Medical Morbidity and Mortality in Schizophrenia: Guidelines for Psychiatrists

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Background: Medical morbidity and mortality rates remain elevated in schizophrenia patients compared with the general population, in part due to potentially reversible medical risk factors. Psychiatrists should address this problem by adopting established strategies for prevention and intervention.

Method: The literature on modifiable medical risk factors relevant to individuals with schizophrenia and corresponding guidelines for prevention and treatment established by expert consensus panels were reviewed.

Results: Schizophrenia patients are at elevated risk for cardiovascular disease due to high rates of cigarette smoking and, increasingly, due to obesity, diabetes, and hypertriglyceridemia. Rates of human immunodeficiency virus infection and infectious hepatitis are also higher in schizophrenia patients. Interventions that have reduced medical morbidity in the general population can be adopted to reduce premature mortality in individuals with schizophrenia.

Conclusions: Patients with schizophrenia have high rates of potentially reversible medical morbidity. Implementation of practice guidelines for identifying and modifying risk factors could substantially improve the health of patients with schizophrenia.

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High rates of medical morbidity and excess mortality have long been associated with chronic mental illness, particularly schizophrenia. This problem is particularly vexing at a time when substantial progress has been made in the pharmacotherapy and rehabilitation of individuals with schizophrenia.[1] Along with improved clinical outcomes and a dramatic decline in medication-induced neurologic side effects has come a shift in emphasis toward improving the quality of life for people with this illness. Medical morbidity remains the domain least improved by recent treatment advances, at least in part due to unhealthy lifestyles, medication side effects, and inadequate medical care.

In recognition of the problem of medical vulnerability among persons with chronic mental illnesses, the Department of Mental Health (DMH) of the Commonwealth of Massachusetts instituted an annual mortality report beginning in 1998 covering all of the approximately 30,000 patients with serious, disabling psychiatric illnesses receiving services through this agency. Annual reviews of client mortality performed in 1998 through 2000 found elevated age-specific 1-year mortality rates for DMH patients compared with the general Massachusetts population.[2] Differences were greatest for patients between the ages of 25 and 44 years, for whom mortality rates were elevated 3-fold compared with age-matched comparison samples over each of the 3 years studied. The factor most strongly contributing to this excess mortality was cardiovascular disease; cardiac deaths were elevated more than 6-fold. Deaths related to respiratory illness (chronic obstructive pulmonary disease and pneumonias) were elevated approximately 5-fold, but, in absolute terms, were much less frequent than cardiac deaths.

Given the magnitude of this problem and the absence of a consistent approach to health promotion and medical screening in most treatment settings for people with chronic mental illness, we review the literature on modifiable medical risk factors in the general population and discuss potential applications to individuals with schizophrenia. Established guidelines developed by consensus panels representing medical specialties are combined to provide a framework for monitoring health status and for intervening to improve health outcomes.[3–10] Because pre-

mature death due to cardiovascular and pulmonary disease is especially elevated in patients with schizophrenia, we highlight modifiable risks for cardiovascular and pulmonary disease in these guidelines. We also review recommendations for screening and prophylaxis for prevalent infectious diseases.

MORTALITY IN SCHIZOPHRENIA

Whereas a meta-analysis of 18 international studies published in 1997 found a mean 1.5-fold elevation in age-adjusted mortality rates for people with chronic mental illness,[11] some reports suggest that mortality rates have been increasing further in recent decades, possibly as a result of deinstitutionalization.[12,13] Suicide and accidents have generally accounted for about 30% of excess mortality,[11] although misattribution of cause of death remains a methodological limitation of these studies. Suicide contributed less to the excess mortality in recent Massachusetts surveys. The contribution of suicide is greatest when samples include younger individuals in the first few years of the illness, who are at maximal risk. Improved pharmacologic approaches may be reducing suicide rates in schizophrenia; clozapine in particular has been associated with a decrease in suicidality, although the evidence has not been entirely consistent.[14,15] Despite high rates of cigarette smoking, cancer has not emerged as a major factor contributing to high age-adjusted mortality rates in most studies, possibly reflecting a protective genetic factor that may partially counter this risk.[16] Substance abuse also may contribute to elevated mortality rates in schizophrenia, although the magnitude of this effect is less well studied and treatment approaches for dual-diagnosed patients are beyond the scope of these guidelines.

CARDIOVASCULAR RISK FACTORS

Several risk factors for coronary disease have been identified in the general population, including cigarette smoking, obesity, hypertension, elevated serum lipids, and diabetes mellitus.[17] Cigarette smoking roughly triples the risk for cardiac disease; the other risk factors roughly double the risk. Because these factors are additive, the risk for cardiac disease is increased almost 12-fold in individuals who have all 5 risk factors compared with those who have none.[18] Other risk factors include a family history of heart disease, sedentary lifestyle, elevated homocysteine level (> 10 μmol/L), and the presence of markers of abnormal coagulation or inflammatory activity (C-reactive protein).[19] Since the first published guidelines in 1964, the American Heart Association has promoted a program of education and monitoring that has been credited with a decline in rates of coronary artery disease. The potential benefit of improving health behavior was demonstrated in a longitudinal study of 85,000 nurses; 83% of coronary heart disease events were avoided by the 3% of individuals who maintained a desirable weight, ate a healthy diet, exercised regularly, drank alcoholic beverages moderately, and did not smoke.[20] Substantial benefit also accrued to those nurses who achieved even 3 of these 5 components: 51% of coronary events were avoided. While achieving a healthy lifestyle may be more difficult for schizophrenia patients, the potential benefits warrant intensive efforts toward this goal on the part of patients and caregivers. Moreover, for many patients with schizophrenia, involvement in day programs or structured living situations may offer an opportunity to modify unhealthy lifestyles.

