Modifiable risk factors for cardiovascular disease in patients with severe mental illness

AUTHORS: L Fredrik Jarskog, MD, Rupal Yu, MD, MPH
SECTION EDITOR: Stephen Marder, MD
DEPUTY EDITOR: Michael Friedman, MD

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INTRODUCTION

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

Modifiable CVD risk factors for CVD include obesity, smoking, diabetes mellitus, hypertension, and dyslipidemia. Concurrent elevation of these risk factors, collectively, is known as metabolic syndrome, which is more common in patients with SMI compared with the general population. The syndrome is also a common side effect of antipsychotic medications, which are used both for psychotic disorders and, with increasing frequency, for nonpsychotic psychiatric disorders (table 1). SMI patients with metabolic risk factors often go undiagnosed, untreated or undertreated for these conditions (See "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications".)

This topic reviews the epidemiology of individual CVD risk factors, as well as the efficacy and administration of interventions to treat them in SMI patients. The epidemiology, pathogenesis, and clinical implications of metabolic syndrome in SMI patients are reviewed separately. Lifestyle interventions for obesity and overweight SMI patients are also reviewed separately. (See "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing

factors, pathogenesis, and clinical implications" and "Lifestyle interventions for obesity and overweight patients with severe mental illness".)

APPROACH TO TREATMENT

This topic describes treatment options for metabolic abnormalities in patients with severe mental illness. Our approach to selecting treatments among these options is described separately. (See "Approach to managing increased risk for cardiovascular disease in patients with severe mental illness".)

MONITORING

Patients with severe mental illness — Patients with severe mental illness should be assessed at regular intervals (table 2) for:

- Personal and family history of diabetes, hypertension or cardiovascular disease (annually)
- Smoking, physical activity and diet (quarterly)
- Weight and body mass index (quarterly)
- Blood pressure (quarterly)
- Fasting blood glucose or HbA1c (annually)
- Lipid profile (annually)

Patients treated with antipsychotics — Patients initiating treatment with any antipsychotic medication should be assessed with greater frequency during the first year and then at least annually. A table provides a recommended monitoring schedule (table 2), largely based on a 2004 consensus statement by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity [9]. It is augmented by more recent European guidelines calling for more frequent glucose and lipid monitoring [10], reflecting more prudent clinical care in a population with substantially impaired general physical health and increased mortality rates.

Monitoring should be tailored to the individual patient. As an example, monitoring should be more frequent if values are abnormal in people receiving chronic antipsychotic therapy.

OVERWEIGHT AND OBESITY

Definitions

- Body mass index (BMI) – A weight-to-height ratio, calculated by dividing one's weight in kilograms by the square of one's height in meters
- Overweight – BMI 25 to <30
- Obesity – BMI >30

Epidemiology — The prevalence of obesity among individuals with severe mental illness (SMI) is increased compared with the general population. Higher prevalence rates have been found for several psychiatric disorders:

- **Schizophrenia** – 49.4 percent met criteria for abdominal obesity per metabolic syndrome criteria in a meta-analysis of 77 studies with a total of 25,692 participants [11]. Much of the research evidence informing management of metabolic abnormalities in SMI patients is based on trials in schizophrenia, a more widely studied group that other SMIs.
- **Nonpsychotic mood disorders**
  - **Bipolar disorder** – The prevalence of abdominal obesity was 48.7 percent in 4573 patients with bipolar disorder in a meta-analysis of 11 studies [12].
  - **Major depression** – The prevalence of abdominal obesity was 41.6 percent in 3118 patients with major depression in a meta-analysis of four studies [13].

Treatment

Lifestyle interventions — A comprehensive lifestyle intervention to promote weight loss involves educating and encouraging patients with regard to their nutrition, diet, and physical activity. Interventions have been customized to address the needs of patients with SMI. The components and efficacy of lifestyle interventions for SMI patients are reviewed separately. (See "Lifestyle interventions for obesity and overweight patients with severe mental illness".)

All SMI patients with obesity or who are overweight, regardless of the availability of a lifestyle intervention or whether they are receiving other treatment, should receive education and encouragement on their nutrition, diet, and physical activity.

