LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Insulin Overdose Among Patients With Diabetes: A Readily Available Means of Suicide

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Have you ever worried that one of your depressed patients might use the insulin that you prescribed to commit suicide? The following case vignette and discussion explore the complex relationship between diabetes and depression, outline important risk factors for suicide, and describe the frequency and lethality of suicide attempts by insulin overdose. In addition, we offer a 5-step approach for the management of depressed patients who are prescribed insulin.

CASE VIGNETTE

Ms A, an 18-year-old woman with insulin-dependent diabetes, was found by her brother while having a generalized tonic-clonic seizure (the direct result of an intentional insulin overdose). He called emergency rescue services, who determined that her fingerstick glucose level was 25 mg/dL and brought her to the emergency department. Her glucose level was stabilized in the emergency department, and she was transferred to the medical service for further observation before transfer to an inpatient psychiatric unit.

Although Ms A had not received any psychiatric treatment before this event, she reported infrequent panic attacks and moderate social anxiety, and she used cannabis and clonazepam daily. Ms A had attempted suicide twice in the past several months; both of these attempts involved overdoses of insulin, and neither resulted in her receiving medical attention. For several years, she had been poorly adherent with her insulin regimen (and her hemoglobin A1c level in the past year was 9.2%–10.4%).

Ms A, who lived at home with her mother, father, and brother, was failing several classes in her senior year of high school, and she had recently quit the soccer team.

WHAT IS THE RELATIONSHIP BETWEEN DEPRESSION AND DIABETES?

Patients with diabetes (type 1 and type 2 combined) have nearly twice the risk of depression as the general population.[1] In a study of the epidemiology of major depressive disorder (MDD) (ie, the National Comorbidity Survey Replication), the estimated lifetime prevalence of depression in the general population was 16.2%.[2] A meta-analysis of the prevalence of comorbid depression in patients with diabetes estimated that the lifetime prevalence was 28.5%.[3] The higher rate of depression in diabetic patients may be due to an increased rate of depression in patients

with diabetes, or an increased rate of diabetes in patients with depression. There is emerging data suggesting this association is in fact bidirectional.[4]

Diabetes is one of the most psychologically and behaviorally demanding chronic medical illnesses, in part because an estimated 95% of diabetes management is carried out by the patient.[5] Depression has been associated with poorer adherence to self-care regimens (including following dietary recommendations, participation in exercise routines, regular glucose monitoring, and medication compliance).[6] Furthermore, depression is associated with cardiac risk factors (including smoking, obesity, and a sedentary lifestyle), dysregulation of the hypothalamic and sympathetic nervous system, and an increase in inflammatory markers, which may impact diabetes directly.[7,8] Not surprisingly, given these perturbations, depression in the context of diabetes is associated with an increased risk of complications (eg, diabetic retinopathy, nephropathy, and neuropathy, as well as macrovascular and sexual complications) and mortality.[9,10]

Despite the impact of depression on the diabetic patient, it is estimated that only one-third to one-half of cases of depression among those with diabetes are recognized.[11–13] In the case of Ms A, a primary care clinician in the habit of regularly screening patients for depression might have picked up on her depression and arranged for psychiatric care that Ms A needed to prevent this nearly catastrophic overdose.

Table 1. Factors Associated With an Increased Risk of Suicide[a]

Factors
Ideas about, plans for, or an intent to commit suicide; past suicide attempts
Mood disorders
Substance use disorders
Access to firearms
Physical illness
Childhood traumas
Psychosocial features
Lack of social support
Unemployment
Recent stressor
Family features
Family history of suicide
Family history of mental illness, including a substance use disorder
Poor relationship with family
History of domestic violence
Psychological features
Panic attacks
Hopelessness
Impulsivity
Aggressivity
Shame
Low self-esteem
Demographic features
Male gender
Being widowed, divorced, or single
Being an adolescent or elderly
White race
Having a gay, lesbian, or bisexual orientation

[a]Based on Jacobs and Brewer.[16]

WHAT ARE THE RISK FACTORS FOR SUICIDE?

