Approach to managing increased risk for cardiovascular disease in patients with severe mental illness

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INTRODUCTION

Lifespans in people with severe mental illness (SMI) are reduced by 15 to 25 years compared with the general population [1-3]. Cardiovascular disease (CVD) represents the most common natural cause of this excess mortality [1,4,5]. People with schizophrenia, for example, are twice as likely to die from CVD [6-8].

The elevated risk of CVD among patients with SMI is caused in part by the increased prevalence of CVD risk factors in this population – obesity, diabetes mellitus, hypertension, and dyslipidemia – compared with the general population. Other factors contributing to increased CVD in patients with SMI include a possible genetic predisposition, as well as behaviors such as smoking, lack of physical exercise, and poor diet leading to excess body weight.

Multiple, concurrent risk factors for CVD are described, collectively, as metabolic syndrome, which is more common in patients with SMI compared with the general population. Metabolic syndrome is also a common side effect of antipsychotic medications. Metabolic abnormalities, however, often go undiagnosed and untreated or undertreated in patients with SMI.

This topic reviews our approach to selecting treatments for CVD risk factors in patients with SMI (algorithm 1). The epidemiology, pathogenesis, and clinical implications of metabolic syndrome in patients with SMI are reviewed separately. The epidemiology, administration of treatments, treatment efficacy of CVD risk factors in patients with SMI and lifestyle

interventions for obesity and overweight patients with SMI are also reviewed separately. (See "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications" and "Modifiable risk factors for cardiovascular disease in patients with severe mental illness" and "Lifestyle interventions for obesity and overweight patients with severe mental illness".)

OVERVIEW

Patients with severe mental illness (SMI) are at risk for cardiovascular disease (CVD) and should be routinely monitored for metabolic abnormalities and receive aggressive treatment when present. A recommended monitoring schedule is summarized in a table (table 1) and reviewed separately. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Monitoring'.)

The overall goal of treating metabolic abnormalities is to prevent the development of type 2 diabetes and CVD. All patients with SMI, regardless of whether they are taking an antipsychotic drug, should receive education about nutrition and weight management and encouragement to increase physical activity.

The selection of a treatment strategy for one or more metabolic abnormalities depends on multiple factors including the patient's history of responsiveness to different antipsychotics, the severity of the metabolic disturbance, and the willingness of the patient to make lifestyle changes. Since there are often multiple contributors to CVD, treatment will often include both medical and lifestyle interventions.

Treatment for metabolic risk in patients with SMI is similar whether or not the patient takes an antipsychotic drug:

- For patients who acquire CVD risk factors as side effects of an antipsychotic medication, the choice and dose of antipsychotic should be reevaluated. (See 'Patients taking an antipsychotic drug' below.)
- All overweight patients with SMI should receive education on weight management and encouragement to increase physical activity, preferably through a lifestyle intervention tailored to the needs of the individual patient. (See 'Obesity and overweight patients' below.)
- Other metabolic abnormalities and risk factors should be treated individually if they persist despite antipsychotic and lifestyle changes. (See 'Other metabolic abnormalities'

below.)

PATIENTS TAKING AN ANTIPSYCHOTIC DRUG

For patients with antipsychotic-induced weight gain, we suggest reviewing the antipsychotic regimen for the feasibility of the options below (see "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Implementation of medication changes'):

Antipsychotic dose reduction — The patient's medication history, clinical status, and current antipsychotic should be reviewed for opportunities to reduce the dose. Dose reduction should be done gradually and under close monitoring for the possibility of symptom exacerbation.

Switching antipsychotic drugs — Studies have shown that switching from an antipsychotic with a relatively high risk of weight gain and dyslipidemia (eg, olanzapine, quetiapine, risperidone) to an antipsychotic with lower risks (eg, aripiprazole or ziprasidone) is often (but not always) effective in promoting weight loss and improving lipid profiles (table 2) [9-11].

Careful monitoring of clinical status is recommended when attempting such a switch. A gradual cross titration from the current to the newer drug over one to three weeks will usually protect patients against an exacerbation of psychosis. For some patients, however, the risks of exacerbation with switching may be unacceptably high, such as those stabilized on clozapine, or on an antipsychotic from which they have previously decompensated following an attempted switch to another drug.

