Medical Risk in Patients With Bipolar Disorder and Schizophrenia

John W. Newcomer, M.D.

Patients with schizophrenia and bipolar disorder are vulnerable to developing key modifiable risk factors for cardiovascular disease, such as obesity, smoking, hypertension, dyslipidemia, and type 2 diabetes mellitus. In addition, mood stabilizers, anticonvulsants, and antipsychotic medications, which are commonly used to treat schizophrenia and bipolar disorder, have been linked to risk for adverse metabolic changes in patients. This article reviews the current literature on the prevalence of medical risk factors in the general population as well as in those patients with schizophrenia or bipolar disorder and discusses treatment strategies and lifestyle changes that patients can make in order to reduce their risks for certain diseases. *(J Clin Psychiatry 2006;67[suppl 9]:25–30)*

ADVERSE EVENTS IN THE TREATMENT OF SCHIZOPHRENIA AND BIPOLAR DISORDER

A variety of adverse event risks are associated with pharmacologic treatment of schizophrenia and bipolar disorder, including extrapyramidal symptoms, tardive dyskinesia, elevated prolactin levels,[1] somnolence, weight gain, hyperlipidemia, hypothyroidism, hepatic toxicity,[2] and impaired memory.[3,4] These adverse events occur at different frequencies with different medications, which forms a large part of the risk-benefit calculation routinely made by clinicians to determine the optimal treatment regimen for each patient.

In the treatment of both schizophrenia and bipolar disorders, tolerability and safety issues are a primary concern when prescribing any medication. Tolerability issues can be defined in relation to nonlethal, time-limited, or manageable adverse events that may be more nuisance-related symptoms than medically significant (e.g., mild parkinsonism, nausea, or sedation); whereas, safety issues can be defined as life-threatening, treatment-related adverse events that can occur on an acute or chronic basis (e.g., neuroleptic malignant syndrome, anaphylaxis, or metabolic syndrome). Tolerability and safety issues may overlap in some areas. For example, weight gain may begin as a tolerability problem but can increase the risks of metabolic syndrome, thereby increasing the risk of life-threatening conditions such as cardiovascular disease or diabetes.

MEDICAL DISORDERS IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Patients with mental illnesses and medical disorders have higher mortality rates than patients with medical disorders alone. For example, individuals with bipolar disorder or unipolar depression and a medical condition were found to have higher standardized mortality ratios (observed deaths/expected deaths) for natural causes of death than the general population that had a medical condition (1.9 in males, 2.1 in females; 1.5 in males, 1.6 in females, respectively).[4] A meta-analysis conducted by Allebeck[5] found that for patients with schizophrenia the standardized mortality ratio for natural causes of death ranged between 1.8 and 4.4. In comparison to general population samples, patients with schizophrenia have been reported to have a 40% increased risk of death from medical causes,[6] and recent U.S. data indicate that persons with a major mental disorder lose approximately 20 to 30 years of potential life due primarily to cardiovascular disease.[7] Cardiovascular disease is a leading cause of death in these patients, as it is in the general population, as well as the leading contributor to excessive deaths.[8]

The Framingham Heart Study[9] sponsored by the National Heart, Lung, and Blood Institute (NHLBI) identified key modifiable risk factors for developing coronary heart disease. Risk factors include obesity, smoking, hyperglycemia, hypertension, and dyslipidemia. Having more than 1 of these risks increases the odds of developing heart disease, which increases with the number of risk factors in an additive or greater manner.[9] Growing evidence

From the Department of Psychiatry, Psychology, and Medicine, and the Center for Clinical Studies, Washington University School of Medicine, St. Louis, Mo.

This article was derived from the planning roundtable "Improving Cognitive Function and Functional Outcome in Severe Mental Illness," which was held January 13, 2006, in Dallas, Tex., and supported by an educational grant from Bristol-Myers Squibb Company.