Cigarette Smoking

Cigarette smoking has been the single most important cause of preventable morbidity and premature mortality in the United States for over 30 years.[21] Approximately 430,000 people in the United States die each year from smoking-related illness.[22] Risk of heart disease is directly related to lifetime exposure to tobacco products; smoking cessation dramatically reduces cardiovascular mortality.[23–25]

As many as 85% of people with schizophrenia smoke cigarettes, compared with 23% in the general population.[26,27] Smoking rates are elevated among people with schizophrenia even when compared with other severely mentally ill patients and after controlling for substance abuse, institutionalization, medication, and socioeconomic status.[28–30] Approximately 20% to 40% of schizophrenia patients smoke more than 30 cigarettes per day,[31] and schizophrenia patients who smoke extract significantly more nicotine per cigarette than do other smokers, presumably through deeper inhalation.[32]

Obesity

There is a linear relationship between body mass index (BMI; weight [kg]/height [m]^2) and obesity-related morbidity and mortality. The most recently published report of the National Health and Nutrition Examination Survey (NHANES, 1999–2000)[33] revealed that the 20-year trend toward steadily higher rates of obesity in the United States continues unabated. Relative to the last survey, conducted from 1988 to 1994, age-adjusted rates of overweight (BMI > 25) have increased from 56% to 65%, obesity (BMI > 30) has risen 8 percentage points to 31%, and extreme obesity (BMI > 40) has increased from 3% to 5%.[33] Obesity contributes significantly to the risk for a number of diseases, including diabetes mellitus, coronary artery disease, hypertension, gallbladder disease, osteoarthritis, and colon, breast, and uterine cancers.[34] Abdominal (visceral) adiposity in particular increases risk for diabetes mellitus and cardiovascular disease.[3]

Mean BMIs were higher among female schizophrenia patients compared with nonpsychiatric controls in 2 large samples, whereas men with schizophrenia were similar to

controls.[35,36] From 1987 to 1996, when use of atypical antipsychotics became common, only young female patients exhibited disproportionate weight gain compared with controls.[36] However, weights were based on patient self-report and so were of uncertain validity.

The greater liability of certain atypical antipsychotics to cause weight gain relative to most (higher potency) conventional antipsychotics coupled with the increased use of atypicals is expected to increase the incidence and severity of obesity among schizophrenia patients.[37–39] Risperidone and chlorpromazine were found to increase visceral adiposity in one study of 46 treatment-naive patients.[40] In a small, preliminary study, the increase in visceral adiposity associated with olanzapine was 48% greater than with risperidone at 10 weeks in a sample of 16 treatment-naive patients, despite similar increases in total adiposity with the 2 drugs.[41] The difference in patterns of adipose distribution between the 2 drugs did not achieve statistical significance due to the small sample size. Clozapine and olanzapine are associated with the most weight gain, followed by the low-potency phenothiazines (e.g., chlorpromazine and thioridazine).[37,38] In a prospective, 5-year follow-up of 89 outpatients, Henderson and colleagues[42] found a mean 31-lb weight gain with clozapine that did not plateau until the fourth year. Compilation of data from several olanzapine trials revealed a mean weight gain of approximately 13 to 15 lb, which appeared to plateau within 1 year of treatment, was not clearly dose-related, and was clinically significant (≥ 7% gain) in 41% of patients.[43–45] Risperidone and quetiapine produce intermediate weight gain, and molindone, ziprasidone, haloperidol, and aripiprazole are associated with relatively modest or no weight gain.

No satisfactory genetic or physiologic explanations currently are available for the dramatic variability in liability for weight gain among individuals and among drugs, although a polymorphism of the 5-HT_{2C} receptor gene has been associated with weight gain. Currently, the risk for obesity cannot be predicted prior to initiating treatment.

Diabetes Mellitus

Type 1 diabetes mellitus usually has onset in childhood, is characterized by insufficient insulin secretion, and can be associated with the potentially fatal complication of diabetic ketoacidosis. Type 2 diabetes mellitus usually occurs in adulthood and is associated with insulin resistance and obesity. Both forms of diabetes increase risk of ischemic heart disease, peripheral vascular disease (often resulting in amputation), stroke, retinopathy, nephropathy, and neuropathy. Diabetes is the seventh leading cause of death in the United States and accounts for 15% of total health care costs.[5] In the adult population, diabetes is believed to have a prevalence of 8%, although approximately 35% of cases remain undiagnosed.[46] It is estimated that the diagnosis of type 2 diabetes mellitus in the general population is made on average 10 years after onset of the illness, often long after complications have developed.[47] The incidence of type 2 diabetes mellitus increases with age and with obesity. Individuals with a family history of diabetes are at increased risk, as are African Americans, Hispanics, Native Americans, and Asians. Hyperlipidemia, hypertension, and a history of gestational diabetes are also risk factors for diabetes.