Weight loss may not occur immediately; patients should be observed for at least two to three months to assess the effectiveness of the change.

OBESITY AND OVERWEIGHT PATIENTS

Patients with serious mental illness (SMI) are at increased risk for obesity compared with the general population. For patients with SMI who are overweight (body mass index between 25 and ≤30), we suggest first-line treatment with either a comprehensive lifestyle intervention or medication, with the choice based on the intervention's availability as well as the patient's preferences, motivation, and capabilities.

Compared with the general population, patients with SMI are more likely to have lifestyles placing them at increased risk of obesity, with less physical activity and unhealthier diets [12-14]. Lifestyle interventions developed to help overweight patients from the general population

to lose weight can present challenges to patients with SMI. (See "Obesity in adults: Overview of management", section on 'Comprehensive lifestyle intervention' and "Lifestyle interventions for obesity and overweight patients with severe mental illness", section on 'Addressing challenges with SMI'.)

For patients with the willingness and capability to participate, a lifestyle intervention should generally be recommended first, proceeding to medication if the intervention is ineffective. Data on weight gain among patients who have recently started taking an antipsychotic [15] support more aggressive management (ie, an earlier introduction of medication treatment).

Preference for lifestyle intervention — In our clinical experience, lifestyle interventions customized to challenges faced by patients with SMI can help them to lose weight and improve other metabolic abnormalities. Clinical trials of the interventions versus inactive controls (which are reviewed separately) have shown mixed results [16]. Their efficacy has not been compared with that of medication for weight loss, nor has the combination of lifestyle interventions and medication been compared with either as monotherapy. (See "Lifestyle interventions for obesity and overweight patients with severe mental illness", section on 'Efficacy'.)

The availability of lifestyle interventions customized for SMI patients is limited, varying widely even in countries where they have been disseminated. (See "Lifestyle interventions for obesity and overweight patients with severe mental illness", section on 'Key components'.)

Based on data from intervention trials, we favor the use of interventions with characteristics associated with better outcomes:

- In SMI patients [17]:
  - Longer duration (three or more months)
  - Manualized, structured approach
  - Focus on both health education and physical activity
  - Active monitoring such as weigh-ins and food diaries
  - Active monitoring of physical activity and fitness levels
- In patients from the general population:
  - Use of multiple components (eg, diet, exercise, and behavioral therapy)
  - Personalization
  - More frequent contact
  - Training for treatment providers

Preference for medication — For most patients with SMI who are overweight and who seek treatment with medication to lose weight, we suggest first-line treatment with metformin rather than other agents. Topiramate or, in the case of patients treated with clozapine, augmentation with aripiprazole are reasonable alternatives, as well as liraglutide if other options are not effective. An option for people who are gaining weight on olanzapine or are about to start olanzapine and wish to limit potential weight gain is the fixed-dose combination treatment olanzapine/samidorphan [18]. Each of these medications have demonstrated efficacy in this population in randomized controlled trials [19-22]. Clinical trials have not compared their efficacy among each other, but in our clinical experience, metformin is best tolerated and most effective. Topiramate and liraglutide may be more effective than aripiprazole but also more likely to cause side effects. The efficacy, side effects, dosing, and contraindications of these medications are reviewed separately. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Adjunctive medications'.)

OTHER METABOLIC ABNORMALITIES

Other metabolic abnormalities should be treated individually if they persist despite antipsychotic and lifestyle changes:

Hyperglycemia/diabetes — Mental health practitioners should feel confident in recognizing signs of hyperglycemia:

- Thirst
- Polyuria
- Weight loss
- Blurry vision

A recommended schedule for routine monitoring for hyperglycemia/diabetes in patients with severe mental illness (SMI) is shown in a table (table 1) and reviewed separately. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Monitoring'.)

