

Prevention of Metabolic Syndrome in Serious Mental Illness

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KEYWORDS

- Metabolic syndrome • Mental illness • Lifestyle management
- Antipsychotic medication

In the past decade, increasing attention has been focused on the nonpsychiatric morbidity and mortality associated with psychiatric disorders. There is evidence from as far back as 1919¹ that individuals with serious mental illnesses had a shortened life span. Nevertheless, many were shocked by recent data showing that, even in the modern era, a person with schizophrenia or bipolar disorder has a 20% to 25% shortening of life expectancy.² The most frequent causes of premature mortality in persons with mental illness are heart disease, cerebrovascular disease, and pulmonary disease.² A systematic review of cohort studies examining total and all-cause mortality in persons with schizophrenia has shown that life expectancy is 20% lower among those with schizophrenia than in the general population,³ with cardiovascular disease (CVD) as the most frequent natural cause of death. These data are in close accord with numerous large epidemiologic investigations that have consistently found higher standardized mortality ratios (SMR) and higher rates of CVD for persons with schizophrenia compared with contemporary cohorts in the general population.⁴⁻⁸ The data for bipolar disorder and other severe mood disorders are similar for persons with schizophrenia with higher SMR and rates of CVD compared with the general population.^{9,10} The rates of metabolic syndrome are also higher in persons with schizophrenia^{11,12} and those with bipolar disorder.^{13,14} Patients with severe mood disorders, including depression, have also been found to be at higher risk for heart

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disease after 2 years of treatment, even though they were not different from the general population at baseline.¹⁵ Thus, in the effort to restore years of life lost by persons with serious mental illness, preventing or postponing the development and progression of heart disease is the natural target of these efforts.

WHAT IS THE METABOLIC SYNDROME?

The term metabolic syndrome was coined to describe a constellation of risk factors (central obesity, insulin resistance, raised blood pressure, and abnormal lipid profile) that were thought to be highly predictive of increased risk for heart disease, especially coronary heart disease.¹⁶ Current criteria for metabolic syndrome are summarized in **Table 1**. Recent meta-analyses confirm that persons with metabolic syndrome have almost double the risk of incident heart disease and coronary artery disease than those without the syndrome.^{17,18} Because insulin resistance is a core component of metabolic syndrome, individuals with the syndrome are also at greater risk for developing diabetes, and diabetes is by itself a risk factor for heart disease.¹⁹

In recent years, questions have been asked about whether the component abnormalities included in the metabolic syndrome are simply additive in their effect on risk, or whether meeting criteria for the syndrome provides any additional predictive power with respect to risk for heart disease.²⁰ Despite these unresolved questions, the term metabolic syndrome is retained in this article, as it is so well known in the field of risk reduction. However, risk reduction is discussed in terms of the various individual risk factors, because there is no treatment for metabolic syndrome per se. Interventions most likely to reduce the risk of CVD include reduction in weight, treatment of hypertension, treatment of dyslipidemia, treatment of insulin resistance and diabetes, and cessation of smoking. Smoking is not discussed in this article, but the importance of smoking as a risk factor for heart disease needs to be mentioned because of the high rates of smoking among persons with serious mental illness.²¹

Table 1

Metabolic syndrome: screening tools and National Cholesterol Education Program (NCEP) and International Diabetes Federation criteria

Hypertriglyceridemic waist phenotype: simultaneous presence of

Fasting triglycerides >2.0 mmol/L

Waist circumference >90 cm

Metabolic syndrome criteria met if any 3 of the following are present

NCEP/ATP-III criteria

International Diabetes Federation

Presence of at least 3 of 5 parameters:

Blood pressure >130/85 mm Hg

Same, or specific treatment

Fasting glucose \geq 6.1 mmol/L (110 mg/dL)

Fasting plasma glucose >100 mg/dL (5.6 mmol/L) or type 2 diabetes diagnosis

Fasting triglycerides \geq 1.7 mmol/L (150 mg/dL)