Corresponding author and reprints: John W. Newcomer, M.D., Washington University School of Medicine, Department of Psychiatry, 660 South Euclid Avenue, Campus Box 8134, St. Louis, MO 63110 (e-mail: newcomerj@psychiatry.wustl.edu).

indicates that patients with schizophrenia and bipolar disorder have an increased prevalence of each of these modifiable risk factors, offering an explanation for the increased cardiovascular mortality observed in this population and suggesting an opportunity to lower risk (Table 1).[10–19]

Obesity is a strong predictor of cardiovascular disease as well as an underlying cause of many of the other risk factors mentioned. For example, as body fat increases body mass index (BMI = weight in kilograms divided by height in meters squared), the relative risk of several medical conditions increases, especially the risk for type 2 diabetes mellitus.[20] Increased adipose tissue is associated with decreases in insulin sensitivity or resistance to insulin action,[21] initially resulting in a compensatory hypersecretion of insulin by pancreatic beta cells. In persons at risk for type 2 diabetes, this compensatory hyperinsulinemia can eventually fail, leading to progressive hyperglycemia. In general, insulin resistance and related hyperinsulinemia increase the risk for a constellation of related changes in physiology known as the insulin resistance syndrome. This syndrome can encompass disturbances in glucose metabolism, uric acid metabolism, and lipid metabolism, with a characteristic dyslipidemia that includes increases in fasting plasma triglyceride, decreases in high-density lipoproteins, and atherogenic changes in low-density lipoproteins. In addition, the syndrome can include a hemodynamic disturbance with increases in sympathetic nervous system activity and sodium retention leading to hypertension, increases in inflammatory markers, and an increased risk of blood clotting—all risk factors associated with cardiovascular disease.[22,23] People with insulin resistance syndrome are at risk for developing several illnesses, including hypertension,[24,25] sleep breathing disorder, nonalcoholic fatty liver disease, polycystic ovarian syndrome, and some types of cancer.[24] Individuals with insulin resistance syndrome are also at an increased risk of developing type 2 diabetes,[23–25] a disease that leads to macrovascular diseases (i.e., atherosclerosis) as well as microvascular diseases such as retinopathy, nephropathy, or neuropathy.

Table 1. Estimated Prevalence of Cardiovascular Disease Risk Factors Among Patients With Schizophrenia or Bipolar Disorder

	Estimated Prevalence (%)	
Modifiable Risk Factors	Schizophrenia	Bipolar Disorder
Obesity[10–12]	42.0	20.8–49.0
Smoking[11,13–16]	54.0–75.0	54.0–67.6
Diabetes[10,14,17–19]	13.0–14.9	8.0–17.0
Hypertension[10,11,14,17,19]	19.0–57.7	35.0–39.0
Dyslipidemia[10,11,19]	25.0	23.0

COGNITIVE DYSFUNCTION IN CARDIOVASCULAR DISEASE AND DIABETES

Cardiovascular diseases such as atherosclerosis can substantially impact cognitive function. For example, comorbid cerebrovascular disease in patients with Alzheimer's disease has been shown to hasten the pathologic and cognitive expression of dementia,[26,27] and cognitive deficits may be adversely affected despite less neurofibrillary pathology.[26–28]

Type 2 diabetes is also associated with cognitive deficits[29] such as impairments in verbal memory,[30,31] learning,[31] attention,[32] manual dexterity,[32,33] reasoning,[31,32] and psychomotor speed.[31,32,34] Although many individuals with diabetes may have macrovascular disease, cognitive deficits may not all be attributable to cerebrovascular disease. Cognitive dysfunction in type 2 diabetes may be related to deficient insulin production within the body, resulting in altered glucose signaling in the brain. Glucose, extracted from capillary beds in the brain, is the energy supply for cognition and is stored as glycogen in astrocytes,[35] with insulin having both a time- and dose-dependent role in regulating the storage of glycogen.[36]

Insulin plays additional important roles in the regulation of cerebral function. For example, insulin receptors are expressed at the hippocampal[37] and cortical synapses,[38] which can increase glucose uptake in these specific regions.[39] Insulin signaling can also increase the levels of certain biogenic amines such as dopamine, acetylcholine, and norepinephrine,[40] as well as modulate membrane potentials, membrane expression of *N*-methyl-D-aspartic acid (NMDA) receptors, and the long-term potentiation of neuronal firing that is thought to underlie memory function.[37] Hyperinsulinemia and insulin resistance in type 2 diabetes are associated with an increased risk of Alzheimer's disease.[41–43] Investigators have hypothesized that this role is related in part to the role of insulin in regulating the amyloid beta (Aβ) 42.[44]

Because cerebrovascular disease and diabetes can lead to impairments in cognitive function, it is important to manage risk factors for these diseases in the general population and also in patients with mental illnesses such as schizophrenia and bipolar disorder, in which cognitive function is already decreased.