Patients with diabetes are at increased risk for suicide, although no clear consensus exists regarding the degree of this increased risk. Compared to those in the general population, individuals with type 1 diabetes (in a British study) had 11 times the suicide rate,[14] while adolescents with diabetes (in a US study) had an increased rate of suicidal ideation but comparable rate of attempts.[15] Interestingly, Goldston and colleagues[15] found that suicidal thoughts were strongly associated with serious noncompliance with medical treatment. Although suicide cannot be predicted, examining a patient's specific risk factors is an essential part of the suicide assessment that can help to stratify one's degree of risk. The American Psychiatric Association Practice Guidelines for the Assessment and Treatment of Patients With Suicidal Behaviors outline a number of important risk factors (Table 1).[16]

In the case of Ms A, these risk factors helped to place her high risk for suicide in perspective. She had several risk factors for suicide (eg, MDD, substance abuse, and multiple past suicide attempts). Ms A's presentation was also concerning for other factors associated with suicide risk (including physical illness and panic attacks). Assessment of risk factors should also include identification of the lethality of the plan or attempt; Ms A's suicide attempts by insulin overdose were potentially lethal.

HOW COMMON ARE SUICIDE ATTEMPTS BY INSULIN OVERDOSE?

Large numbers of patients with diabetes present to emergency departments each year with hypoglycemic episodes of "unknown" etiology; it is likely that a significant proportion of these represent intentional overdoses. However, published data on this topic are rare, and they consist mostly of case reports or small case series. The difficulty in estimating the incidence of suicide attempts via intentional insulin overdose stems from the relatively narrow therapeutic index of insulin (ie, a very small therapeutic dose range above or below which could cause significant toxicity or lack of efficacy) and from patients who conceal the intent of their actions.

A common method used to estimate the number of deliberate insulin overdoses is to analyze inquiries made to regional poison control centers. In the 2005 annual report of the American Association of Poison Control Centers,[17] only 3,934 of the 2,424,180 inquiries (0.16%) reported drug exposures involving insulin. Though rare, most

Table 2. Steps for the Safe Management of Depressed Patients Prescribed Insulin

1. Regularly assess for symptoms of depression	Employ 1 or more screening tools (that are available for use by primary care physicians); 1 key component of all of these screening tools are the questions: • During the past 2 weeks, have you felt down, depressed, or hopeless? • During the past 2 weeks, have you felt little interest or pleasure in doing things? Positive results on a screening instrument (eg, cases in which either of these questions is answered yes, nearly every day) should trigger a more complete diagnostic interview and an appropriate plan for nearly monitoring and treatment
2. Refer to a mental health provider (sooner rather than later)	Involve a mental health provider in all cases involving marked depression and/or suicidality; consider making a referral in cases of mild-to-moderate depression, particularly when accompanied by significant suicide risk factors
3. Work closely with mental health providers	Communicate regularly (even if only briefly) with mental health care providers, as this can add crucial information to insulin management decisions and may provide valuable insights about patient compliance and self-care that help guide diabetes care
4. Monitor thoughts of suicide when following a patient with depression	Be alert to whether the patient has suicidal thoughts, a plan, or the intent to harm himself/herself; some questions that may help elicit suicidal thoughts include: • Have you ever felt that life was not worth living? • Did you ever wish you would go to sleep and not wake up? • Have things ever reached the point that you have thought of harming yourself?
5. Consider safeguarding insulin when working with a significantly depressed or suicidal patient	Enlist the aide of inpatient psychiatric units; these can provide some additional safety by supervising insulin administration On an outpatient basis, family members can control access to insulin and can monitor dosing Discontinuation of an insulin pump may be necessary during an acute episode of depression with suicidality Although not feasible for most patients, switching to a noninsulin agent that is safer in the case of overdose is reasonable when medically sound

cases of insulin overdose reported to poison control centers have involved intentional attempts of suicide. One retrospective outcome study of 160 cases of insulin overdose reported to a regional poison control unit found that nearly 90% were either suicidal or parasuicidal, whereas only 5% of cases were deemed accidental.[18]

HOW LETHAL ARE SUICIDE ATTEMPTS BY INSULIN OVERDOSE?