>150 mg/dL (1.7 mmol/L) or active treatment

HDL-C

Men <1.0 mmol/L 40 mg/dL

Women <1.3 mmol/L 50 mg/dL

<40 mg/dL (1.03 mmol/L) for men,

<50 mg/dL (1.29 mmol/L) for women

Waist circumference

Men >102 cm

Women >88 cm

Ethnicity specific, in whites, men >94 cm, women >80 cm

METABOLIC SYNDROME AND OBESITY IN SERIOUS MENTAL ILLNESS

There has been a marked increase in overweight and obesity in the past 25 years, with the prevalence of obesity among all adults rising from 13% to 32% for both genders, and among all racial/ethnic and age groups.²² Obese individuals have an increased risk of several adverse health outcomes, notably hypertension, diabetes, CVD, arthritis, disability, and mortality.²³ Obesity is an independent risk factor for CVD²⁴ and the degree of obesity correlates with CVD risk.²⁵

Exceptionally high rates of obesity have been reported for patients with schizophrenia.^{11,26} A survey by Dickerson and colleagues²⁷ found rates of obesity as high as 50% in women and 42% in men in a random sample of outpatients with schizophrenia compared with US population data and much higher rates of severe obesity (body mass index [BMI], calculated as weight in kilograms divided by the square of height in meters) $>40 \text{ kg/m}^2$. The mean baseline BMI in the CATIE study was 29.7 kg/m^2 , with 36.6% of men and 73.4% of women classified as having central obesity, defined by a waist circumference in excess of 102 and 88 cm, respectively.²⁸

LIFESTYLE MANAGEMENT TO PREVENT WEIGH GAIN AND REDUCE WEIGHT

The foundation of risk reduction in both heart disease and diabetes lies in changing lifestyle, specifically eating and exercise, with the purpose of maintaining a healthy weight (preventing or treating obesity) and increasing physical activity and fitness. Guidelines for weight management were proposed by the National Heart, Lung and Blood Institute (NHLBI) in 1998, as an aid to reduce and postpone the incidence of heart disease. The Canadian Cardiovascular Society and Guidelines²⁹ and the American Diabetes Association also state that "You can prevent or delay the onset of type 2 diabetes through a healthy lifestyle."³⁰ These recommendations are supported by several large clinical trials demonstrating that weight loss does delay or prevent the onset of type 2 diabetes in at-risk individuals^{31,32} and reduce the risk of heart disease.³³

Preventing weight gain can, in turn, prevent many of the obesity-related risk factors for CVD (ie, insulin resistance and type 2 diabetes mellitus, dyslipidemia, hypertension, and vascular inflammation).³⁴ In terms of weight loss, evidence supports that even small reductions in body weight can lead to substantial improvements in a metabolic risk profile predictive of CVD and type 2 diabetes mellitus.^{35–37} Weight loss of as little as 5% of initial body weight, if the decrease is predominantly adipose tissue volume, can postpone the onset or prevent CVD, type 2 diabetes, hypertension; hyperlipidemia, cardiorespiratory failure and other chronic degenerative diseases.^{38,39}

With regard to glucose metabolism, insulin sensitivity improves rapidly before much weight loss occurs and continues to improve with continued weight loss.⁴⁰ In patients who are already obese, for example, and have a risk profile predictive of type 2 diabetes mellitus, a 5% weight loss at the end of 1 year of dietary therapy can decrease fasting blood glucose, insulin, hemoglobin A_{1c} concentration, and the dose of oral hypoglycemic therapy.⁴¹ Modest (5%) weight loss can also have preventative effects, decreasing the 4- to 6-year cumulative incidence of diabetes by more than 50% in obese persons with already impaired glucose tolerance.³²

In terms of lipid abnormalities, weight loss decreases serum levels of low-density lipoprotein-cholesterol (LDL-C) and triglycerides, whereas increases in serum levels of high-density lipoprotein-C (HDL-C) are typically seen only after weight loss is sustained.⁴² The greatest relative improvements in serum triglycerides and LDL-C usually occur within the first 2 months of weight loss versus weight gain.^{43,44} A sustained weight loss of 5% is needed to maintain a decrease in serum triglyceride

concentrations; serum total cholesterol and LDL-C revert toward baseline if weight loss is not maintained.⁴⁵

Changes in body weight changes can correlate with systolic and diastolic blood pressure in a dose-dependent manner; therefore, greater weight loss is generally associated with decrease in blood pressure, and weight gain with increase in blood pressure.⁴⁶ Weight loss and subsequent regaining of weight results in a steady increase in blood pressure toward baseline and beyond.