METABOLIC SYNDROME IN PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

The National Cholesterol Education Program (NCEP) defines the metabolic syndrome as a constellation of lipid and nonlipid risk factors of metabolic origin, closely linked to a generalized metabolic condition called insulin resistance in which the normal actions of insulin are impaired. NCEP has developed a working definition of metabolic syndrome in which having 3 or more criteria qualifies for a diagnosis (Table 2).[45] People with metabolic

Table 2. Identification of Metabolic Syndrome (≥ 3 Risk Factors Required for Diagnosis)[a]

Risk Factor	Defining Level
Abdominal obesity	Waist circumference
Men	> 40 in (> 102 cm)
Women	> 35 in (> 88 cm)
Triglycerides	≥ 150 mg/dL
HDL cholesterol	
Men	< 40 mg/dL
Women	< 50 mg/dL
Blood pressure	≥ 130/85 mm Hg
Fasting blood glucose	≥ 110 mg/dL

[a]Reprinted with permission from the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[45]
Abbreviation: HDL = high-density lipoprotein.

syndrome have a 1.29 to 2.78 hazard ratio,[46–49] 2.01 odds ratio,[50] and 1.5 to 3.0 relative risk[51–54] for cardiovascular disease, and a 3.5 hazard ratio[46] and 1.3 to 4.2 odds ratio[50,55,56] for diabetes. Having 3 to 5 criteria means that risk is dramatically multiplied: up to 3.7 times the relative risk for coronary heart disease,[46] up to 24.5 times the risk for diabetes,[46] and up to 10 times the risk for increased C-reactive protein, which is associated with both cardiovascular disease and diabetes.[57]

Using established NCEP criteria for metabolic syndrome, McEvoy et al.[58] compared baseline characteristics of subjects with schizophrenia entering the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study[59] with characteristics of persons in the general population based on data from the National Health and Nutrition Examination Survey (NHANES) III.[60] Metabolic syndrome was found to be present in 51.6% of women and 36.0% of men with schizophrenia, while healthy women and men had rates of 25.1% and 19.7%, respectively. Compared with the general-population NHANES group, patients with schizophrenia had a higher prevalence of almost all criteria for metabolic syndrome, including increased waist circumference, high triglyceride levels, low high-density lipoprotein levels, and increased blood pressure, as well as more impairment in fasting blood glucose levels in women. The only exception to the fact that CATIE schizophrenia subjects generally have a higher prevalence of meeting all metabolic syndrome criteria was that men with schizophrenia entering the CATIE study had a prevalence of abnormal fasting blood glucose (as measured by the American Heart Association cutoff of ≥ 100 mg/dL) similar to their NHANES counterpart. In general, compensatory hyperinsulinemia buffers changes in plasma glucose, so that glucose control can be maintained for some years in the face of insulin resistance, even when changes in adiposity, plasma lipid levels, and blood pressure are already evident.

The most important predictor of metabolic syndrome is increased adiposity. In the United States, 27% of the general population[11] is obese compared with an estimated 42% of patients with schizophrenia[11] and 49% of patients with bipolar disorder.[10] Using the NHLBI overweight and obesity guidelines for BMI,[61] Park et al.[62] found metabolic syndrome present in patients with the following weight classifications: 4.6% of normal weight men (BMI from 18.5 to 24.9 kg/m^2), 22.4% of overweight men (BMI from 25 to 29.9 kg/m^2), and 59.6% of obese men (BMI ≥ 30 kg/m^2), with similar results being reported for women.

PHARMACOTHERAPY FOR PATIENTS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Psychotropic drugs prescribed to patients with schizophrenia or bipolar disorder can induce or exacerbate some of the modifiable risk factors associated with cardiovascular disease and diabetes.[63] As indicated in labeling information provided in the Physicians' Desk Reference,[64] weight gain, hypertension, hyperglycemia, and diabetes are all potential adverse effects associated with antipsychotic treatment.

Weight gain, in particular, is a commonly observed adverse effect associated with antipsychotics and other psychotropic drugs such as the antimanic agents lithium, valproic acid, and carbamazepine.[64] However, different medications carry a different magnitude of risk for inducing clinically significant effects on weight. Comparing antipsychotics used in the CATIE study (Table 3),[65] olanzapine produced the largest mean increase in weight per month of treatment, while ziprasidone and perphenazine treatment actually produced a mean decrease in weight per month of treatment. It should be noted, however, that any decrease in weight with the latter agents is most likely the result of a change from prior medication rather than an intrinsic effect of these antipsychotics to reduce weight. In a study[66] comparing use of lithium or valproate in combination with olanzapine versus lithium or valproate alone (i.e., either agent in combination with placebo), significant weight gain was associated with adjunctive olanzapine (21.1% with lithium and 28.8% with valproate) as opposed to placebo (4.9% and 8.2%, respectively).

