Current Psychiatry

Safe and effective care for your patients with diabetes

Jeff Susman, MD

Chair, Department of Family Medicine,
University of Cincinnati College of Medicine,
Cincinnati, Ohio

Diabetes mellitus is often associated with psychiatric problems and psychiatric treatment can complicate diabetes management. This case-based review will increase your awareness of drug-drug and drug-disease interactions.

Type 2 diabetes mellitus is one of the most common and costly chronic diseases, afflicting 16 million people nationwide. According to American Diabetes Association statistics, the disease each year costs the United States more than $100 billion in health-care expenses and lost productivity.

Diabetes is associated with many psychiatric conditions, yet psychiatrists may not be aware that patients under treatment for mental disorders are suffering from diabetes or have problems related to their psychopharmacologic therapy. With changing criteria for the diagnosis of diabetes, new evidence about the prevention and treatment of this disease, and a growing link between diabetes and psychiatric issues, the practicing psychiatrist should be knowledgeable about such possible interactions.

The following three cases illustrate these challenges and offer pearls for patient management.


Jeff Susman, MD

PATHOPHYSIOLOGY OF DIABETES

Type 1 diabetes is caused by an autoimmune phenomenon leading to beta-cell failure and absolute deficiency in insulin. Type 2 diabetes is characterized by tissue receptor resistance to insulin (aggravated by genetic factors, obesity, aging, and other problems), beta cell dysfunction (with defects in the timing and amount of insulin secretion), and changes in hepatic glucose output and glucose transport. Patients with type 2 diabetes will initially lose phase one (early) insulin secretion in response to a glucose load.

Unregulated production of hepatic glucose ultimately leads to abnormal fasting blood sugars. The beta cells will initially compensate, but will eventually fail. Thus, postprandial blood sugars will increase, reflecting the loss of early insulin secretion, but return relatively rapidly to normal. Gradually, fasting blood sugars will also rise as insulin resistance becomes more pronounced and the imbalance in hepatic glucogenesis occurs. Eventually, with absolute beta cell failure, patients with type 2 diabetes will require insulin to offset their insulinopenic state.

Case 1: Diabetes and depression

L.S., age 54, has a five-year history of type 2 diabetes. On referral, he presents with increasing lethargy, difficulty concentrating, and irritability. His mental status examination discloses anhedonia, moderate irritability, depressed mood, loss of appetite, and overall lethargy. He emphatically denies suicidal thoughts, but feels "overwhelmed with life." His referring physician notes that he also suffers from hyperlipidemia and hypertension, and continues to smoke one pack per day. His current medications include atorvastatin, enalapril, glucophage, and one baby aspirin per day. His weight is 247 pounds. Other than mild background retinopathy and mild peripheral neuropathy, his last physical examination was normal. His last HbA1c was 8.8%, and his creatinine was 1.7.

How do you manage this patient?

The challenge Type 2 diabetes mellitus affects more than one in 17 persons in the U.S., and physicians diagnose approximately 800,000 cases yearly. Yet one third of individuals with diabetes are undiagnosed, and multiple studies suggest we are falling short of accepted guidelines for care. Diabetes remains the leading cause of blindness, renal failure, and non-traumatic amputation in adults. While care for patients with diabetes will largely fall to primary care physicians (it is the third most common problem seen by family physicians) and endocrinologists, psychiatrists will often also see these patients.

Case 1 concluded While this patient's history clearly suggests major depressive disorder, the possibility of other medical complications (e.g., worsening renal function or lactic acidosis from metformin therapy) should be entertained. A serum lactate level was normal and a metabolic panel, including renal function, was stable. The patient responded well to the addition of a selective serotonin reuptake inhibitor (SSRI) for his major depressive disorder.

Comment Many patients with diabetes will present with symptoms and signs suggestive of depression and anxiety. Patients with diabetes are more likely to develop depression, a disorder that worsens the outcomes for such individuals. These patients are likely to take multiple medications and have many medical comorbidities. Therapy of psychiatric disorders in patients with diabetes may be complicated by drug-drug and drug-disease interactions. When patients with diabetes present with symptoms of a mental disorder, a careful assessment is essential.