Changes to antipsychotic regimen — For many individuals, antipsychotic medication represents a major cause of weight gain. For each individual with antipsychotic associated weight gain, the benefits of medication change need to be weighed against the risks of recurrent psychosis. If clinically appropriate, a dose reduction can be considered, although the

evidence for a dose dependent relationship with weight gain for most antipsychotics is limited [14]. Another option is to change the antipsychotic medication to one less likely to cause weight gain (table 3 and table 4).

- Lowering the dose of their present antipsychotic regimen – When appropriate, we lower the antipsychotic dose slowly (eg, every one to two months) and in small amounts (eg, 25 percent or less) while monitoring carefully for psychotic symptom exacerbation. We obtain weights at each clinic visit and encourage patients to measure weights at home.

- Changing to another antipsychotic regimen with less potential to cause weight gain – Examples include aripiprazole or ziprasidone [15,16]. In cases where the individual is taking olanzapine with good clinical effect but is also gaining weight, it is reasonable to offer the fixed-dose combination olanzapine-samidorphan. It should be noted that the current evidence base for samidorphan is limited to attenuation of weight gain in people who are starting olanzapine as opposed to producing weight loss in people who have already gained weight on olanzapine [17].

Olanzapine-samidorphan is a fixed-dose combination of the second-generation antipsychotic olanzapine with samidorphan, an opioid antagonist found to attenuate olanzapine-induced weight gain [18]. A randomized trial of 561 patients with schizophrenia compared the combination of olanzapine-samidorphan with olanzapine only for 24 weeks [17]. At the end of the study, the mean increase in body weight was lower in the olanzapine-samidorphan group (3.2 versus 5.1 kg in the olanzapine group). Additionally, subjects in the olanzapine-samidorphan group were less likely to gain 10 percent or more of their body weight (odds ratio 0.5, 95% CI 0.31-0.80) and had smaller increases in waist circumference (a proxy for central fat accumulation and risk of greater cardiovascular disease and diabetes). However, samidorphan was not associated with any improvements in laboratory-based metabolic endpoints including cholesterol, triglyceride, glucose, HbA1C, or insulin levels. Treatment with combined olanzapine-samidorphan resulted in similar improvements in symptoms of schizophrenia compared to olanzapine only group with similar adverse effects including somnolence, increased appetite, and dry mouth.

Further discussion of how to make changes to antipsychotic regimen due to side effects can be found elsewhere. (See "Schizophrenia in adults: Maintenance therapy and side effect management", section on 'Implementation of medication changes'.)

Adjunctive medications — Pharmacologic options for weight loss in individuals with SMI are limited. Adjunctive medications to reduce antipsychotic-induced weight gain can be used concurrently with, or provide an alternative to behavioral modifications for patients who are not

motivated for change. Several medications without a US Food and Drug Administration (FDA) indication for weight loss have shown efficacy for weight loss in clinical trials in SMI patients with antipsychotic-associated weight gain:

- **Metformin** – A 2014 meta-analysis of 10 clinical trials with a total of 757 patients found metformin to be an efficacious treatment for weight loss, with a mean difference in weight reduction favoring metformin compared with placebo of 3.17 kg (95% CI -4.44 to -1.90 kg).

  As an example, in the largest clinical trial of metformin for weight loss in this population, 148 nondiabetic outpatients with schizophrenia or schizoaffective disorder (BMI >27) were randomized to 16 weeks of metformin, titrated up to 2000 mg per day, or placebo [19]. All subjects also received weekly diet and exercise counseling during the study. Over 16 weeks, metformin demonstrated a mean weight reduction compared with placebo showed a weight change of (-3.0 versus 1.0 kg). Metformin was also associated with significant improvements in triglycerides and hemoglobin A1c. Metformin was well tolerated, with only diarrhea reported more frequently for metformin than for placebo.

  Preventative use of metformin is under investigation; it may be moderately effective in preventing weight gain in antipsychotic-naïve individuals starting an antipsychotic. A clinical trial randomly assigned 40 nonobese patients with first-episode schizophrenia either to olanzapine (15 mg/day) plus metformin (750 mg per day) or olanzapine (15 mg/day) plus placebo [20]. After 12 weeks, the metformin group experienced a lower mean weight gain compared with the placebo group (1.9 versus 6.9 kg).