Diabetes is defined by a fasting plasma glucose concentration greater than or equal to 126 mg/dL (7 mmol/L) or a random plasma glucose concentration greater than 200 mg/dL (11.1 mmol/L) when accompanied by symptoms of diabetes. Impaired fasting glucose is defined as a fasting plasma glucose concentration between 100 and 125 mg/dL. Fasting plasma glucose is more specific than a glucose tolerance test and, for reasons of relative ease and lower cost, is recommended by the American Diabetes Association as the screening test of choice,[48] although it may be difficult for some patients with schizophrenia to comply with the necessary 8 hours without caloric intake. A positive screening test should always be confirmed by a repeat fasting plasma glucose or an oral glucose tolerance test. Glycosylated hemoglobin (HbA_{1c}) testing reflects the average blood sugar level over 2 to 3 months and is useful for monitoring glucose control long-term, but is not recommended as a diagnostic screening test for diabetes.[49]

Several reports have suggested higher rates of type 2 diabetes mellitus in patients with schizophrenia compared with the general population, even before the introduction of atypical antipsychotics.[50] In a sample of medication-naive first-episode schizophrenia patients, Ryan and colleagues[51] found evidence of insulin resistance and impaired glucose tolerance, with 15% of subjects exhibiting impaired fasting glucose in the presence of elevated cortisol levels. Waist circumference did not differ between groups in this study. A large number of published case reports have linked treatment-emergent type 2 diabetes mellitus to the use of atypical agents, with clozapine and olanzapine most frequently cited.[52] Case reports filed with the U.S. Food and Drug Administration and the World Health Organization have implicated clozapine, olanzapine, and, to a lesser degree, risperidone.[53–56] Weight gain may not be a necessary condition for the development of type 2 diabetes mellitus in this population. There are several reports of diabetes developing in the absence of weight gain and resolving after discontinuation of the antipsychotic.[53,54] In an analysis of 45 cases of new onset or exacerbation of existing diabetes mellitus during treatment with an atypical agent, Jin et al.[52] found that 50% of 32 patients with available data had gained no weight, although 84% were 5% or more above ideal weight. Of the new-onset cases, 42% presented with diabetic ketoacidosis, which represents an unusually high incidence, albeit in a sample of reports prone to publication bias.

A possible relationship between diabetes and antipsychotic medication has been examined in 9 retro-

spective pharmacoepidemiologic studies utilizing 8 large databases.[56–64] In one study, psychotic patients treated with either conventional or atypical antipsychotics had a large elevation in rates of diabetes compared with general (nonpsychotic) patients, whereas differences between atypicals and haloperidol were small.[58] Higher rates of diabetes compared with conventional-treated or untreated schizophrenia patients have been associated with olanzapine in 5 of 6 studies,[56,58–61,64] with clozapine in 3 of 4 studies,[56,57,59,61] and with risperidone in 2 of 6 studies.[56,58–61,64] Significant elevations in prevalence rates of diabetes compared with conventional antipsychotics were observed in a subset of younger patients, but not overall, with clozapine in one study[57] and with risperidone in another,[61] suggesting that the age at onset of diabetes but not lifetime risk may be affected. In general, the increased incidence of diabetes in all schizophrenia patients compared with controls appears to be of a greater magnitude than the relative increases associated with individual agents, although olanzapine and clozapine appear to confer the largest risk. Consistent with this impression, Newcomer and colleagues[65] found evidence for decreased insulin sensitivity with olanzapine and clozapine compared with haloperidol and untreated normal controls in a nonrandomized cross-sectional study, whereas risperidone exhibited a smaller effect that did not differ significantly from that of haloperidol.

While the mechanism remains unclear, certain atypical antipsychotics may increase risk of diabetes indirectly via weight gain (particularly visceral adiposity) or possibly by direct effects on insulin sensitivity[65,66] or glucose transport.[66,67] It is likely that elevation of fasting glucose concentrations may be delayed in some at-risk patients because the pancreas compensates for insulin resistance by increasing secretion of insulin for a variable period of time. Many factors may be complicating the identification in population studies of a putative direct effect of certain atypical agents on glucose metabolism. In addition to a possible abnormality of glucose metabolism associated with schizophrenia, variability in other risk factors including weight, ethnicity, genetic liability, diet, and sedentary lifestyle may further obscure the relative effect of individual medications. In addition, methods for identifying cases of diabetes have not been adequately sensitive or systematic in most studies performed to date, and the risk of selection bias or publication bias is also a considerable problem in this literature.

Lipid Disorders

High total cholesterol and low-density lipoprotein (LDL) cholesterol levels are strong independent risk factors for coronary heart disease.[68] Increased risk for heart disease begins at a total cholesterol level of 160 mg/dL, well below the average level in the United States. Low levels of high-density lipoprotein (HDL) cholesterol, defined as less than 40 mg/dL in men and 50 mg/dL in women, are also firmly established as an independent risk factor for coronary artery disease. Like LDL cholesterol, the relationship between HDL cholesterol and coronary disease is continuous and graded, except HDL cholesterol is inversely related.[4] An increase in HDL cholesterol of 1 mg/dL (0.026 mmol/L) equates with an independent relative risk reduction in the incidence of coronary events by 2% in men and 3% in women.[69]

Hypertriglyceridemia is also an independent risk factor for coronary artery disease. A meta-analysis of epidemiologic studies calculated that an increase of 1 mmol/L (88 mg/dL) of plasma triglyceride increases the risk of cardiovascular disease by 32% in men and by 76% in women.[70] Triglyceride levels less than 150 mg/dL are defined as "desirable," levels of 150 to 199 mg/dL are defined as "borderline high," and levels greater than 200 mg/dL are considered "high" and should be addressed with lifestyle modification, medication, or both. Levels above 500 mg/dL are considered "very high"; above 1000 mg/dL, pancreatitis is an additional risk. Clozapine and olanzapine recently have been linked to hypertriglyceridemia.[42,71] Although other lipid and lipoprotein constituents such as apolipoprotein B and lipoprotein(a) may provide more accurate assessments of risk, the traditional lipid panel, including total cholesterol, HDL cholesterol, and triglycerides and a calculated LDL cholesterol, remains the standard approach for cardiac risk assessment.