DIAGNOSING DIABETES

The diagnosis of diabetes depends on the demonstration of either fasting glucose intolerance (plasma glucose ≥ 126) or abnormal response to glucose challenge (plasma glucose ≥ 200 following a 75 gm glucose challenge). Testing is repeated and not done at a time of stress, such as during an acute illness. The HbA1c is not recommended for the diagnosis of diabetes.

Risk factors for type 2 diabetes mellitus include:

- Obesity
- Family history of diabetes
- Race/ethnicity (African-American, Hispanic, Asian-American, Pacific Islander)
- Age ≥ 45
- Sedentary lifestyle
- Previous history of impaired glucose tolerance
- History of gestational diabetes or birth weight of child of 4 kg or more
- Hypertension
- HDL ≤ 35 mg per dL or triglyceride ≥ 250 mg per dL

Case 2: A patient on risperidone who develops diabetes

G.L., 47, has a longstanding history of schizophrenia. She has been on risperidone for one year and has done well, but has gained 14 pounds and now weighs 212 pounds. G.L. complains of difficulty seeing and returns for assessment. What next?

Psychiatric drug use and diabetes The incidence of mental health problems is increased in individuals with diabetes and psychiatric disorders may increase diabetic morbidity. Certain medications commonly used by psychiatrists may trigger diabetic complications and some hypoglycemic agents may be associated with potential drug-drug interactions or other difficulties *(Tables 1 and 2)*.

Approximately 40% of patients with type 2 diabetes remain undiagnosed. It is estimated that diagnosis is delayed by 4 to 7 years after the development of their disease, and

Table 1

Therapeutic options for type 2 diabetes treatment

Class	Representative agents	Mechanism of action	Side effects, cautions, and notes	Common uses
First-generation sulfonylureas	Tolbutamide (Orinase), chlorpropamide (Diabinese), tolazamide (Tolinase)	Stimulate insulin secretion	Weight gain, hypoglycemia, fever, disulfiram type reaction. Caution: if significant hepaticor renal impairment; MAOIs may exacerbate hypoglycemia	Generic versions are least expensive oral hypoglycemics
Newer-generation sulfonylureas	Glipizide (Glucotrol, Glucotrol XL), glyburide (DiaBeta, Glynase), glimepiride (Amaryl)	Stimulate insulin secretion	Weight gain, hypoglycemia. Caution: with significant hepatic impairment; glyburide has active metabolite that may accumulate with renal dysfunction; MAOIs may exacerbate hypoglycemia	More potent; glipizide may lack some of the side effects of first-generation agents; common initial monotherapy
Metglitinides	Repaglinide (Prandin), nateglinide (Starlix)	Stimulate insulin secretion	Very short half life—must be given right before meals; metabolized by CYP-450 3A4 (may be induced by medications such as carbamazepine); highly protein bound; contraindicated in pregnancy	May help patients who have transient loss of diet control, postprandial hyperglycemia
Biguanides	Metformin (Glucophage, Glucophage XR)	Reduce hepatic glucose output and enhance insulin sensitivity	Gastrointestinal problems common initially; must be withheld before imaging with contrast media; lactic acidosis; contraindicated if renal or hepatic dysfunction, CHF, dehydration, hypoxemia; metallic taste	Overweight patients; favorable effects on lipids; fasting hyperglycemia
Thiazolidinediones	Pioglitazone (Actos), rosiglitazone (Avandia)	Enhance insulin sensitivity (cellular uptake of insulin) and inhibit hepatic glucose production	Hepatic toxicity; delayed onset of action; weight gain and fluid retention; contraindicated with CHF, liver disease	Useful as monotherapy or in combination; does not cause hypoglycemia and might ameliorate hyperlipidemia
Alpha-glucosidase inhibitors	Acarbose (Precose), miglitol (Glyset)	Inhibit breakdown and absorption of carbohydrates	Flatulence; need for high carbohydrate diet; cannot correct hypoglycemia with sucrose, maltose, or starch (but do not cause hypoglycemia on their own); contraindicated in patients with substantive renal and hepatic disease	Early in treatment for postprandial hyperglycemia; less potent than other agents
Combination agents	Glyburide/metformin (Glucovance)	As above	As above	Failure to meet goals on one agent alone; may reduce side effects of higher doses of either agent alone
Insulin	Short acting (Lispro and regular—aspart pending release); intermediate (NPH and Lente); long-acting (Ultralente and glargine)	Replace insulin, reduce hepatic glucose production, increase glucose uptake	Hypoglycemia; weight gain; must currently be injected	Failure to meet goals with oral agents or unable to take oral agents or to overcome glucose toxicity