At least in part, the weight gain associated with treatment can help to explain the reported effects of different medications on insulin resistance and the risk of hyperglycemia, dyslipidemia, and metabolic syndrome.[63] The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes[67] concluded that different levels of risk are associated with different treatments, ranging from an increased risk of weight gain, diabetes, or dyslipidemia, with some agents to limited or no evidence of risk for those adverse events with other agents (Table 4).

Metabolic effects of antipsychotic treatment, including alterations in plasma of cholesterol, triglycerides, and

Table 3. Comparison of CATIE Outcome Measures for Antipsychotic Agents (Mean ± SE)[a]

Effect	Olanzapine	Quetiapine	Risperidone	Perphenazine	Ziprasidone
Weight change (lb)	9.4 ± 0.9	1.1 ± 0.9	0.8 ± 0.9	–2.0 ± 1.1	–1.6 ± 1.1
Blood glucose (mg/dL)	15.0 ± 2.8	6.8 ± 2.5	6.7 ± 2.0	5.2 ± 2.0	2.3 ± 3.9
Glycosylated hemoglobin (%)	0.41 ± 0.09	0.05 ± 0.05	0.08 ± 0.04	0.10 ± 0.06	–0.10 ± 0.14
Cholesterol (mg/dL)	9.7 ± 2.1	5.3 ± 2.1	–2.1 ± 1.9	0.5 ± 2.3	–9.2 ± 5.2
Triglycerides (mg/dL)	42.9 ± 8.4	19.2 ± 10.6	–2.6 ± 6.3	8.3 ± 11.5	–18.1 ± 9.4

[a]Data from Lieberman et al.[65]
Abbreviation: CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness.

Table 4. Atypical Antipsychotics and Metabolic Syndrome[a]

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole[b]	+/–	–	–
Ziprasidone[b]	+/–	–	–

[a]Reprinted with permission from the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.[67]
[b]Newer drugs with limited long-term data.
Symbols: + = increase effect, – = no effect, D = discrepant results.

glycosylated hemoglobin, were observed in the CATIE study, as shown in Table 3.[65] Increases in fasting plasma triglycerides can be an indicator of insulin resistance, and CATIE patients randomly assigned to olanzapine experienced a 40 mg/dL increase in triglycerides. Patients randomly assigned to ziprasidone demonstrated a decrease in triglycerides, and because ziprasidone is not a lipid-lowering agent, this decrease may indicate the removal of previous adverse effects or a correction of preexisting dyslipidemia.

CONCLUSION

Individuals with schizophrenia or bipolar disorder have a higher prevalence of modifiable metabolic syndrome risk factors such as obesity, compared with the general public, which results in increased morbidity and mortality from related medical conditions. Increased adiposity is associated with increases in insulin resistance, increasing risk for hyperglycemia, hypertension, dyslipidemia, cardiovascular disease, and diabetes mellitus, which may also contribute to cognitive dysfunction. Even modest interventions in any one of the independent risk factors can result in significant clinical benefits.[68] For example, lowering blood cholesterol by 10% results in a 30% decrease in risk for coronary heart disease. Decreasing blood pressure by 6 mm Hg (> 90 mm Hg in diastolic pressure) in patients with hypertension can decrease the risk for coronary heart disease by 16% and stroke by 42%. Cigarette smoking cessation decreases the risk of coronary heart disease by 50%, even in elderly patients. Maintaining a BMI of ≤ 25 results in a 35% to 55% reduction in the risk for coronary heart disease. Finally, an active lifestyle that includes one 20-minute walk per day can result in a 35% to 55% reduction of coronary heart disease.[68] Recent research[63,65–67] has shown that increases in these risk factors may be attributable to certain pharmacotherapies used to treat these patients, while alternate pharmacotherapies may either avoid that risk or even lead to improvements in metabolic variables. The principles of primary prevention suggest the importance of interventions to promote active and healthy lifestyles in order to substantially reduce the risks for disease.