Hypertension

Hypertension is defined as a systolic blood pressure (BP) greater than 140 mm Hg or a diastolic BP greater than 90 mm Hg.[10] The risk of cardiovascular disease, beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg.[10] Individuals with a systolic BP of 120 to 139 mm Hg or a diastolic BP of 80 to 89 mm Hg should be considered as prehypertensive and require lifestyle modifications to prevent heart disease.[10] The risk of hypertension increases with age; almost half of individuals 65 years or older in the United States have hypertension, and rates are substantially increased among African Americans. In NHANES III, conducted between 1999 and 2000, only 69% of respondents with hypertension knew they had hypertension, only 58% were being treated, and hypertension was controlled in 31%.[72] Hypertension significantly increases risk for myocardial infarction, congestive heart disease, stroke, and renal failure.[73]

The concept of hypertension as a complex clinical syndrome has evolved over the past 2 decades. It is increasingly clear that high blood pressure is a relatively late-developing component of a cluster of pathologic changes that may include loss of vascular elasticity, obesity, abnormal lipid metabolism, insulin resistance, and renal disease and that these changes reflect complex genetic and environmental factors. Target organ damage typically associated with hypertension, such as left ventricular hypertro-

phy and renal changes, has been found to precede blood pressure elevation in young adults with a genetic predisposition for hypertension. The earliest changes, known as "vascular remodeling," involve hypertrophy of vascular and myocardial walls with resulting loss of compliance or elasticity. These changes begin in the distal vasculature; loss of compliance in proximal blood vessels and overt hypertension reflect later stages of the syndrome.

INFECTIOUS DISEASES

It is estimated that about 1 in 300 Americans is positive for antibody to human immunodeficiency virus (HIV). Estimates of the rate of HIV seropositivity among patients with schizophrenia have been quite variable, due in part to the tendency for oversampling of inner-city, homeless, and inpatient populations.[74–76] Studies of outpatient, nonurban samples of chronically mentally ill patients have reported seropositivity rates between 3% and 6%.[77,78] In a representative, multistate sample of 931 outpatients with severe mental illness, the HIV seroprevalence rate was 2.9%, approximately 8 times the estimated U.S. population rate.[77]

In the same sample, rates of hepatitis B (23.4%) and hepatitis C (19.9%) were elevated by 5- and 11-fold, respectively.[77] Among other samples of individuals with severe mental illness, rates of hepatitis C seropositivity have ranged between 9% and 20%[79,80] compared with an estimated prevalence in the general population of 1.8%. Approximately 80% of seropositive individuals will develop chronic infection, and as many as 20% will progress to hepatic cirrhosis. Hepatitis C represents a growing epidemic and is currently the most common diagnosis in patients requiring liver transplant in the United States.

Several behaviors that confer risk of viral transmission have been found to occur more frequently in the severely mentally ill than in the general population and are believed to contribute to elevated rates of acquired immunodeficiency syndrome (AIDS) and hepatitis.[81] These behaviors include trading sex for drugs,[82,83] intravenous drug use,[78,84,85] and having multiple partners combined with infrequent condom use.[82,86] Women with severe mental illness are thought to be at especially high risk of contracting HIV.[87] Further, there is evidence to suggest that the male-to-female ratio of HIV seroprevalence is substantially decreased in the severely mentally ill population (4:3) relative to the general population (5:1).[77]

PULMONARY INFECTIONS

Pneumonia and influenza together constitute the sixth leading causes of death in the United States.[88] The agent most commonly responsible for community-acquired pneumonia is *Streptococcus pneumoniae*, a gram-positive diplococcus with 90 identified serotypes differentiated by variations in polysaccharides of the bacterium's external capsule. Tuberculosis has reemerged in the United States as an important cause of morbidity, with approximately 16,000 cases of active pulmonary infection identified in 2001. About 10 to 15 million people in the United States have "latent infection" (a reactive skin-test without pulmonary infection); 1 in 10 will develop active infection.[89] While the prevalence of tuberculosis has not been estimated in patients with chronic mental illness, the risk of acquiring tuberculosis is increased for those living in long-term care facilities and homeless shelters. The influenza viruses, a final important source of pulmonary infection, belong to the group of RNA myxoviruses and are serotyped A, B, and C on the basis of surface antigens.

PHYSICIAN MONITORING AND INTERVENTIONS

Smoking Cessation

Pharmacotherapy is universally recommended for treatment of nicotine dependence in the absence of specific contraindications[9,90]; the combination of behavioral and pharmacologic treatments is recommended over pharmacotherapy alone. First-line pharmacotherapies for treatment of nicotine dependence include bupropion and nicotine replacement therapy. These treatments can approximately double the smoking cessation rate over placebo.[9] Brief advice from a physician to quit smoking has been found to improve cessation rates dramatically, and cognitive-behavioral programs focused on practical problem-solving, skills training, and the provision of support are an integral part of the current guidelines for smoking cessation interventions for the general population.[90]

Over the past 5 years, evidence has accumulated to suggest that combined behavioral and pharmacologic approaches to smoking cessation are safe and of benefit for individuals with schizophrenia. Abstinence rates ranging from 10% to 55% have been reported for schizophrenia patients treated with combinations of pharmacologic and behavioral interventions.[91,92] As in the general population, physician monitoring and cognitive-behavioral interventions are recommended.[93]

When patients with schizophrenia report that they are interested in quitting smoking, clinicians are often pessimistic about their capacity to alter smoking behavior. Patients with major mental illness are given advice to stop smoking less frequently than patients without psychiatric illness.[94] It is also likely that clinicians may hesitate to recommend smoking cessation because of the concern that smoking cessation will prompt relapse of psychiatric symptoms. In addition, clinicians may worry about cardiovascular complications in patients they believe have a high likelihood of smoking concurrently with NRT.

Some,[91,95] although not all,[96] studies have found mild worsening of psychotic symptoms immediately after smoking cessation attempts in schizophrenia patients.