A review of the literature shows that although intentional insulin overdoses are rarely reported, they may result in severe neurologic sequelae or death if not quickly identified and treated. Several recent studies have employed a systematic approach to analyze the outcomes of patients who attempted suicide via insulin poisoning. In 1 prospective study of 25 patients admitted to an intensive care unit for severe insulin self-poisoning, 4 patients developed significant complications (eg, severe hypoglycemic encephalopathy) resulting in 2 deaths.[19] von Mach and colleagues[18] examined outcomes for 160 cases of insulin overdose reported to a regional poison control unit and found more favorable outcomes; the large majority of patients (94.7%) achieved a full recovery, while 2.7% patients developed cerebral defects and 2.7% died.

Among the antidiabetic agents taken in lethal overdoses, sulfonylureas were responsible for the greatest number of reported deaths (likely due to the larger number of type 2 diabetics, who represent 80% of diabetics), whereas insulin caused the greatest absolute number of problems that were classified as "major" or "serious."[20] Of those complications, hypoglycemic encephalopathy was 1 of the most feared. Early clinical signs in hypoglycemia reflect the appearance of physiologic protective mechanisms initiated by hypothalamic sensory nuclei. Such symptoms include diaphoresis, tachycardia, anxiety, and hunger. If left untreated, these symptoms give rise to more serious central nervous system symptoms with a progression through confusion, lethargy, and delirium to seizures and coma. Prolonged hypoglycemia may lead to irreversible brain damage. The cortex, caudate, putamen, and hippocampus are the brain regions most vulnerable to hypoglycemia.[19]

In general, patients should be hospitalized following an insulin overdose, as prolonged hypoglycemia and/or electrolyte imbalances are common. A delay of more than 6 hours between the overdose and medical treatment is 1 factor leading to a poor prognosis.[19] Treatment of overdose involves correction of hypoglycemia (eg, by oral intake and use of dextrose), incision and drainage of the injection site, use of glucagon and/or octreotide, and close monitoring for hypokalemia. The type of insulin administered must be taken into account in order to determine the period of treatment and monitoring a patient may require. For example, treatment planning for a patient admitted after a large overdose of a long-acting insulin preparation (eg, insulin glargine, which is typically prescribed as a 24-hour dosing regimen) may involve glucose supplementation for up to several days.[21] As with any

other intentional medication ingestion, physicians must be aware of the possibility of suicide via insulin overdose and take appropriate precautions to safeguard their patients. These precautions include screening toxicology studies to rule out a polydrug ingestion (eg, benzodiazepines, tricyclic antidepressants), initiation of standard suicide precautions in the emergency department, psychiatric consultation after medical admission, and evaluation by (or transfer to) a psychiatric unit after resolution of hypoglycemia (ie, when medically cleared).

FIVE STEPS CLINICIANS CAN TAKE TO SAFELY MANAGE DEPRESSED PATIENTS PRESCRIBED INSULIN

Careful management of depressed patients who are prescribed insulin is essential to reduce morbidity and mortality. In these situations, documentation of a thoughtful assessment and plan is also critical from a risk-management perspective. Five steps can guide the clinical approach (Table 2).

WHAT HAPPENED TO MS A?

Ms A's hospitalization for depression lasted 6 weeks. While on the inpatient unit, she was closely monitored by the inpatient nurses when checking fingerstick glucose levels and when administering her insulin (according to a sliding scale). She was started on a selective serotonin reuptake inhibitor, citalopram (20 mg/d). Two weeks later, the citalopram was increased to 40 mg/d, and sustained-release bupropion (100 mg/d) was added with a modest improvement of her symptoms. She became involved with individual, group, milieu, and family therapy. At the time of her discharge, she endorsed occasional suicidal thoughts (but was without a plan or the intent to end her life). Psychiatric follow-up (including individual therapy and psychopharmacology) was arranged.

CONCLUSIONS

The case of Ms A highlights the importance of integrating the evaluation and treatment of depression with diabetes management in primary care. Patients with diabetes and untreated or undertreated depressive symptoms are more apt to be poorly adherent to their diabetes regimen; they may discontinue treatment or—most dramatically—misuse their life-sustaining medical treatment to hasten their own demise. Prompt treatment of depression may also prevent the progression of depressed mood to active suicidality and may also reduce the burden of long-term diabetes-related complications. Timely assessment can speed interventions and enable the patient with diabetes to engage in his or her treatment and life.