  Common side effects of metformin include nausea, vomiting, diarrhea and abdominal discomfort. Infrequently, metformin is associated with headaches, myalgia, weakness, and low vitamin B12 levels. Rarely, metformin can produce hypoglycemia, but normally only in the setting of serious malnutrition or alcohol use disorder.

  Metformin is not recommended for use in patients with:

  - Congestive heart failure or other serious cardiac disease
  - Serious kidney disease (estimated glomerular filtration rate [eGFR], <45 mL/min/1.73 m^2)
  - Serious liver disease (use caution with liver function tests >3 times normal)
  - Metabolic acidosis
  - Alcohol use disorder
  - Recent use of iodinated contrast material
  - Pregnancy

Prior to prescribing metformin:

- Obtain medical history to rule out serious heart, kidney, and liver disease, as well as alcohol use disorder (moderate alcohol use is safe).
- Obtain eGFR, liver function panel, serum bicarbonate, and complete blood count. In patients with anemia, obtain vitamin B12 level, supplement as needed.

Dosing/titration

- Begin metformin 500 mg every morning for one week, then increase to 500 mg twice daily for one week.
- Increase by 500 mg every week, as tolerated, up to 1000 mg twice daily.
- If gastrointestinal symptoms emerge, hold titration (or hold dose) until side effect subsides, then restart at last tolerated dose.
- If gastrointestinal symptoms persist, try metformin extended-release formulation.

Monitoring while taking metformin

- eGFR at least annually, or every six months if eGFR<60 mL/min/1.73 m^2
- Liver function tests annually
- Assess alcohol use regularly
- Consider vitamin B12 annually, especially in patients with anemia

- **Topiramate** – Although less well studied, topiramate shows evidence of efficacy for weight loss in SMI patients with antipsychotic-associated weight gain. A 2016 meta-analysis of seven clinical trials with a total of 327 patients found a mean difference in weight reduction favoring topiramate compared with placebo of 3.17 kg (95% CI -5.55 to -0.73 kg) [21].

  As an example, a clinical trial randomly assigned 66 overweight inpatients with schizophrenia to topiramate (200 mg/day or 100 mg/day), or placebo [22]. After 12 weeks in the 53 patients completing the trial, weight reduction was greater among patients treated with 200 mg/day or 100 mg/day of topiramate compared with placebo (-5.35 or -1.68 versus -0.3 kg). Paresthesia was the only side effect more common in the active treatment groups compared with placebo. A limitation of the trial was that intent to treat data were not presented.

Common dose-dependent side effects of topiramate in nonpsychiatric populations include paresthesias, sedation, dizziness, and memory difficulties. Rare but serious side effects include nephrolithiasis, secondary angle closure glaucoma, metabolic acidosis, and hyperammonemia [23]. In our experience, slow titration and moderate dosing generally has led to efficacy and tolerable side effects, although paresthesias may occur in as many as 30 percent of patients at topiramate 200 mg per day.

Prior to prescribing topiramate:

- Obtain medical history to rule out serious kidney and liver disease, and rule out history of glaucoma and nephrolithiasis.
- Obtain eGFR, liver function panel, serum bicarbonate. For eGFR <70 mL/min/1.73 m^2, reduce target dose of topiramate by 50 percent.
- Concomitant valproate not recommended due to increased risk of hyperammonemia.

Suggested dosing/titration:

- Begin topiramate 25 mg nightly at bedtime for week 1, then increase to 50 mg nightly at bedtime for week 2.
- Increase to topiramate 50 mg twice daily for week 3, then increase by 50 mg per week, as tolerated, up to 100 mg twice daily.
- Can increase or decrease by 25 mg increments if tolerability problems emerge.

Monitoring while taking topiramate:

- eGFR, liver function panel, and serum bicarbonate three months after starting therapy, then every six months.
- If mild metabolic acidosis develops, lower dose of topiramate. For moderate metabolic acidosis or for significant liver enzyme elevation, topiramate should be discontinued, and further assessment by primary care clinician or internist is recommended.

- **Aripiprazole** – Clinical trials have found antipsychotic-associated weight gain in patients treated with clozapine or olanzapine to be reduced by treatment with adjunctive aripiprazole [24]. A meta-analysis of three clinical trials with a total of 266 patients found a mean difference in weight reduction favoring aripiprazole compared with placebo of 2.13 kg (95% CI -2.87 to -1.39) [24].