However, exacerbation of psychiatric symptoms was not observed in trials that utilized bupropion or NRT.[91,97,98] Persistent smoking while using a nicotine patch does not appear to pose a high risk for cardiac events; it is probably safer to smoke fewer cigarettes while receiving NRT than it is to smoke without NRT. This is because nicotine is absorbed much more readily from smoking than from patches. In addition, cardiovascular risk does not increase substantially with increasing nicotine blood levels above those typically obtained with smoking.[99]

Several quit attempts are commonly required before long-term abstinence from tobacco is achieved.[100] Clinicians should therefore assess readiness to attempt smoking cessation at every outpatient visit. For individuals who are unwilling to make a quit attempt, clinicians may improve motivation by exploring reasons that the individual would like to quit and perceived obstacles to quitting, as well as potential benefits. A strong correlation has been demonstrated between contact time with a provider and rates of successful abstinence. Practical assistance with planning and problem-solving, skill building (e.g., refusal skills, coping skills), bolstering social support around quitting, and employing aversive smoking techniques (e.g., rapid smoking) are techniques associated with the highest abstinence rates in the general smoking population.[90] Effectiveness has been found to be independent of the format (individual or group), contact type (in-person or telephone), or professional affiliation of the provider (e.g., social worker, nurse). Self-help approaches have been found to be of only marginal effectiveness in promoting abstinence.

Several factors complicate the application of existing psychosocial smoking cessation programs to individuals with schizophrenia. Schizophrenia patients may have few pleasurable activities aside from smoking, can be sensitive to withdrawal effects, may have limited social support, are apt to have a high density of smokers in their immediate environment, and may have impaired ability to monitor and characterize urges or craving. In response to these issues, psychosocial and pharmacologic interventions must be tailored for this population.[91,101–105] Smoking cessation should be initiated in schizophrenia patients only after management of psychiatric symptoms is optimized and if major depression is not present. The patient and other caregivers should be educated about nicotine withdrawal symptoms such as insomnia and irritability that can mimic early symptoms of psychotic relapse. Supportive and behavioral therapy should be offered in addition to an 8- to 12-week trial of bupropion or NRT. In patients with a history of depression, bupropion or nortriptyline are recommended. Schizophrenia patients should be monitored closely for changes in clinical symptoms during and after a smoking cessation attempt and for the emergence of medication side effects. Smoking cessation changes the pharmacokinetics of medications metabolized by cytochrome P450 1A2, often necessitating a decrease in dose; for example, smoking cessation was associated with a 57% increase in serum clozapine concentrations in one study.[106]

Weight Loss

Interventions for weight loss are recommended for individuals who are obese (BMI of ≥ 30) and those who are overweight (BMI of 25–29) and have 2 additional cardiovascular risk factors (e.g., smoking, hypertension, diabetes, or hypercholesterolemia).[3] Males with a waist circumference of ≥ 102 cm (40 in) and women with a waist circumference of ≥ 88 cm (35 in) and at least 2 risk factors for cardiovascular disease should also be advised to lose weight, regardless of their BMI, reflecting the additional risk of abdominal adiposity.[18] Waist circumference may be particularly important among schizophrenia patients treated with atypical agents.[40,41] It has been recommended that clinicians initiate an intervention, which may include switching to a more weight-neutral agent (ziprasidone or aripiprazole) if weight gain exceeds 5% of total body weight,[6] BMI increases by 1 unit,[107] or waist circumference exceeds 35 in for a woman or 40 in for a man.[107]

In the general population, behavioral weight loss programs that combine low-calorie diets, cognitive-behavioral therapy, and exercise have been shown to produce weight loss in the range of 5% to 10% over a 6-month period. It is advised that obese individuals initially target a 10% weight reduction over a period of 6 months with a rate of weight loss of no more than 2 lb per week.[18] Weight loss as little as 5% has been found to improve lipid profiles, lower blood pressure, and, in diabetics, improve glycemic control.[108] There is evidence that counseling and encouragement to adopt a more active lifestyle can improve cardiovascular health for sedentary women.[109] Unfortunately, up to 95% of individuals who successfully lose weight in behavioral programs regain that weight within 5 years.[110] Like diabetes or hypertension, obesity is a chronic condition requiring continuous monitoring and intervention over the long term.

Although weight loss tends to be determined more by caloric restriction than physical activity, physical activity is perhaps the most important predictor of successful maintenance of weight loss. Caloric intake should be determined on an individual basis, seeking to create a daily caloric deficit of 500 kcal. For women, this usually means a target intake of 1000 to 1200 kcal, and for men, 1200 to 1500 kcal per day, although controlled feeding studies have shown that energy balance may require at least 500 kcal more than these estimates, which may have been influenced by underreporting on dietary intake questionnaires or diet records. Diets should reduce high-sugar beverages and saturated and trans fat, as well as calories in general.

Cognitive-behavioral approaches to weight loss include the following types of interventions: self-monitoring, cognitive restructuring, stimulus control procedures, contin-

gency management, and social support for weight loss. Self-monitoring involves training the individual to create a written record that tracks eating behaviors, exercise, and emotional state. The goal of self-monitoring is to identify activities or emotions that trigger eating behavior. Cognitive restructuring modifies beliefs that interfere with behavioral changes necessary to lose weight. For example, "I didn't stick with my diet today, so I might as well binge on ice cream and cookies" might be modified with the more balanced thought "Although I slipped up on my program of healthy eating earlier today, I can get back on track starting with my next meal." Stimulus control refers to techniques targeting behaviors associated with eating, such as encouraging eating only at the dining table and refraining from eating while watching television. Contingency management instructs individuals to establish rewards for behaviors that support their weight loss efforts, for example, buying a new item of clothing as a reward for walking 3 days over the past week. Successful weight loss has been associated most strongly with self-monitoring, with programs of longer duration, and with continued involvement in regular exercise.[111,112]

Obesity in patients with schizophrenia may be even more difficult to treat due to antipsychotic medication effects, poor insight and motivation, limited control over diet, difficulty with planning, and poor impulse control. The relative effectiveness of psychoeducational programs focused on weight loss in this population requires further study, although a preliminary report by Wirshing and colleagues[113] was encouraging. Similarly, the safety and efficacy of pharmacologic approaches to weight reduction in patients with schizophrenia require further study.