Table 2

Selected psychiatric drugs that interact with diabetes agents and patients with diabetes

Drug Class	Effect
MAOIs	Hypoglycemia; may displace metglitinides and other protein-bound agents from serum proteins and cause hypoglycemia
SSRIs	Hypoglycemic unawareness
Tricyclics	May exacerbate autonomic neuropathy, orthostatic hypotension
Nefazodone	Highly protein bound and metabolized by CYP-3A4 (may effect metglitinide metabolism)
Bupropion	Liver metabolism
Carbamazepine	CYP-3A4 metabolized; may induce metglitinide metabolism
Valproate	Highly protein bound
Phenytoin	May decrease hypoglycemic effect of sulfonylureas
Benzodiazepines	Some (e.g., triazolam, alprazolam) metabolized by CYP/liver
Buspirone	Protein bound; CYP-3A4 metabolism
Antipsychotics	Weight gain may exacerbate or precipitate diabetes; liver metabolized

Note: Except for case reports, most of these agents are only theoretically implicated in the above drug-drug interactions (DDIs) or drug-disease interactions. Remember to assess **all** medications used in persons with diabetes, many of which do have substantial potential for DDIs.

patients frequently present with established retinopathy, renal disease, or macrovascular disease. As the diagnostic criteria have changed and more patients are obese and lead sedentary lifestyles, the prevalence of recognized diabetes is increasing.

The growing association of impaired glucose tolerance with progression to diabetes, the availability of effective interventions, and the high burden of morbidity for unrecognized diabetes suggest that more aggressive screening may be warranted.

Case 2 concluded Weight gain associated with atypical antipsychotic agents is all too common, and will often tip a patient "over the edge" from impaired glucose tolerance to type 2 diabetes. G.L. was referred to her primary care physician for assessment. Her fasting blood glucose was 312. Repeat FBG was 299. An ophthalmologic evaluation disclosed background changes consistent with diabetic retinopathy. Type 2 diabetes was diagnosed.

This patient deserves aggressive attention to modifiable risk factors, and warrants therapy for diabetes. Appropriate modification of diet, exercise, smoking and other risk factors—and medical comanagement—are critical. This includes attention to the psychotropic drugs she is taking.

Comment Medications commonly used by psychiatrists (e.g., atypical antipsychotics) may be associated with weight gain that exacerbates or precipitates type 2 diabetes.

The psychiatrist also must be aware of other potential medical comorbidities of treatment. Drug-drug interactions may occur with agents that are hepatic metabolized, including commonly used therapies for bipolar disorder (*Table 2*).

Metglitinides are metabolized by the CYP-3A4 system and drugs such as barbiturates and carbamazepine may induce this enzyme and reduce effectiveness. MAO inhibitors are associated with hypoglycemia with a number of agents, including sulfonylureas, and highly protein-bound agents such as the MAO inhibitors may displace repaglinide and increase its hypoglycemic activity. Fluoxetine and other SSRIs may cause hypoglycemic unawareness. Oral hypoglycemia agents themselves can be associated with hypoglycemia, and the onset may be confused with anxiety or panic attacks. The older sulfonylureas may cause inappro-

Commonly used psychiatric medications may cause weight gain that exacerbates or precipitates type 2 diabetes

priate ADH (SIADH). Biguanides are occasionally associated with potentially catastrophic lactic acidosis.