Unfortunately all large clinical trials of prevention of heart disease and diabetes have systematically excluded patients with severe mental illnesses. Studies on weight reduction in patients with schizophrenia have been taking place only in the last few years.⁴⁷ Studies on prevention of weight gain are much fewer. In this article, the evidence on efficacy of weight loss studies and on prevention of weight gain are reviewed, focusing on studies using a randomized controlled design.

There are now several good randomized, controlled, clinical trials of standard behavioral strategies for weight reduction as listed in **Table 2**, and reviewed in detail elsewhere.⁴⁷ Almost all of the studies have reported either greater weight loss or less weight gain in subjects who were assigned to the behavioral treatment as opposed to standard care or similar alternative.

In terms of true prevention studies, the evidence base is much smaller, not because of negative studies, but because of the small number of efforts undertaken up to the present time. One recently published study⁵¹ evaluated a dietician-delivered nutritional counseling program to prevent weight gain in patients starting treatment with olanzapine. Fifty-one individuals were randomized to either 6 one-on-one nutrition education sessions, provided by a registered dietician, or to usual care. The primary outcomes were changes in weight and BMI at 3 and 6 months after baseline assessments. Subjects in the intervention group had gained less weight than the controls at both 3 and 6 months (2.0 kg vs 6.0 kg at 3 months [$P < .002$] and 2.0 kg vs 9.9 kg at 6 months [$P < .013$]). At 6 months the BMI of the intervention group had increased by 0.8 kg/m² versus an increase of 3.2 kg/m² in the controls ($P < .017$). However, the proportion of patients in whom weight gain could be completely prevented was not reported. In a pilot randomized controlled trial, Brar and colleagues⁵² applied the standard weight loss strategies in a stepped manner to prevent weight gain in 51 subjects who were starting on a variety of novel antipsychotics. They found that 63% of subjects randomized to the intervention did not gain weight compared with only 22% of those randomized to usual care ($P = .02$).

There have also been attempts to explore the potential for preventing antipsychotic-induced weight gain by pharmacologic means. On a theoretical basis, it was proposed that histamine H₂ blockers might interfere with antipsychotic-induced weight gain. However, it was found that nizatidine had only a transient effect of ameliorating olanzapine-induced weight gain.⁵⁷ Poyurovsky and colleagues⁵⁸ investigated another H₂ blocker, famotidine, in a double-blind placebo-controlled trial on patients starting treatment with olanzapine. They found no difference in weight gain between subjects who were randomized to receive famotidine and the controls.

Metformin, an insulin-sensitizing biguanide, is indicated for lowering blood sugar in type 2 diabetics, and is often associated with weight loss. The possibility that it might prevent weight gain associated with olanzapine has been investigated. Early small pilot studies suggested some benefit for weight loss.^{59,60} However, a randomized double-blind placebo-controlled trial failed to show any evidence that metformin attenuated olanzapine-induced weight gain.⁶¹ However, a recent trial did find that metformin was more effective in producing weight loss than behavior therapy alone, but that the combination of behavior therapy and metformin was more effective than either of them alone.⁶²

Table 2
Randomized controlled clinical trials of lifestyle interventions for weight loss in schizophrenia

