produce 1 case of diabetes. Altogether, the second-generation antipsychotics were associated with a range of from 53 more cases to 46 fewer cases of diabetes per 1000 patients compared with the first-generation antipsychotics; however, few studies controlled for confounding factors, such as body weight, family history, and physical activity, Dr Citrome pointed out.

In spite of the propensity for some agents to cause weight gain and dyslipidemia, the study showed little difference between individual second-generation antipsychotics and first-generation antipsychotics. "Although prolonged exposure to an individual agent can cause problems, the attributable risk remains unknown. The choice of antipsychotic cannot predict who will develop type 2 diabetes," Dr Citrome said, adding that side effects must be balanced against the need for efficacious psychiatric treatment.

Depression Treatment Improves Diabetes Outcomes

Other forms of mental illness are also intertwined with diabetes. Major depressive disorder occurs in 10%, and subclinical depression in 10% to 40%, of persons with diabetes. On the flip side, depressed persons have a greatly increased risk of developing type 2 diabetes compared with nondepressed persons, and when the 2 conditions coexist, diabetic outcomes worsen, said Patrick J. Lustman, MD, of Washington University, St. Louis.



Patrick J. Lustman, MD

For example, a study stratifying patients with diabetes by depression scores (*Am J Epidemiol.* 2005;161:652-660) showed a 54% increase in mortality among the most severely depressed, but even subclinical depression was associated with some risk. Other studies have also found mortality risk to be greatly increased for patients with both diabetes and depression (*Diabetes Care.* 2005;28:1339-1345). "Depression somehow causes a susceptibility to dying," Dr Lustman concluded.

Among patients with diabetes, those who are depressed have poorer glycemic control compared with those who are not depressed, a higher risk of comorbidities and mortality, increased functional impairment, and poorer adherence to diet, exercise, and self-management strategies, said Norbert Hermanns, PhD, of the Research Institute of the Diabetes Academy Mergentheim, Bad Mergentheim, Germany.

Depression also appears to increase the risk of developing diabetes. In the prospective Stockholm Diabetes Prevention Program of 5500 patients, men (but not women) with the highest level of depressive symptoms had a nearly 4-fold greater risk for type 2 diabetes, and a nearly 2-fold greater risk for a prediabetic state, compared with the least depressed, reported Claes-Göran Östenson, MD, of the Karolinska Institute, Stockholm, Sweden.

Based on such emerging data, Dr Hermanns emphasized, "Depression in diabetes has to be taken seriously." The recent World Health Survey (*Lancet.* 2007;370:851-858) showed that the combination of diabetes and depression has the most negative impact on health among a dozen or so serious medical conditions.

Despite its seriousness, depression remains undetected and untreated in 50% to 75% of patients with diabetes. Coexisting depression has a "diagnostic" effect on the clinical management of diabetes.

unless it is followed by a structured management, Dr Hermanns said.

And new data show that adequate treatment of depression improves diabetic outcomes. The dual norepinephrine/ dopamine reuptake inhibitor bupropion (Wellbutrin) and selective serotonin reuptake inhibitors can improve glycemic control, but the same cannot be said for nortriptyline (Pamelor), a norepinephrine reuptake inhibitor, Dr Lustman reported (*Diabetes Care*. 2007;30:459-466).

KEY POINTS

- Diabetes prevalence in patients with mental illness is 2 to 3 times greater than in the general population.
- Some atypical antipsychotics have been shown to increase risk for new-onset diabetes.
- Before prescribing an atypical antipsychotic, assess the patient's glucose tolerance.
- The combination of diabetes and depression has the most negative impact on health among a dozen serious medical conditions.

[Normal Version](#)