Diabetes Mellitus

In view of the increased prevalence of type 2 diabetes mellitus among patients with schizophrenia, screening this population with a fasting plasma glucose (FPG) test is warranted. The use of atypical antipsychotics and some of the low-potency typical antipsychotics may further increase the risk of diabetes. A consensus development panel composed of experts from endocrinology and psychiatry recommended monitoring of weight every 4 weeks for 3 months, then quarterly, and measuring FPG at baseline, week 12, and annually after starting an atypical antipsychotic agent.[6] Education of patients and family members about diabetes is also very important.

The initial interventions for glycemic control in patients with type 2 diabetes mellitus, impaired fasting glucose, or impaired glucose tolerance include diet and exercise. Two studies have demonstrated the benefit of these interventions in preventing progression from impaired fasting glucose or impaired glucose tolerance to frank diabetes.[114,115] The lifestyle modifications required for benefit were modest (5%–7% weight reduction and 3150 min/week of moderate exercise). The American Diabetes Association has provided recommendations for nutrition[7] and physical activity.[116] Instruction in diabetes self-management should be part of the overall plan of care.

The goals for glycemic control include maintaining an HbA_{1c} level < 7.0%. If lifestyle modifications do not achieve this goal within 3 months, addition of oral agents or insulin should be considered. Pharmacologic therapy may be begun earlier for patients whose degree of hyperglycemia may require more rapid intervention; it may be delayed an additional 3 months for patients who appear to be achieving glycemic control by lifestyle modifications. Less stringent treatment goals may be appropriate for patients with limited life expectancy, older adults, individuals with comorbid conditions, and those with severe or frequent hypoglycemia.[8]

Prevention of the cardiovascular consequences of diabetes requires control of blood pressure and lipids, the use of aspirin (unless contraindicated), and cessation of smoking. These interventions, along with glycemic control, have reduced diabetes complications, including cardiovascular disease.[117] The goal for blood pressure control in patients with diabetes is < 130/80 mm Hg.[8] The goals for lipid levels are LDL < 100 mg/dL, triglycerides < 150 mg/dL, and HDL > 40 mg/dL.[8] The risk of developing diabetic kidney disease can be specifically assessed by testing the urine for the presence of microalbumin. It has been demonstrated that treating diabetics with angiotensin-converting enzyme inhibitors or with angiotensin-receptor blockers reduces the incidence of renal complications of diabetes in those with elevated urine microalbumin levels. People with diabetes should have urine screened for microalbumin levels yearly and a comprehensive eye examination with regular follow-up.

Lipids

Patients with elevated cholesterol or triglycerides and no other cardiac risk factors often can be managed with lifestyle modifications, including diet and exercise. Diet should aim to lower weight, replace saturated and trans fats and cholesterol with unsaturated fats, increase fiber intake, and increase omega-3 fatty acids. The National Cholesterol Education Program Adult Treatment Panel III[4] provides comprehensive guidelines for assessing risk of coronary heart disease and for therapy. Patients with diabetes or other serious cardiovascular risk factors (e.g., evidence of atherosclerosis or prior cardiac event) should be treated aggressively with pharmacotherapy to achieve an LDL cholesterol of < 100 mg/dL. A less aggressive goal of < 130 mg/dL is recommended for patients without diabetes or cardiovascular disease but with 1 or 2 other risk factors (e.g., smoking, low HDL cholesterol). It is also recommended that high triglycerides and low HDL cholesterol be treated in individuals at high risk. The "statins" (3-hydroxy-3-methylglutaryl [HMG] Co-A reductase inhibitors) have emerged as the most effective

drugs for lowering LDL cholesterol and reducing overall mortality rates, although the statins have only a modest effect on HDL cholesterol and triglycerides.[4] Fibrates are highly effective for lowering triglycerides and for reducing coronary disease and stroke, especially when overweight, insulin resistance, and other components of the metabolic syndrome are present.[4] Fibrates raise HDL cholesterol, and fenofibrate mildly lowers LDL cholesterol. Nicotinic acid (niacin) has moderately beneficial effects on all components of the lipid profile.

Hypertension

In clinical trials, antihypertensive treatment has reduced the incidence of stroke by 35% to 40%, myocardial infarction by 20% to 25%, and congestive heart failure by more than 50%.[118] The Dietary Approaches to Stop Hypertension study demonstrated that a diet rich in vegetables, fruits, and low-fat dairy products, combined with reduced intake of saturated fats, sweets, and sugar-containing beverages, can lower blood pressure.[119] Weight loss, exercise, reduced consumption of alcohol and salt, and maintenance of adequate dietary intake of potassium, calcium, and magnesium have also been shown to improve hypertension.[73] Patients who fail dietary and lifestyle interventions should be treated with antihypertensive medication and monitored closely.