In a meta-analysis of three clinical trials with 260 patients with schizophrenia with antipsychotic-induced weight gain, adjunct aripiprazole reduced patient body weight compared with placebo (mean difference = -2.13 kg [95% CI -2.87 to -1.39 kg]) [24]. As an example, in the largest trial to date, 207 people with schizophrenia taking stable doses of clozapine and who had gained at least 2.5 kg with clozapine were randomized to 16 weeks of aripiprazole 5 to 15 mg/day (dosed flexibly, mean dose = 11 mg/day) or placebo [25]. Weight change was greater with aripiprazole compared with placebo (-2.53 versus -0.38 kg), with a between-group difference of -2.15 kg. Total cholesterol and low density lipoprotein levels also improved with aripiprazole.

Side effects of aripiprazole that have been reported when taken together with clozapine include nausea, anxiety, and akathisia [25].

Begin aripiprazole 5 mg nightly at bedtime for week 1. Increase in 5 mg increments per week up to 15 mg nightly, as tolerated.

- **Liraglutide** – Liraglutide is a glucagon-like peptide-1 agonist that was approved for weight loss by the FDA in 2014. Emerging data indicates liraglutide may be safe and effective for weight loss in overweight and obese individuals with SMI. In a clinical trial, 103 overweight or obese individuals with schizophrenia spectrum disorders and prediabetes taking clozapine or olanzapine were randomly assigned to receive liraglutide or placebo for 16 weeks [26]. Patients receiving liraglutide lost weight, while patients receiving placebo had an average weight gain (-4.7 versus 0.5 kg).

  Common side effects include nausea, abdominal discomfort, and diarrhea. Rarely, liraglutide has been associated with hypoglycemia, pancreatitis, cholelithiasis, and cholecystitis. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.

  Begin liraglutide 0.6 mg subcutaneously per day for week 1. Increase to 1.2 mg per day for week 2 and then to a final target dose of 1.8 mg per day starting week 3, as tolerated. In our experience, the titration may need to be slowed due to gastrointestinal side effects.

DIABETES

Epidemiology — People with severe mental illness (SMI) have a higher prevalence of diabetes compared with the general population. Studies of people with schizophrenia, bipolar disorder, and schizoaffective disorder have found a prevalence of type 2 diabetes two- to threefold higher

compared with the general population [27]. The role of type 2 diabetes in the development of cardiovascular disease is described separately. (See "Overview of established risk factors for cardiovascular disease", section on 'Diabetes mellitus'.)

Antipsychotic medication use contributes to the development of diabetes. As an example, a population-based study in Taiwan examined cohorts of patients with newly diagnosed schizophrenia prescribed either a first-generation antipsychotic (FGA) or a second-generation antipsychotic (SGA) medication beginning between 1997 and 2000. FGA (1631 patients) and SGA (224 patients) cohorts were followed until 2008 and compared with age- and sex-matched, non-schizophrenia controls. FGA treatment was associated with developing diabetes (hazard ratio 1.32, 95% CI 1.01-1.755), an association that was greater in patients treated with SGA (hazard ratio 1.82, 95% CI 1.30-2.55) [28].

A 2012 systematic review found no difference between FGA and SGA in the risk of developing metabolic syndrome or diabetes; however, the strength of evidence was insufficient for a conclusive determination [29].

Further increasing the burden of diabetes in people with mental illness is that they receive less intensive medical care leading to poorer diabetes control and increased risks of complications [30-32]:

- In a national, cross-sectional study of 313,586 veterans with diabetes in the United States, those with psychiatric disorders were less likely to have been evaluated for hemoglobin (HbA1c), low density lipoproteins, glycemic or lipemic control, or ophthalmic complications [30]. A trend towards poorer diabetes control was seen in patients with increasing number of mental health conditions.

- A retrospective matched cohort study derived from administrative data of over 5000 individuals in Ontario, Canada, found that individuals with schizophrenia were more likely to have had an emergency department visit or hospitalization for hypoglycemia, hyperglycemia, or diabetes-related infection (21 versus 14 percent) [32]. Such complications can largely be managed or prevented with adequate monitoring, resources, and patient support.