Authors	Intervention	N	Duration	Results
Harmatz & Lapuc, ⁴⁸ 1968	Diet only Diet + group therapy Diet + negative reinforcement	21	10 wk	0% -2% -7%
Rotatori et al, ⁴⁹ 1980	Behavior therapy adapted from Down syndrome intervention	14	14 wk	Intervention -7.3 lb Controls +0.4 lb
Littrell et al, ⁵⁰ 2003	Weekly groups on diet and exercise versus usual care	70	16 wk	Intervention -0.3 kg Controls +4.3 kg
Evans et al, ⁵¹ 2005	Six 1-hour nutrition education sessions within 3 months in patients started on olanzapine versus usual care	51	6 mo	Intervention +2 kg Controls +9.9 kg (increase of $\geq 7\%$ bodyweight: 13% of intervention group, and 64% of controls)
Brar et al, ⁵² 2005	Behavior therapy; nutrition, exercise and behavioral interventions versus usual care	72	14 wk	Intervention -2 kg Controls -1.1 kg (5% weight loss in 32.1% of intervention subjects vs 10.8% in controls)
Weber and Wyne, ⁵³ 2006	Cognitive/behavioral group intervention in outpatients with schizophrenia on novel antipsychotics versus usual care	17	16 wk	Cognitive/behavioral group -5.4 lb Controls -1.3 lb
Jean-Baptiste et al, ⁵⁴ 2007	Weekly group behavioral sessions, food replacement (by reimbursement)	18	16 wk	Intervention group -2.8 kg Controls +2.7 kg
Khazaal et al, ⁵⁵ 2007	Weekly cognitive behavior therapy groups versus single nutrition education session	61	12 wk	Intervention group -2.9 kg Psychoeducation group -0.08 kg
Wu et al, ⁵⁶ 2008	Lifestyle intervention (education, diet, exercise) versus usual care, versus metformin (Met) versus Met plus lifestyle	128	12 wk	Lifestyle group -1.4 kg Met group -3.2 kg Met + lifestyle group -4.7 kg Usual care group +3.1 kg

MEDICATION CHOICE TO REDUCE THE RISK OF DEVELOPING METABOLIC SYNDROME

Choice of antipsychotic medication may provide one of the rare opportunities for primary prevention in psychiatry. It is well established that the risk of weight gain and worsening of other metabolic parameters, such as dyslipidemia, varies between various antipsychotic agents.⁶³ For example, data from the registration trials show that the risk for clinically significant weight gain (using >7% gain more than baseline as the cutoff) was about 10 times greater when comparing olanzapine with placebo, although for drugs such as ziprasidone, aripiprazole, and paliperidone it was only about twice the risk of placebo. **Fig. 1** shows the proportions of subjects who gained 7% or more weight in short-term trials when randomized to antipsychotics or placebo. Thus, if the initial choice of antipsychotic is based on the associated risk of metabolic abnormalities, there is a compelling argument to be made for choosing a low-risk agent to start with. If the initial choice does not prove to be efficacious, the clinician can always switch to another agent after explaining the risk to the patient and obtaining their agreement to the choice. The results of the CATIE²⁸ and CTULASS⁶⁴ pragmatic clinical trials found that some of the older antipsychotics, such as perphenazine, were also associated with low risk of worsening metabolic indicators, such as weight and lipid levels. The older antipsychotics are generally thought to carry a greater risk of tardive dyskinesia compared with the newer agents, and this hazard needs to be discussed with the patient and caregivers if the prescriber is recommending one of the older agents. Ideally, decisions about choice of medication need to be made in collaboration with the patient who should be informed of the competing risks of the various choices so they can participate in the choice of medications in a well-informed manner.

Children and youth are particularly susceptible to weight gain when treated with antipsychotics.^{63,65} For this reason, and because any metabolic abnormalities experienced at a young age are likely to have an adverse influence on risk for a long time, the choice of drug in children needs to be considered with even greater thought toward future consequences than in adults. The recently completed TEOSS study found that molindione, another older agent, had a more benign metabolic profile than olanzapine, but equivalent efficacy in youth with early onset schizophrenia.⁶⁶

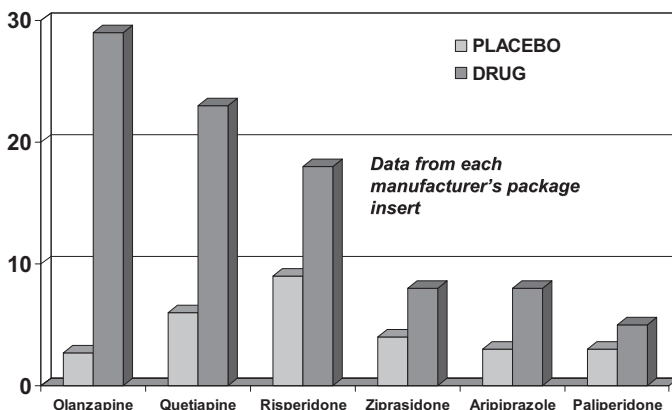


Fig. 1. Proportion of subjects gaining $\geq 7\%$ of weight in short-term randomized clinical trials involving novel antipsychotics.