Infectious Diseases

Effective vaccines for influenza and pneumococcal infections are available. Commonly used polyvalent pneumococcal polysaccharide vaccines for adults contain the 23 capsular polysaccharides that are responsible for up to 90% of invasive infections. The primary goal of vaccination is to prevent invasive pneumococcal disease, a serious complication of pneumococcal pulmonary infections most common in the elderly. Vaccination is recommended for patients 65 years or older and all adults with chronic illnesses, such as cardiovascular disease, chronic pulmonary disease (excluding asthma), diabetes, alcohol dependence, and chronic liver disease. Re-vaccination should occur upon reaching age 65. The influenza vaccine is prepared from inactivated virus updated yearly to match strains responsible for seasonal epidemics. Annual re-vaccination is necessary as virus strains change their genetic composition. Targets for influenza vaccination are groups at high risk for influenza-related complications, such as persons 50 years or older and adults with respiratory disorders. Vaccination against influenza should occur annually a few weeks prior to the onset of the flu season, usually in the late fall. Further information about vaccinations can be found on the Centers for Disease Control and Prevention Web site (www.cdc.gov) and the American Academy of Family Physicians Web site (www.aafp.org/clinical).

Patients who have spent time in an institutional setting (including group residences or day programs), who are immigrants from high-prevalence regions such as Southeast Asia or Africa, or who have been homeless should be screened for tuberculosis. Inquiry should be made into the health status of sex partners; unsafe sex practices; use of condoms; use of illicit drugs, particularly intravenously or intranasally; and needle sharing.[83] The presence of a single risk factor is an indication for HIV and hepatitis testing. Annual assay of serum antibodies for hepatitis B and C is indicated in patients with risk factors of intravenous drug use or unsafe sexual behavior.[120] Blood is assayed for the presence of antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen, hepatitis surface antibody itself, and antibody to hepatitis C. Patients who are hepatitis B surface antibody–negative, but who have liver disease or behaviors conferring ongoing risk of acquisition of blood-borne viruses, should be offered vaccination against hepatitis B. In addition to routine assessment of HIV risk, documentation of HIV status in the psychiatric chart is important since as many as 90% of severely mentally ill patients are unaware of their HIV status[78] and this information rarely appears in psychiatric records.[75] Pretest and posttest counseling is essential if HIV testing is provided.[121] Brief educational interventions have been demonstrated to decrease unsafe sexual behavior[122] and to improve AIDS knowledge,[123] suggesting that these approaches hold promise for reducing prevalence of hepatitis and HIV in the severely mentally ill. It is important that education about sexually transmitted diseases be modified to take into account cognitive deficits associated with schizophrenia.

HEALTH CARE ACCESS, CONTINUITY OF CARE, AND POLYPHARMACY

Patients with schizophrenia often have complex health care needs resulting in treatment by several specialists and involving complex medication regimens. A fragmented health care system can exacerbate the difficulties encountered by severely mentally ill patients in obtaining care. Even if access to care is secure, optimal treatment is not always rendered or accepted, and clinical outcomes have been shown in several examples to be worse for individuals with schizophrenia than in the general population. In a sample of 88,241 Medicare recipients over age 65 years who were hospitalized following a myocardial infarction, patients with a diagnosis of schizophrenia were 34% more likely to die within 1 year.[94] The higher mortality rate among schizophrenia patients could be accounted for statistically by indicators of the quality of treatment received. In another national sample, cardiac catheterization rates were 41% lower in schizophrenia patients compared with patients without psychiatric diagnoses following myocardial infarction, resulting in substantially less access to revascularization procedures.[124]

Increasingly, schizophrenia patients receive combinations of several psychotropic medications, in part driven by advances in pharmacotherapy, possibly partly due to fragmented care and overreliance on medication.[125] Polypharmacy has been identified as one risk factor for sudden death[126] and when practiced unsystematically may place patients at unnecessary risk for adverse effects and potential medical morbidity. Drug-drug interactions are probably underrecognized in schizophrenia patients, especially if psychiatric and medical treatment is provided in parallel care systems.

The optimal mode of medical health care delivery in the chronically mentally ill population is unclear, and many workable solutions may exist. In one model, Druss and colleagues[127] created an integrated clinic in which medical care providers were onsite at the mental health clinic and communicated regularly with psychiatric clinicians. This arrangement improved measures of medical outcomes compared with usual treatment delivery, without increasing total costs. Regardless of the system for medical care, psychiatrists must assume a primary role for these vulnerable patients. This role should include assessing the quality of medical care that a patient receives, arranging for the full range of health monitoring and preventive care, providing education and support regarding health and lifestyle decisions, and advocating as necessary to ensure that optimal care is made available and is accepted by the patient. Communication and collaboration with medical caregivers are essential.

While the medical guidelines (Appendix 1) that we have compiled for the care of schizophrenia patients may seem like an excessive burden to place on already-beleaguered psychiatrists, these recommendations may be prioritized according to the patient's risk factors. Ideally, most will be implemented by colleagues in primary care settings. It should be emphasized, however, that very large benefits in health and longevity can accrue from seemingly small educational or preventive interventions.

Drug names: aripiprazole (Abilify), bupropion (Zyban and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, Fazaclo, and others), fenofibrate (Tricor and others), haloperidol (Haldol and others), molindone (Moban), nortriptyline (Pamelor and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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

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Appendix 1 appears on page 194.
For the CME Posttest for this article, see pages 273–274.