Treatment — Once feasible changes to patients' antipsychotic regimens are made, subsequent treatment options for type 2 diabetes are the same for patients whether or not she or he takes an antipsychotic or has an SMI. Initial management of hyperglycemia in adults with type 2 diabetes consists of patient education including nutrition and self-management skills and pharmacotherapy. (See 'Changes to antipsychotic regimen' above and "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)

A lifestyle intervention developed to address cardiovascular disease risk factors in patients with SMI, diabetes, and excess weight has been developed and tested. A randomized clinical trial supports the efficacy of the intensive, multimodal lifestyle intervention for cardiovascular risk factors in middle-aged and older outpatients with schizophrenia and type 2 diabetes mellitus outpatients [33].

The trial randomly assigned 62 outpatients with the co-occurring conditions aged 40 and over to receive the intervention or usual care (along with pamphlets from the American Diabetes Association). The intervention group received weekly 90-minute sessions providing education on diet, exercise, and other diabetes self-care activities. Concrete behavioral change strategies were utilized, including weekly weighing, pedometers, healthy food samplings, and positive reinforcements for group attendance and behavioral change.

After 24 weeks, the intervention group had a superior mean weight change compared with usual care (-2.3 versus 3.1 kg). The intervention group also had superior outcomes on body mass index, waist circumference, triglycerides, and diabetes knowledge. At six-month follow-up, improvements in all but diabetes knowledge were maintained [34].

While they have been tested in clinical trials, diabetes intervention programs designed specifically for people with SMI are difficult to find. The Behavioral Health Home model has shown progress in reducing chronic disease burden as well as health care costs, but these programs are only available to publicly insured patients in some states in the United States [35,36].

Care should be coordinated between mental health providers (of both medication and psychotherapy), the primary care provider or endocrinologist and care management/social work (if involved). For patients with SMI who participate in treatment of their mental illness but cannot or choose not to attend general medical visits, the psychiatrist (if comfortable doing so) should initiate treatment for diabetes in an effort to bridge care and reduce morbidity. (See "Approach to managing increased risk for cardiovascular disease in patients with severe mental illness", section on 'Site of treatment'.)

Monitoring of SMI patients with type 2 diabetes includes a fasting blood glucose or HbA1c every three months (for patients not at goal; otherwise and every six months) and a foot exam, retinopathy screening, and urine microalbuminuria annually, along with monitoring of other metabolic abnormalities (table 2). (See 'Monitoring' above.)

HYPERTENSION

Epidemiology — Approximately 29 percent of the United States adult population has hypertension [37]. Hypertension is two to three times more frequent among people with schizophrenia and bipolar disorder compared with the general population [38].

Disparities in the identification and treatment of hypertension have been observed between patients with severe mental illness (SMI) and the general population [39,40]. As an example, a naturalistic cohort study of 542 outpatients with SMI, found that 42 percent were identified as having a blood pressure of >140/90; 74 percent of these individuals were not treated with antihypertensive medication [39]. Thirty-seven percent of those with hypertension who were reassessed at one year were still hypertensive.

Treatment — There are no randomized clinical trials examining interventions to lower blood pressure as a primary outcome among patients with SMI [41]. Treatment of hypertension for SMI patients is the same as for the general population, which is reviewed separately. (See "Overview of hypertension in adults".)

Considerations informing the diagnosis and treatment of hypertension in SMI patients include:

- Patients who are acutely psychotic may present with elevated blood pressure which normalizes after treatment of their mental illness. In such patients, it is prudent to monitor blood pressure closely over time and check out-of-office readings if possible.
- SMI patients are more vulnerable to side effects and drug-drug interactions due to receiving multiple medications. As an example, angiotensin converting enzyme inhibitors/angiotensin receptor blockers are relatively contraindicated for people taking lithium due to risk of lithium toxicity [42].
- Although beta blockers are not recommended as first-line agents for the general population, people with antipsychotic-associated tachycardia (as seen with clozapine) and hypertension may benefit from adding a beta blocker first to address both conditions.

Monitor the blood pressure of SMI patients with high blood pressure at three month intervals. Counseling on lifestyle changes and assessing for medication adherence and side effects should be a part of every visit.