SWITCHING ANTIPSYCHOTIC MEDICATION

Patients who experience weight gain in the course of treatment present opportunities for secondary prevention of metabolic syndrome. Because there are well-established differences in the weight gain liability of the different antipsychotics, patients who gain weight on one of the agents known to be associated with a high risk of weight gain might be candidates for a switch to an agent with a lower risk. Several recent studies have indeed shown that a significant proportion of patients might show improvement in metabolic syndrome components after such a switch. Reductions in body weight and lipids occurred when patients were switched from olanzapine or risperidone to ziprasidone,⁶⁷ from olanzapine to aripiprazole,⁶⁸ or from aripiprazole to usual care (ie, olanzapine, quetiapine, risperidone).⁶⁹ Effect sizes of weight loss and metabolic improvements are in line with what can be expected from an adjunct pharmacological weight loss intervention.^{67,68} Antipsychotic efficacy and side effect profile considerations need to be carefully balanced because the greater efficacy of some of the antipsychotics²⁸ are also associated with higher risk of metabolic side effects.⁷⁰ Clozapine presents a particularly difficult dilemma for patients and clinicians when other antipsychotics have not been efficacious, because it has consistently been shown to have both higher efficacy and higher risk of metabolic complications than other antipsychotics.^{28,71} These decisions are best approached in collaboration with a well-informed patient and his/her caregivers.

INFLAMMATION IN METABOLIC SYNDROME

Because antipsychotic-induced weight gain in patients with schizophrenia may preferentially manifest as an increase in central body fat content rather than muscle mass or intercellular water,^{72,73} this increased central adiposity renders patients with schizophrenia especially prone to metabolic adverse events.⁷⁴ This is because the accumulation of excess fat in central adipose tissue is often accompanied by a chronic subacute state of inflammation, shown by changes in both inflammatory cells and biochemical markers of inflammation.⁷⁵ These changes can be seen systematically in the tissues involved, in terms of increased circulating levels of inflammatory markers. In particular, increased levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF- α), and interleukin-6 promote vascular endothelial damage through modulation of vascular nitric oxide and superoxide release, thus providing an important link between obesity and CVD^{76,77}; they also mediate common denominators of cardiometabolic risk, including liver and muscle insulin resistance, lipid metabolism, and hypertension, thereby contributing to the increased prevalence of the metabolic syndrome in central obesity.⁷⁸ At the same time, the potentially protective adipokine, adiponectin, is reduced. All these changes have been implicated as cause of the metabolic risk factors.¹⁶ It is possible that, in the future, indices of inflammation will be added to the criteria for metabolic syndrome.

METABOLIC MONITORING

As the prescribers of most psychotropic medications that may initiate or accelerate the development of metabolic syndrome, psychiatrists have been urged or, in some situations, mandated to monitor adverse metabolic changes their in patients. An influential recommendation appeared recently from a consensus panel convened by the American Psychiatric Association, the American Diabetes Association, the American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity.³⁰ The recommendations of this consensus meeting are summarized

in **Table 3**. Despite these recommendations, the rate of monitoring for various components of metabolic syndrome remains low in treatment settings. Some community settings, in which most individuals with serious mental illness receive treatment, do not have facilities for monitoring lipids and blood sugar.⁷⁹ The obvious solution is to increase the capabilities of the community treatment providers. However, this may not occur as rapidly as necessary, but some elements of metabolic monitoring can be implemented in most settings. Because weight gain and central adiposity are so closely correlated with changes in lipids and blood sugar, a minimum requirement could be weight and waist circumference monitoring in all settings. The authors also believe that blood pressure should be monitored at least once a year. Blood pressure can be measured by an automated device if a physician is not available, willing and/or skilled in taking blood pressure. Once adverse changes are detected using these simple clinical tools, affected patients could be referred to settings where blood work and interventions, if necessary, can be performed. Although these latter recommendations may fall short of the current official recommendations, the authors believe that, from a public health perspective, more individuals at risk may receive interventions if these measures were in place than is currently the case.