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This study used several methods (semistructured and structured interview instruments and self-report questionnaires) to examine the prevalence and impact of suicidal thoughts and behavior among 91 adolescents with insulin-dependent diabetes mellitus. Within this population, the rate of suicidal ideation among the diabetic adolescents (13.2% 1-year prevalence, 26.4% lifetime prevalence) was higher than expected. Two factors associated with noncompliance with prescribed medical regimens were the presence of suicidal thoughts or of a diagnosed psychiatric condition.

Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med.* 2000;160(21):3278–3285.

The authors compared results from questionnaires given to 367 patients with types 1 and 2 diabetes with corresponding medical data from primary care clinics. Using regression analyses, they showed that depressive symptom severity was associated with poorer diet and medication regimen adherence, functional impairment, and higher health care costs in diabetic patients. Patients with higher-severity depressive symptoms had a higher percentage of days in nonadherence to oral hypoglycemic regimens (15% vs 7%).

de Groot M, Anderson R, Freedland KE, et al. Association of depression and diabetes complications: a meta-analysis. *Psychosom Med.* 2001;63(4):619–630.

This meta-analysis analyzed the relationship between depression and diabetes complications in 27 studies (N = 5,374) of type 1 and type 2 adult patients with diabetes. They found a consistent association between depression and complications of diabetes (P = .00001, z = 5.94). Depression was significantly associated with a variety of diabetes complications (diabetic retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction). Effect sizes were in the small to moderate range (r = 0.17 to 0.32).

von Mach MA, Meyer S, Omogbehin B, et al. Epidemiological assessment of 160 cases of insulin overdose recorded in a regional poisons unit. *Int J Clin Pharmacol Ther.* 2004;42(5):277–280.

In this retrospective study of 160 inquiries received by a regional poison center concerning insulin overdoses, the authors sent questionnaires to physicians asking for follow-up information on etiology, concomitant medications taken by the patient, symptoms, and outcome. Of these patients, most (53%) were female, averaging 44 years of age. Nearly 90% involved suicidal or parasuicidal intent, whereas only 5% were accidental overdoses. Benzodiazepines (37.5%) were the most frequently ingested concomitant medication, followed by ethanol (15.6%). Although insulin overdose caused a high number of "major" or "serious" presenting symptoms, most patients (94.4%) achieved a full recovery. A few patients (2.4%) were left with cerebral defects.

Jacobs DG, Brewer ML. Application of the APA practice guidelines on suicide to clinical practice. *CNS Spectr.* 2006;11(6):447–454.

This thorough and practical article discusses the general approach to a suicidal patient. The authors present charts from The American Psychiatric Association Practice Guideline for the Assessment and Treatment of Patients with Suicidal Behaviors, part of the Practice Guidelines for the Treatment of Psychiatric Disorders Compendium, and a summary of the assessment information in a format that can be used in routine clinical practice. Case reports are used to illustrate important elements of the psychiatric assessment process.

Mégarbane B, Deye N, Bloch V, et al. Intentional overdose with insulin: prognostic factors and toxicokinetic/toxicodynamic profiles. *Crit Care.* 2007;11(5):R115.

This prospective study examined prognostic factors in insulin overdoses with relation to plasma insulin concentrations. The authors used logistic regression to model the toxicokinetic/toxicodynamic relationships among 25 patients with serious insulin poisoning (2 patients died). Delay to therapy in excess of 6 hours (odds ratio = 60.0, 95% CI = 2.9–1,236.7) and ventilation for longer than 48 hours (odds ratio = 28.5, 95% CI = 1.9–420.6) were identified as independent prognostic factors. This study underscores the importance of careful monitoring of serum glucose level and adjusted glucose infusion rate to optimize prognosis after an insulin overdose.

Katon WJ. The comorbidity of diabetes mellitus and depression. *Am J Med.* 2008;121(suppl 2):S8–S15.

This thorough review article discusses the difficult problem of comorbid diabetes and depression. The article outlines data suggesting that depression is associated with nonadherence to diabetes self-care (eg, following dietary recommendations, medication compliance, and glucose monitoring), which results in worse clinical outcomes. Additionally, the article reviews a number of studies that have evaluated the effect of antidepressant medication in patients with diabetes and depression.