DYSLIPIDEMIA

Epidemiology — Dyslipidemia, the development of increased cholesterol or triglyceride levels or reduced high density lipoprotein, is an easily recognized and treatable cardiovascular risk factor among people with severe mental illness (SMI).

The relationship between total cholesterol and elevated low density lipoprotein and risk of cardiovascular disease (CVD) is well established [43]. The role of hypertriglyceridemia as a cardiovascular risk factor is increasingly being recognized. (See "Hypertriglyceridemia in adults: Management".)

It is estimated that 25 to 69 percent of people with schizophrenia have some degree of dyslipidemia [38]. It is unclear how much this increased risk is attributable to antipsychotic medication compared with behavioral risk factors. While all antipsychotic medications increase the risk of unfavorable changes in cholesterol, certain second-generation antipsychotics, such as clozapine and olanzapine, are particularly associated with increases in total and low density lipoprotein cholesterol [44].

Treatment — There are no clinical trials of the efficacy of treatment for dyslipidemia as a primary outcome in patients with SMI. Dyslipidemia treatment in SMI patients is the same as in the general population, which is reviewed separately. (See "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease".)

Monitoring of SMI patients for dyslipidemia is described in a table (table 2) and reviewed below. Nonfasting lipid profiles are more convenient for the patient and yield low density lipoprotein-cholesterol values of similar prognostic value [45]. A fasting lipid profile is warranted if the non-fasting results show hypertriglyceridemia. Use of lipid profile results in a CVD risk assessment to calculate patient risk of CVD is reviewed separately. (See 'Monitoring' above and "Atherosclerotic cardiovascular disease risk assessment for primary prevention in adults: Our approach".)

Lower lipid thresholds for starting statin treatment should be considered for SMI patients compared with the general population, particularly for younger SMI patients. For SMI patients ages 21 to 39, we recommend calculating a 10-year CVD risk as if they were age 40. If the 10-year CVD risk is >7.5 percent, our recommendations are as follows:

- Emphasize and offer support for behavioral modifications (improved nutrition and increased physical activity). (See "Lifestyle interventions for obesity and overweight patients with severe mental illness".)
- Control blood pressure, either by lifestyle changes or medication. (See 'Hypertension' above.)
- Encourage smoking cessation and offer pharmacotherapy. (See 'Tobacco smoking' below.)

- Consider initiation of a moderate-intensity statin medication. (See "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease".)

We recognize this approach to statin initiation in SMI patients under age 40 is not evidence based. However, we believe that the potential long-term benefits of this strategy outweigh the potential risks in efforts to reduce the disproportionate burden of poor CVD outcomes in this population.

TOBACCO SMOKING

Epidemiology — Individuals with severe mental illness (SMI) have a high prevalence of cigarette smoking (30 to 62 percent) compared with the general population in the United States. The prevalence of smoking in people with bipolar disorder and major depression is somewhat lower than for schizophrenia but still substantially elevated compared with the general population [46]:

- **General population in the United States** – 16.8 percent [47].
- **Schizophrenia** – 62 percent of people with schizophrenia were current smokers in a meta-analysis of studies from 20 countries [48]. Subjects with schizophrenia were five times more likely to smoke compared with subjects from the general population. Smoking rates were higher in male subjects with schizophrenia compared with females (71 versus 44 percent).
- **Bipolar disorder** – 45 percent of people with bipolar disorder were current smokers in 51 studies comprising 41,710 people.
- **Major depression** – 30 percent of people with major depression were current smokers in 18 studies with 105,856 people.

Pathogenesis — The basis for high smoking rates in people with SMI is multifactorial and likely includes complex interactions between disease-specific genetic and neurobiological factors, in addition to psychosocial and treatment-related factors. As an example, genetic linkage analysis has localized the P50 auditory sensory gating deficit in schizophrenia to chromosome 15q13-14, which is the site of the alpha-7 nicotinic acetylcholine receptor subunit. It has been hypothesized that increased rates of smoking in people with schizophrenia is due in part to efforts to activate the alpha-7 subunit, which has inherently low affinity to nicotine and which also demonstrates reduced cortical expression in schizophrenia [49].