Case 3: Disordered eating in an adolescent with type 1 diabetes

B.C., a 17-year-old with type 1 diabetes mellitus, is referred to a psychiatrist for a possible eating disorder. She was diagnosed with diabetes when she was 4. Over the past year her diabetes self-care has become increasingly erratic. B.C.'s mother notes that the patient often skips her insulin altogether, is preoccupied with her weight, and consumes large amounts of junk food. B.C. also admits to purging when she has been particularly lax with her diet.

Interaction between psychiatric and endocrine disorders

Disordered eating appears to be frequent in adolescent girls and women with diabetes. Conscious underdosing of insulin and irregular eating habits may occur when patients are concerned about their body image, feel a stigma about using insulin, or fear they won't fit in with friends.

It also appears that depression may be associated with diabetes, perhaps through an intervening effect on diet and exercise. The incidence of depression in patients with diabetes is up to 28%, and women with diabetes appear to have a greater risk for depression than men. Patients with diabetes who are depressed are less likely to adhere to their diabetes program and more likely to have worse glycemic control and increasing risk of complications.

CURRENT VIEWS ON MANAGEMENT

Diabetes treatment requires a comprehensive approach embracing education, regular history and physical examinations, routine laboratory evaluations, and establishment of counseling goals. The foundation of care lies on appropriate diet and exercise.

Increasingly, a "stepped care approach" to medication is being advocated based on the patient's stage of disease. For individuals with early type 2 diabetes, risk factor modification, diet, and exercise may be sufficient. Later, as further insulin resistance occurs, oral hypoglycemic agents must be added. A number of therapeutic options are available *(Table 1)*. Finally, late in the course of type 2 diabetes, as absolute insulin deficiency occurs, combination therapy and insulin are used. Insulin is also often required for initial therapy to "rescue" the overstressed beta cells and overcome "glucose toxicity."

Little evidence exists to guide the choice of treatment of type 2 diabetes, and nuances of therapy are beyond the scope of this article. However, several points are worth reinforcing:

- Ideal treatment is geared to normalizing the blood sugar at all times and achieving a near normal A1c (6.5% to 7%).
- Lifestyle modifications are important, and even relatively small changes in weight can substantially increase insulin sensitivity.
- Risk factor modification (e.g., smoking, lipids, hypertension) is extremely important.
- Therapy for type 2 diabetes is not static. As the disease progresses, more aggressive therapy is often required.

WHAT YOU SHOULD KNOW ABOUT PREVENTION

Of course, prevention is the best treatment of diabetes, and promising data are emerging. Increased physical activity (irrespective of BMI) and weight control appear to reduce both the risk of developing type 2 diabetes and the risk of progression from impaired glucose tolerance to overt diabetes. Smoking cessation may also play a role by improving insulin sensitivity. The Diabetes Prevention Program, a multicenter trial sponsored by the National Institutes of Health, should provide definitive data on primary prevention; recommendations based on the initial results of this trial are being developed.

The value of secondary prevention (screening) for type 2 diabetes has been debated. The American Diabetes Association recommends screening all individuals age 45 and older, while the U.S. Preventive Services Task Force suggests there is insufficient evidence to recommend for or against routine screening.

The all-cause mortality rate is doubled for individuals with diabetes. Good data from controlled trials suggest that improved glycemic control diminishes the microvascular complications of diabetes (e.g., retinopathy). A goal of a normal or near normal HbA1c (6.5% to 7.0%) is recommended.

The leading causes of mortality in patients with type 2 diabetes include coronary heart disease and complications of diabetes. The influence on macrovascular complications such as myocardial infarction is less clear. Thus, cardiac risk factors must be managed aggressively.