TREATMENT OF COMPONENTS OF THE METABOLIC SYNDROME

When metabolic syndrome is present, or when any one of the risk factors appears, treatment to reduce or normalize the level of the risk factor is the obvious medical response. Primary goals in the clinical management of individuals who have developed the metabolic syndrome are to reduce the risks for clinical atherosclerotic disease and diabetes. First-line therapy should be directed toward the major risk factors: LDL-C, hypertension, and diabetes. Prevention of type 2 diabetes mellitus is another important goal when it is not present in a person with the metabolic syndrome. The prime emphasis in management of the metabolic syndrome is to mitigate the modifiable, underlying risk factors (obesity, physical inactivity, and atherogenic diet) through lifestyle changes.¹⁶

Weight reduction has already been discussed; lifestyle changes aimed at weight reduction are the recommended initial approach to mild increases of metabolic syndrome components in all influential guidelines including the Adult Treatment Panel (ATP)-III recommendations, NHLBI,¹⁶ and Canadian Cardiovascular Society.²⁹ Weight loss predictably lowers cholesterol, blood pressure, blood glucose, and insulin resistance.¹⁶

Treatment of Hyperglycemia and Type 2 Diabetes Mellitus

Recent efforts in the mental healthy population have centered around preventing the onset of type 2 diabetes mellitus, including preemptive lifestyle changes and early

	Baseline	4 Weeks	8 Weeks	12 Weeks	Every 3 Months	Yearly	5 Years
Personal/family history	x					x	
Weight (BMI)	x	x	x	X	x		
Waist circumference	x					x	
Blood pressure	x			x		x	
Fasting plasma glucose	x			x		x	
Fasting lipid profile	x			x			x

detection using Homeostatic Model Assessment (HOMA) of insulin resistance incorporating fasting glucose and insulin to detect increasing insulin resistance before hyperglycemia becomes manifest. However, such efforts highlight the complexity of discerning between diabetes prevention and early intervention.⁸⁰ Primary prevention may be difficult to achieve, especially if metabolically active antipsychotic medications are prescribed and secondary prevention becomes paramount. However, as with obesity, weight reduction, increased physical activity, or both will delay (or prevent) onset of type 2 diabetes. Several available studies on nonpsychiatric populations have demonstrated a reduction or delay in the development of type 2 diabetes, focusing on metformin, thiazolidinediones, and acarbose.^{81–83} In addition, orlistat, acarbose, and lifestyle modification have been shown to reduce adverse cardiovascular outcomes but manifestation of type 2 diabetes.^{80,84–86} Neither metformin nor thiazolidinediones are recommended solely for the prevention of diabetes because their cost-effectiveness and long-term safety have not been documented. For patients with established type 2 diabetes, a reduction in CVD risk from treatment of dyslipidemia and hypertension has been reported.¹⁶

Thiazolidinediones are peroxisome proliferator-activated receptor gamma (PPAR γ) agonists that improve insulin sensitivity and stimulate adipogenesis. Thiazolidinediones for antipsychotic-induced hyperglycemia are under study.⁸⁷ Because of their action at the cellular level, mediated via an increase in PPAR gene expression, which, as a nuclear steroid hormone receptor, induces transcriptional upregulation of fatty acid transport proteins, they facilitate fatty acid entry into cells and the enzymes involved in the β -oxidation of fatty acids, potentially causing an increase in body fat. Hepatic dysfunction and cardiovascular risk are associated with this class of medications.⁸⁸ Cardiovascular benefits with glitazones are uncertain because of possible adverse cardiovascular events associated with these agents, and decisions to treat with these agents should be made on a case-by-case basis.

Metformin inhibits hepatic gluconeogenesis, reduces gastrointestinal glucose absorption, induces peripheral glucose uptake, and decreases the release of fatty acids via feedback regulation. Metformin has recently garnered some attention because a small trial showed that it attenuated olanzapine-induced weight gain and moderated insulin resistance. In this 12-week, double-blind, placebo-controlled trial, 128 newly treated Chinese patients with schizophrenia receiving antipsychotics were randomized to 4 arms after gaining more than 10% of preintervention body weight: placebo, metformin 750 mg daily, metformin 750 mg daily plus lifestyle changes, or lifestyle changes alone. The combination treatment of metformin and lifestyle changes showed the greatest benefit for weight loss, and, as expected, insulin sensitivity improved with metformin and lifestyle changes, and metformin alone.⁶²