Appendix 1. Medical Care of Schizophrenia Patients: Guidelines for Psychiatrists[a]

1. Initial evaluation
   a. Perform a complete medical history, substance abuse history, family medical history, and review of systems.
   b. Record weight, waist circumference, height, blood pressure, and pulse. Calculate BMI. Assess activity level.
   c. Ask specific questions about risk behaviors. Topics include risk of viral transmission, time spent in institutions, exposure to domestic or partner violence, use of seatbelts and bike helmets, smoking, and substance use.
   d. Establish communication with the patient's primary care physician and any other relevant medical care providers. If the patient is not receiving consistent medical care, a referral should be made and facilitated as necessary.
   e. Obtain results of the most recent physical examination, laboratory, electrocardiogram, and other relevant tests—if not completed within the previous 6 months, an appropriate medical evaluation should be arranged.
   f. Assess the patient's level of knowledge regarding health factors (weight, diet, exercise, smoking, high-risk sexual behaviors, and substance abuse) and receptiveness to change and provide psychoeducational resources as appropriate. General information on primary prevention of disease should be provided.
2. Every visit
   a. Review all new somatic symptoms and changes in medication prescribed by other caregivers.
   b. Monitor compliance with medical treatment.
   c. Review exposure to infectious disease, particularly unsafe sexual behaviors and parenteral drug use.
   d. If the patient is currently smoking, explore and encourage receptiveness to smoking cessation.
   e. Review use of illicit drugs and alcohol and offer treatment as appropriate.
3. Semiannually (every 6 months)
   a. Communicate with primary care physician.
   b. Assure that weight, height, waist circumference, and BMI have been recorded in last 6 months (if treatment with an atypical antipsychotic has recently been started, weight should be recorded every 4 weeks for 12 weeks, then quarterly).
   c. Assure that blood pressure and pulse have been recorded in the last 6 months.
   d. Review psychoeducational needs and refer to nutritional counseling, smoking cessation program, exercise program, safe-sex education, and substance abuse treatment as appropriate.
4. Annually
   a. Assure that fasting glucose and blood pressure have been measured annually (if treatment with an atypical antipsychotic has recently been started, blood pressure and fasting glucose should be measured after 12 weeks).
   b. Confirm that all necessary screening studies have been completed, including mammography, Pap smear, and colonoscopy as appropriate. Psychiatric interventions for anxiety or paranoia may be needed to facilitate completion of these tests. If patients are under 65 years of age and have had normal lipid profiles, measurement of lipids every 5 years may be frequent enough (if treatment with an atypical antipsychotic has recently been started, a fasting lipid profile should be performed after 12 weeks).
   c. Review immunization status (PPD, hepatitis B, pneumococcal, and tetanus).
   d. Review residential safety including smoke detectors and removal of firearms.
   e. Review health habits including exercise and use of seatbelts and bicycle helmets.
   f. Formulate goals with patient for health enhancement and primary prevention.

Special circumstances

1. Overweight patients: BMI ≥ 30 or BMI ≥ 25 and 2 obesity-related risk factors, OR waist circumference ≥ 88 cm or 35 in (women) or waist circumference ≥ 102 cm or 40 in (men) and 2 obesity-related risk factors
   a. Refer for nutritional counseling and exercise program after medical clearance.
   b. Weight reduction programs should last at least 6 months and be continuously followed up.
   c. Consider a switch to a weight-neutral antipsychotic agent (ziprasidone, aripiprazole, molindone).[b]
2. Abnormal fasting glucose
   a. Refer for nutritional counseling and exercise program after medical clearance.
   b. Refer for medical assessment.
   c. Educate patient and family members about warning signs of diabetes out of control (polyuria, polydipsia, weight loss).
   d. Consider a switch from clozapine or olanzapine to alternative agents.[b]
3. Smoking
   a. Assess receptiveness to smoking cessation.
   b. Offer advice and encouragement to stop smoking.
   c. Refer for smoking cessation program offering behavioral interventions and NRT or bupropion.
   d. Provide frequent contact during attempts to stop smoking—monitor for signs of increased medication levels in response to smoking cessation.
   e. Encourage repeated attempts to quit in the face of failed attempts.
4. Hypertension
   a. Refer for nutritional counseling and exercise program after medical clearance.
   b. Review salt and alcohol intake and overall diet, particularly intake of fruit and vegetables.
   c. If patient is a smoker, encourage smoking cessation program.
   d. Refer for medical evaluation and treatment.
5. Hyperlipidemia
   a. Refer for nutritional counseling and exercise program after medical clearance.
   b. Assure yearly measurement of fasting serum lipids.
   c. Refer for medical evaluation.
   d. If the patient is treated with clozapine or olanzapine, consider a switch to another antipsychotic medication.[b]
6. High-risk behaviors for HIV or hepatitis
   a. Refer for intensive behavioral education program.
   b. Refer for counseling and HIV and hepatitis screening as appropriate.
7. Starting an atypical antipsychotic
   a. Record weight (BMI), waist circumference, blood pressure, fasting glucose, and fasting lipid profile at baseline.
   b. Repeat weight and waist circumference measurements every 4 weeks for 12 weeks, then quarterly.
   c. Repeat blood pressure and fasting glucose measurements at 12 weeks, then annually.
   d. Repeat lipid profile at 12 weeks, then every 5 years.
   e. Monitor closely if the patient gains 5% or more of his or her initial weight, BMI increases by 1 unit, waist circumference is 35 in or greater in women or 40 in or greater in men, or elevated fasting glucose or undesirable lipid levels develop. Implement interventions listed above as appropriate.

[a]Based on references 3–10 and 107.
[b]In stable patients, medication switches should be considered only if other interventions fail to reduce medical risk. The effectiveness of the current medication must be carefully weighed against the relative risk of medical morbidity—particularly in patients with histories of suicidality who have responded preferentially to the current medication. Risk of weight gain is greatest with clozapine and olanzapine, intermediate with risperidone and quetiapine, and least with aripiprazole and ziprasidone. Dyslipidemia and diabetes are most strongly associated with clozapine and olanzapine; an association with risperidone and quetiapine is uncertain, and limited data have not indicated an association with aripiprazole or ziprasidone.[6]
Abbreviations: BMI = body mass index, HIV = human immunodeficiency virus, NRT = nicotine replacement therapy, PPD = purified protein derivative.