Diabetic retinopathy is the leading cause of blindness, diabetic nephropathy is the most common reason for end-stage renal disease, and diabetic neuropathy is the most frequent origin of amputation in the United States. Tertiary screening is directed toward early detection and treatment of these complications.

Related resources *Oriented to mental health issues*

- Wirshing DA. Adverse effects of atypical antipschotics. *J Clin Psych*. 2001;62:(suppl 21)7-10.
- Goodnick PJ, Henry JH, Buki VMV. Treatment of depression in patients with diabetes mellitus. *J Clin Psych*. 1995;56:4,128-136.
- Carney C. Diabetes mellitus and major depressive disorder: an overview of prevalence, complications, and treatment. *Depression Anxiety*. 1998;7:149-157.
- Jacobson AM. The psychological care of patients with insulin-dependent diabetes mellitus. *N Engl J Med.* 1996;334(19), 1249-53.
- Glasgow RE, Fisher EB, Anderson BJ, et al. Behavioral science in diabetes. Contribution and opportunities. *Diabetes Care*. 1999;22(5):832-43.
- Hoffman RP. Eating disorders in adolescents with type 1 diabetes. *Postgrad Med*. 2001;109(4)67-74.
- Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? *Diabetes Care*. 2000;23(10):1556-62.
- Rubin RR, Peyrot M. Psychological issues and treatments for people with diabetes. *J Clin Psychol*. 2001;57(4):457-78.
- Golden MP. Special problems with children and adolescents with diabetes. *Primary Care Clin*. 1999; 26(4):885-94.

DRUG BRAND NAMES

Alprazolam • Xanax
Atorvastatin • Lipitor
Bupropion • Wellbutrin
Buspirone • Buspar
Carbamazepine • Tegretol, Epitol, Atretol
Enalapril • Vasotec
Fluoxetine • Prozac
Nefazodone • Serzone
Phenytoin • Dilantin
Risperidone • Risperdal
Triazolam • Halcion
Valproate • Depacon

DISCLOSURE

The author reports that he has been a speaker or consultant for SmithKline Beecham, Organon, Wyeth-Ayerst Pharmaceuticals, and Pfizer.

Case 3 concluded B.C. is concerned about weight gain, her friends making fun of her need for injections, and hypoglycemic reactions while playing varsity volleyball. Her concerns are explored and intensive counseling is undertaken. At the same time, she is referred to an endocrinologist for further evaluation, and the diabetes care team initiates therapy with an insulin pump.

After an initial rocky period, B.C.'s therapy is stabilized and her hypoglycemic episodes reduced. B.C. discusses her concerns with other teens in a diabetes support group and is introduced at the local college to a star volleyball player (who also suffers from diabetes). As B.C. graduates, she is offered a scholarship at a top university. Her HbA1c is at normal levels.

Comment Younger individuals with diabetes face substantial challenges in adjusting to their disease. The incidence of disordered eating, depression, anxiety, and adjustment disorders is increased.

What's more, diabetes in children and adolescents affects the whole family. Parents and siblings are often stressed over the patient's care needs and mood swings, and may also present with mental disorders.

General references on diabetes

- Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:997.
- United Kingdom Prospective Diabetes Study Group. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837-53.
- Reasner CA, Defronzo RA. Treatment of type 2 diabetes mellitus: a rational approach based on its pathophysiology. *Am Fam Phys*. 2001;63(9):1687-92.
- Clark CM, Fradkin JE, Hiss RG, et al. Promoting early diagnosis and treatment of type 2 diabetes. *JAMA*. 2000;284(3):363-4
- Evans RM, Brown EF, Krosnick A, eds. *Managing diabetes. A CME program for primary care physicians*. Chicago: American Medical Association, 2001.

Bottom Line

Type 2 diabetes may complicate the treatment of primary psychiatric disorders. Depression, eating disorders, and other common psychiatric disorders may negatively affect the outcomes of patients with diabetes. It is important to recognize the complications of diabetes and work collaboratively with primary care clinicians and endocrinologists.