Drug names: aripiprazole (Abilify), carbamazepine (Tegretol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), valproic acid (Depakene, Myproic Acid, and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

REFERENCES

1. Halbreich U, Kinon BJ, Gilmore JA, et al. Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects. Psychoneuroendocrinology 2003;28(suppl 1):53–67
2. Nasrallah HA, Mulvihill T. Iatrogenic disorders associated with conventional vs atypical antipsychotics. Ann Clin Psychiatry 2001;13:215–227
3. Perlick D, Stastny P, Katz I, et al. Memory deficits and anticholinergic levels in chronic schizophrenia. Am J Psychiatry 1986;143:230–232
4. Osby U, Brandt L, Correia N, et al. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844–850
5. Allebeck P. Schizophrenia: a life-shortening disease. Schizophr Bull 1989;15:81–89
6. Harris EC, Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11–53
7. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chronic Dis [serial online] Apr 2006. Available at: http:www.cdc.gov/pcd/issues/2006/apr/05_0180.htm. Accessed June 30, 2006
8. Osby U, Correia N, Brandt L, et al. Time trends in schizophrenia mortality in Stockholm county, Sweden: cohort study. BMJ 2000;321:483–484
9. Wilson PWF, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837–1847
10. Fagiolini A, Frank E, Scott JA, et al. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 2005;7:424–430
11. Hennekens CH, Hennekens AR, Hollar D, et al. Schizophrenia and increased risks of cardiovascular disease. Am Heart J 2005;150:1115–1121
12. McElroy SL, Frye MA, Suppes T, et al. Correlates of overweight and