Patients with new-onset diabetes (hemoglobin A1C >6.5 percent, fasting blood glucose ≥126 mg/dL or random glucose ≥200 mg/dL) should be referred to a primary care clinician or endocrinologist for evaluation and treatment, but diabetes treatment may be possible in the mental health setting with primary care/internist consultation if there are no other options. (See 'Site of treatment' below.)

Initial management of type 2 diabetes is reviewed separately. (See "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)

The patient should also be referred to a lifestyle intervention developed for patients with SMI with diabetes, if available. If SMI-specific resources are not available, community-based resources that serve all patients with diabetes include diabetes self-management classes, nutrition, and physical activity programs. To enhance adherence to diabetes-care recommendations, we engage the patient's social supports and use motivational interviewing to set and monitor goals. We also involve peer support when available. Lifestyle interventions for patients with SMI with diabetes are reviewed separately, as is motivational interviewing (as applied to substance use disorders). (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Diabetes' and "Substance use disorders: Motivational interviewing".)

Hypertension — A recommended schedule for routine monitoring of blood pressure in patients with SMI is shown in a table (table 1) and reviewed separately. Diagnosis of hypertension as well as selection and initiation of an antihypertensive agent are reviewed separately. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Monitoring' and "Overview of hypertension in adults".)

Dyslipidemia — A recommended schedule for routine monitoring for dyslipidemia in patients with SMI is shown in a table (table 1) and reviewed separately. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Monitoring'.)

Management of dyslipidemia is reviewed separately. (See "Management of low density lipoprotein cholesterol (LDL-C) in the secondary prevention of cardiovascular disease".)

TOBACCO SMOKING

For patients with severe mental illness (SMI) attempting to stop smoking, we suggest first-line treatment with varenicline and nicotine replacement therapy (NRT) accompanied by smoking cessation education or a support group rather than other medication or psychosocial treatment. Bupropion is a reasonable alternative to varenicline if the latter is poorly tolerated or the patient continues to smoke after three months of treatment.

There is limited evidence comparing the efficacy of smoking cessation medications, but varenicline appears to be more effective for smoking cessation compared with either NRT or bupropion in patients with SMI. A clinical trial in 4116 SMI patients found that varenicline

achieved greater abstinence compared with NRT (1.51, 95% CI 1.19-1.93), and compared with bupropion (1.41, 95% CI 1.11-1.79) over 24 weeks [23].

In patients with bipolar disorder and depression (or mood disorders), as well as schizophrenia (or other psychotic disorders), clinical trials have found varenicline [24-28], bupropion [24,25,29,30], and NRT [24,31] to be similarly efficacious as compared with placebo. An exception is that NRT has not been found to be efficacious in patients with schizophrenia/psychotic disorders [30], although this finding is confounded by a relatively small sample size. Earlier, smaller trials found inconsistent results for NRT, and for bupropion in bipolar disorder or depression (or mood disorders), but a large trial provided more robust evidence of efficacy [30].

The efficacy of smoking cessation medications in patients with SMI is reviewed in greater detail separately. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Tobacco smoking'.)

In the general population, varenicline [32], bupropion sustained release [33], and NRT [24,34,35] are all efficacious for smoking cessation compared with placebo. The efficacy of smoking cessation medications in the general population is reviewed in greater detail separately. (See "Pharmacotherapy for smoking cessation in adults".)

Earlier concerns that varenicline and bupropion might exacerbate symptoms of SMI were not borne out in subsequent, larger analyses [36]. (See "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Safety'.)

Some data suggest that antidepressants can lead to improvement in negative symptoms of schizophrenia [37]. Antidepressants, including bupropion, can precipitate mania and must be used with caution in patients with bipolar disorder who are not also treated with a mood stabilizer. (See "Overview of smoking cessation management in adults", section on 'Nicotine withdrawal'.)

In addition to medication, we suggest adjunctive treatment with a cessation education or support group rather than a specific psychosocial intervention. In contrast to the general population, in which a number of psychosocial interventions have shown efficacy for smoking cessation, these treatments have not been shown to be efficacious in patients with SMI. (See "Behavioral approaches to smoking cessation".)

Among patients with SMI treated for smoking cessation, closer monitoring is warranted for those with more severe illness, suicidality, and/or unstable symptoms. Referral to or coordination with the patient's psychiatrist or other mental health provider is recommended.