Adjunctive Therapy for Hyperlipidemia

Consistent with ATP-III and American Diabetes Association (ADA) guidelines, patients should have their cholesterol levels (total cholesterol, LDL-C, and HDL-C) and triglycerides measured on a regular basis. Established criteria allow for further stratification of CVD risk categories according to LDL and HDL levels. ATP-III recommends that atherogenic dyslipidemia can become a target for lipid-lowering therapy after the goal for LDL-C has been attained. That is, as long as LDL-C remains increased, it is the primary target of therapy, even in the metabolic syndrome, and other lipid risk factors are secondary.¹⁶ If indicated, initial steps call for therapeutic lifestyle changes that include a low-fat and high-fiber diet, increased physical activity, and weight management. If unsuccessful, drug therapies including statins, bile acid sequestrants,

niacin, and fibric acid may be initiated. Referral to a primary care or internal medicine physician is recommended.

Statins

Statins have proven efficacy for the prevention of CVD morbidity and mortality. Statins preferentially lower LDL-C and triglyceride levels, and have minor positive effects on HDL levels. The mode of action is interference with 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA), a key enzyme for cholesterol synthesis preferentially located in the liver. The net effect is lower cholesterol content in hepatocytes, and secondary stimulation of LDL receptor expression and increased LDL removal. Statins show benefits in managing the metabolic syndrome in several studies,⁸⁹ confirmed by a randomized controlled trial using rosuvastatin and atorvastatin.^{90,91} In addition to their lipid-lowering potency, these outcomes suggest that statins improve other aspects of the metabolic syndrome than hyperlipidemia through modulation of inflammatory and thrombogenic responses.⁹² Statins have a relatively benign safety profile. Myotoxicity, ranging from mild increase in creatine kinase levels to rhabdomyolysis, as well as hepatotoxicity can occur. The incidence of rhabdomyolysis is low, less than 0.1%. Most statins are metabolized by cytochrome P-450 isoenzymes and require close monitoring if administered with clozapine, olanzapine, and risperidone. Statins do differ in their absorption, plasma protein binding, excretion, solubility, and perhaps efficacy, and choice of medication should be made on an individual basis. Few trials have specifically assessed the safety of statins in schizophrenia.⁸⁹

Treatment of High Blood Pressure

The goal for antihypertensive therapy without the presence of diabetes is a blood pressure less than 140/90 mm Hg, and in the presence of diabetes the goal is less than 130/80 mm Hg.⁹³ Lifestyle changes deserve increased emphasis in people with metabolic syndrome; the goal should be to reduce blood pressure as much as possible even in the absence of overt hypertension and to gain other metabolic benefits of lifestyle changes.¹⁶ Effective lifestyle changes can include weight control, more physical activity, alcohol moderation, sodium reduction, and increased consumption of fresh fruits, vegetables, and low-fat dairy products.⁹³ Angiotensin-converting enzyme (ACE) inhibitors are first-line therapy for hypertension in the metabolic syndrome, especially when type 2 diabetes is present. Alternatives include angiotensin receptor blockers, which may lower the risk for diabetes,⁹⁴ and diuretics, or a combination thereof.

INTEGRATION OF PSYCHIATRIC AND NONPSYCHIATRIC MEDICAL CARE

Psychiatrists may accept the responsibility for monitoring the presence or appearance of hypertension, dyslipidemia, or insulin resistance, but, at the present time, they are not likely to undertake to treat these conditions, nor would this be the best care for the patient. The data available show that patients with severe mental illnesses typically receive lower quality primary medical care and have worse outcomes than those without mental illness,⁹⁵ that survival after a myocardial infarction was reduced by 35% if the individual had schizophrenia, and that these individuals were less likely to have received evidence-based interventions such as ACE inhibitors, aspirin, and reperfusion. In the CATIE trial, at baseline, 30% of those with diabetes, 62% of those with hypertension, and 88% of those with abnormal lipids, were not receiving treatment for these abnormalities. A Canadian study of rehospitalization after a cardiac event found that those with schizophrenia were significantly more likely than those with no mental illness to be rehospitalized (adjusted hazard ratio 1.43, 95%

confidence interval [CI] 1.22–1.69) for a cardiac event in the following 4 years.⁹⁶ These differences in outcome for heart disease treatment suggest that there are problems with access or delivery of care to people with severe mental illnesses, and that it is likely that this difference in the quality of care contributes to worse nonpsychiatric medical outcomes.