obesity in 644 patients with bipolar disorder. J Clin Psychiatry 2002; 63:207–213
13. Davidson S, Judd F, Jolley D, et al. Cardiovascular risk factors for people with mental illness. Aust N Z J Psychiatry 2001;35:196–202
14. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. Schizophr Res 2005;80:45–53
15. Herran A, de Santiago A, Sandoya M, et al. Determinants of smoking behavior in outpatients with schizophrenia. Schizophr Res 2000;41:373–381
16. Ucok A, Polat A, Bozkurt O, et al. Cigarette smoking in patients with schizophrenia and bipolar disorders. Psychiatry Clin Neurosci 2004;58: 434–437
17. Dixon L, Postrado L, Delahanty J, et al. The association of medical comorbidity in schizophrenia with poor physical and mental health. J Nerv Ment Dis 1999;187:496–502
18. Cassidy F, Ahearn E, Carroll BJ. Elevated frequency of diabetes mellitus in hospitalized manic-depressive patients. Am J Psychiatry 1999;156: 1417–1420
19. Kilbourne AM, Cornelius JR, Han X, et al. Burden of general medical conditions among individuals with bipolar disorder. Bipolar Disord 2004;6:368–373
20. Calle EE, Thun MJ, Petrelli JM, et al. Body-mass index and mortality in a prospective cohort of US adults. N Engl J Med 1999;341:1097–1105
21. Banerji MA, Lebowitz J, Chaiken RL, et al. Relationship of visceral adipose tissue and glucose disposal is independent of sex in black NIDDM subjects. Am J Physiol 1997;273(2 pt 1):E425–E432
22. Reaven G. Sydrome X: 10 years after. Drugs 1999;58(suppl 11):19–20
23. Steinberg HO, Baron AD. Vascular function, insulin resistance and fatty acids. Diabetologia 2002;45:623–634
24. Caballero AE. Endothelial dysfunction in obesity and insulin resistance: a road to diabetes and heart disease. Obes Res 2003;11:1278–1289
25. Reaven GM. Banting lecture 1988: role of insulin resistance in human disease. Diabetes 1988;37:1595–1607
26. Esiri MM, Nagy Z, Smith MZ, et al. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. Lancet 1999;354:919–920
27. van der Flier WM, Middelkoop HA, Weverling-Rijnsburger AW, et al. Interaction of medical temporal lobe atrophy and white matter hyperintensities in AD. Neurology 2004;62:1862–1864
28. Kalaria RN. Small vessel disease and Alzheimer's dementia: pathological considerations. Cerebrovasc Dis 2002;13(suppl 2):48–52
29. Kalmjin S, Feskens EJ, Launer LJ, et al. Glucose intolerance, hyperinsulinemia and cognitive function in a general population of elderly men. Diabetologia 1995;38:1096–1102
30. Strachan MW, Deary IJ, Ewing FM, et al. Is type II diabetes associated with an increased risk of cognitive dysfunction? a critical review of published studies. Diabetes Care 1997;20:438–445
31. Reaven GM, Thompson LW, Nahum D, et al. Relationship between hyperglycemia and cognitive function in older NIDDM patients. Diabetes Care 1990;131:16–21
32. Meneilly GS, Cheung E, Tessier D, et al. The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. J Gerontol 1993;48:M117–M121
33. Gregg EW, Beckles GL, Williamson DF, et al. Diabetes and physical disability among older US adults. Diabetes Care 2000;23:1272–1277
34. Ryan CM, Geckle MO. Circumscribed cognitive dysfunction in middle-aged adults with type 2 diabetes. Diabetes Care 2000;23:1486–1493
35. Magistretti PJ, Pellerin L, Rothman DL, et al. Energy on demand. Science 1999;283:496–497
36. Sorg O, Magistretti PJ. Vasoactive intestinal peptide and noradrenaline exert long-term control on glycogen levels in astrocytes: blockade by protein synthesis inhibition. J Neurosci 1992;12:4223–4231
37. Skeberdis VA, Lan J, Zheng X, et al. Insulin promotes rapid delivery of N-methyl-D-aspartate receptors to the cell surface by exocytosis. Proc Natl Acad Sci U S A 2001;98:3561–3566
38. Apelt J, Mehlhorn G, Schliebs R. Insulin-sensitive GLUT4 glucose transporters are colocalized with GLUT3-expressing cells and demonstrate a chemically distinct neuron-specific localization in rat brain. J Neurosci Res 1999;57:693–705
39. Bingham EM, Hopkins D, Smith D, et al. The role of insulin in human brain glucose metabolism: an ^{18}fluoro-deoxyglucose positron emission tomography study. Diabetes 2002;51:3384–3390
40. Figlewicz DP, Bentson K, Ocrant I. The effect of insulin on norepinephrine uptake by PC12 cells. Brain Res 1993;602:161–164
41. Ott A, Stolk RP, van Harskamp F, et al. Diabetes mellitus and the risk of dementia: the Rotterdam study. Neurology 1999;53:1937–1942
42. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study. Diabetes 2002;51:1256–1262
43. Luchsinger JA, Tang MX, Shea S, et al. Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004;63:1187–1192
44. Watson GS, Craft S. Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease. Eur J Pharmacol 2004;490:97–113
45. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–3421
46. Sattar N, Gaw A, Scherbakova O, et al. Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. Circulation 2003;108:414–419
47. Hu G, Qiao Q, Tuomilehto J, et al. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004;164:1066–1076
48. Hunt KJ, Resendez RG, Wiliams K, et al. National Cholesterol Education Program versus World Health Organization metabolic syndrome in relation to all-cause and cardiovascular mortality in the San Antonio Heart Study. Circulation 2004;110:1251–1257
49. Ford ES. The metabolic syndrome and mortality from cardiovascular disease and all-causes: findings from the National Health and Nutrition Examination Survey II Mortality Study. Atherosclerosis 2004;173: 309–314
50. Ninomiya JK, L'Italien G, Criqui MH, et al. Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey. Circulation 2004;109: 42–46
51. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA 2002;288:2709–2716
52. Girman CJ, Rhodes T, Mercuri M, et al. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Am J Cardiol 2004;93:136–141
53. McNeill AM, Rosamond WD, Girman CJ, et al. The metabolic and 11-year risk of incident cardiovascular disease in the atherosclerosis risk in communities study. Diabetes Care 2005;28:385–390
54. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24: 683–689
55. Lorenzo C, Okoloise M, Williams K. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio Heart Study. Diabetes Care 2003; 26:3153–3159
56. Etamadi A, Saadat N, Azizi F. New definition of IFG: impacts on metabolic syndrome definition and prediction of diabetes. Presented at the 40th Annual Meeting of the European Association for the Study of Diabetes; Sept 5–9, 2004; Munich, Germany
57. Ridker PM, Buring JE, Cook NR, et al. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14719 initially healthy American women. Circulation 2003;107: 391–397
58. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res 2005;80:19–32
59. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr Bull 2003;29:15–31
60. Alexander CM, Landsman PB, Teutsch SM, et al. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210–1214

61. National Institutes of Health. National Heart Lung and Blood Institute. The Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report; 1998 NIH Publication No. 98-4083. Available at: http://www.nhlbi.nih.gov/guidelines/obesity/e_txtbk/index.htm. Accessed March 6, 2006
62. Park YW, Zhu S, Palaniappan L, et al. The metabolic syndrome: prevalence and associated risk factors findings in the US population from the Third National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med 2003;163:427–436
63. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic side effects: a comprehensive literature review. CNS Drugs 2005;19 (suppl 1):1–93
64. Physicians' Desk Reference. 60th ed. Montvale, NJ: Thompson PDR; 2006
65. Lieberman JA, Stroup TS, McEvoy JP, et al., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–1223
66. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002;59:62–69
67. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry 2004;65:267–272
68. Hennekens CH. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. Circulation 1998;97:1095–1102