SITE OF TREATMENT

For some patients with severe mental illness (SMI), the mental health care setting is their only site of clinical care. Some patients are unable or unwilling to follow through on a referral to primary care or attend regular visits for a chronic condition.

Given the risks of cardiovascular and other disease in patients with SMI and their impact on mortality, we often treat metabolic abnormalities (eg, by prescribing medications to treat hyperglycemia, hyperlipidemia, and/or hypertension). The provider's level of comfort in doing so may be influenced by the presence of organizational support, or the availability of a primary care clinician or specialist for consultation [38].

In complex cases we consult a provider with expertise in treating metabolic abnormalities (eg, internal medicine, endocrinology). In many cases treatment is facilitated by a care manager or other allied health professional. Such personnel can also facilitate collaboration among clinicians, as well as patient navigation of often complex health care systems.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Smoking cessation, e-cigarettes, and tobacco control".)

SUMMARY AND RECOMMENDATIONS

- Our approach to managing increased risk for cardiovascular disease in patients with severe mental illness (SMI) is summarized in an algorithm (algorithm 1).
- All overweight patients with SMI should receive education about nutrition and weight management and encouragement to increase physical activity. (See 'Overview' above.)
- For patients with antipsychotic-induced weight gain, the antipsychotic regimen should be reviewed for opportunities to reduce the dose and/or switch the antipsychotic from one with a higher risk of weight gain (eg, olanzapine, quetiapine, risperidone) to one with a lower risk (eg, aripiprazole or ziprasidone). Changes should be made slowly with careful monitoring to avoid an exacerbation of psychosis. (See 'Patients taking an antipsychotic drug' above.)

- For patients with SMI with obesity or who are overweight, we favor first-line treatment for weight reduction with either a comprehensive lifestyle intervention or medication. The choice between them is based on their availability, as well as the patient's preferences, motivation, and capabilities. (See 'Obesity and overweight patients' above.)

- Lifestyle interventions have been customized to address challenges faced by individuals with SMI. Other characteristics of lifestyle interventions associated with better outcomes are those with a longer duration, a manualized, structured approach, both health education and physical activity, and active monitoring. (See 'Preference for lifestyle intervention' above.)

- For most patients with SMI with metabolic syndrome treated with medication to lose weight, we suggest first-line treatment with metformin rather than other medications (**Grade 2C**). Topiramate, liraglutide, or, in the case of patients treated with clozapine, augmentation with aripiprazole are reasonable alternatives. For patients starting olanzapine or gaining weight on olanzapine, the combination treatment olanzapine/samidorphan can limit continued weight gain. (See 'Preference for medication' above.)

- For patients with SMI attempting to stop smoking, we suggest first-line treatment with varenicline and nicotine replacement therapy (NRT) rather than bupropion and NRT (**Grade 2B**). Bupropion is a reasonable alternative if the latter is poorly tolerated or if patient continues to smoke after three months' treatment. (See 'Tobacco smoking' above.)

- Earlier concerns that varenicline and bupropion might exacerbate symptoms of SMI have not borne out in subsequent, more robust analyses. (See 'Tobacco smoking' above and "Modifiable risk factors for cardiovascular disease in patients with severe mental illness", section on 'Safety'.)

- For patients with SMI attempting to stop smoking, we suggest adjunctive treatment with a smoking cessation education or support group rather than a particular psychosocial intervention (**Grade 2C**). (See 'Tobacco smoking' above and "Behavioral approaches to smoking cessation".)

- For patients who continue to smoke after taking varenicline/NRT for three months, we favor switching to bupropion and NRT rather than other medications. (See 'Tobacco smoking' above.)

- For patients with SMI with hyperglycemia, hyperlipidemia, and/or hypertension who are unwilling or unable to follow through on a referral to primary care, the psychiatrist should

consider treating the conditions. Their ability to do so may be influenced by a level of comfort, the presence of organizational support, or the availability of a primary care clinician or specialist for consultation. (See 'Site of treatment' above.)

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