It has been proposed that a system that integrates the practitioners of both psychiatric and nonpsychiatric care might result in improved health outcomes for the seriously mentally ill. Druss and colleagues⁹⁵ randomized patients to either an integrated clinic in which both primary care and psychiatry were colocated, or to usual care in which there was no direct integration of psychiatric and nonpsychiatric medical services. They were able to show that there were improvements in ease of access to primary medical and preventative services. A recent study⁹⁷ tested the benefits of a medical case management model, using nurse case managers, in a randomized, controlled clinical trial. At the end of a year, the intervention group were found to have received significantly more recommended preventive services compared with the controls (58.7% vs 21.8%); have received more “evidence-based services for cardiometabolic conditions” (34.9% vs 27.7%); were more likely to have a primary care provider (71.2% vs 51.9%). A subset of subjects had sufficient data to calculate the Framingham Cardiovascular Risk Index and, in this subset, those in case management had significantly lower risk (6.9) than the controls (9.8). Kilbourne and colleagues⁹⁸ studied a self-management program for patients with bipolar disorder in a randomized, controlled clinical trial of persons recruited from a Veterans Administration hospital. The psychoeducational program (BCM) addressed symptom management and behavior change related to both mood disorder and risk factors for cardiovascular disease. They found that the controls showed worsening of both the mental and physical components of the SF-12, whereas those randomized to BCM showed some improvement in both components. These studies demonstrate the tantalizing possibility that the mortality gap between people with serious mental illness and the rest of the population might be narrowed or even eliminated by a variety of measures focusing on their nonpsychiatric health issues and integrating them into the overall treatment approach. It is disappointing that there has not been more funding to systematically study these approaches. To determine whether there is an effect on actual CVD outcomes will also require funding of long-term studies, because such outcomes take years to develop. Persons with serious mental illness have also been systematically excluded from large trials involving prevention of CVD and diabetes, thus data on the efficacy of those interventions on the risk in these highly vulnerable individuals are not available.

SUMMARY

The metabolic syndrome is highly prevalent in schizophrenia and other serious mental illnesses, and represents a constellation of risk factors for cardiovascular disease and type 2 diabetes mellitus. Genetic factors, treatment with antipsychotic medication, socioeconomic status, and lifestyle likely interact to account for the high risk of metabolic syndrome, diabetes, heart disease, and premature mortality in people with serious mental illness. Although some newer medications do seem to be more metabolically benign than their predecessors, others, like clozapine, have no substitute. Within a preventative framework, minimizing risk by choosing a low-risk medication if possible and regular monitoring of risk factors should allow for intervention before comorbidities become manifest. If any components of metabolic syndrome appear, lifestyle management to reduce weight and increase

physical activity and fitness is the initial intervention recommended. These interventions should be available in the usual settings of care for persons with serious mental illness. If not sufficient, antipsychotic medication can be changed if this is clinically indicated and agreed to by the patient. If the prior measures fail to reduce the risk factors for diabetes and heart disease, specific pharmacological interventions must be considered in collaboration with a primary care practitioner. Given the high risk of developing diabetes and cardiovascular disease in persons with serious mental illness, psychiatrists who treat these individuals need to ensure they are familiar with these risks, monitor metabolic parameters in their patients, and educate their patients (and caregivers) about the risks and how to prevent them. Mental health treatment facilities, including community mental health centers, need to offer their patients/clients access to evidence-based lifestyle interventions and to adequate primary care. The National Institutes of Health and other national agencies responsible for studying innovations in health care need to ensure that persons with serious mental illness are included in trials of interventions aimed at heart disease and diabetes, and also fund interventions specifically for the mentally ill. Our collective failure to follow these recommendations will probably mean no reduction in the 20- to 25-year mortality gap between people with serious mental illness and the rest of the population, in the near future.

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