From a psychosocial perspective, epidemiologic studies show substantially higher rates of smoking in people with low socioeconomic status and in those with a disability [50]; people with serious mental illness often meet criteria for both categories. Smoking to relieve side effects associated with antipsychotic medications such as sedation and neuroleptic-induced dysphoria has long been considered an attempt at self-medication [51]. Clozapine has been found to reduce smoking in people with schizophrenia, thought to be related to its ability to enhance acetylcholine release in hippocampus and increase P50 sensory gating [49].

Treatments

Bupropion — Bupropion, compared with placebo, has been found to be efficacious in increasing smoking cessation in patients with schizophrenia, bipolar disorder, and depression. (See 'Nicotine replacement treatment' below.)

- **Schizophrenia** – A 2013 Cochrane meta-analysis of five randomized clinical trials with 214 patients with schizophrenia found bupropion with or without nicotine replacement therapy (NRT) to be efficacious for smoking cessation [52]. At six months, bupropion was associated with nearly three times greater likelihood of continued abstinence compared with placebo. As examples:

  - A 2007 trial randomly assigned 51 patients with schizophrenia who smoked at least 10 cigarettes per day to 12 weeks of bupropion (150 mg twice daily) or to placebo. All subjects also received NRT and cognitive-behavioral therapy for smoking cessation. Participants who received bupropion, compared with placebo, had a greater rate of smoking reduction at week 12 (60 versus 31 percent) and week 24 [53].

  - A 2016 trial, which found bupropion sustained-release (SR) to be efficacious compared with placebo in a larger sample of patients with various SMI diagnoses, found a nonsignificant trend for the medication in a secondary analysis of 98 patients with psychotic disorders [54].

- **Bipolar disorder and depression** – While earlier, smaller trials showed equivocal results for bupropion in patients with bipolar disorder and depression [55,56], a secondary analysis of a large 2016 randomized trial that included 1455 patients with major depression or bipolar disorder found bupropion SR to be efficacious [54]. After 24 weeks, the continuous abstinence rate was greater for bupropion compared with placebo (odds ratio 1.75, 95% CI 1.27-2.41) [54].

Common side effects for bupropion include headache, dry mouth, and insomnia. Bupropion can increased blood pressure, which should be monitored carefully after initiation, especially in a

patient with a history of hypertension. Bupropion has been associated with a dose-dependent increased risk of seizure (0.1 percent at 300 mg per day) and should not be used in patients with a history of seizure.

Bupropion SR can be started at 150 mg once daily for three days (longer if poorly tolerated), then increased to 150 mg twice daily for the remainder of the treatment period, 8 to 12 weeks. The dose should not exceed 300 mg total per day. Patients are advised to start bupropion treatment one to two weeks prior to a target smoking quit date. The twice daily dosing interval should be at least eight hours to reduce seizure risk. The second dose can be taken earlier in the evening to avoid insomnia.

Varenicline — Varenicline, compared with placebo, has been found to be efficacious in smoking cessation in patients with schizophrenia, bipolar disorder, and depression:

- **Schizophrenia** – The 2013 meta-analysis included two randomized clinical trials showing varenicline to be efficacious and safe in 137 patients with schizophrenia [52]. Participants who took varenicline were nearly five times as likely to abstain from smoking at the end of treatment compared with placebo.

  As an example, a trial randomly assigned 127 smokers (>15 cigarettes per day) with schizophrenia or schizoaffective disorder to 12 weeks of varenicline (1 mg twice daily) or placebo [57]. At 12 weeks, patients in the varenicline group were more likely to meet abstinence criteria compared with the placebo group (19 versus 4.7 percent). Varenicline was generally well tolerated, with nausea, headache, and insomnia reported more frequently for varenicline compared with placebo. There was no evidence that psychiatric symptom side effects were more frequent or severe for varenicline compared with placebo.

- **Bipolar disorder and depression** – Multiple randomized clinical trials have found varenicline to be largely efficacious for smoking cessation in patients with bipolar disorder [54,58-60] and major depression [54,58,61]. As an example, the 2016 trial randomly assigned 734 patients with major depression and bipolar disorder to 12 weeks of varenicline (1 mg twice daily) or placebo. Patients assigned to varenicline were more likely to achieve continuous abstinence during the trial compared with placebo (odds ratio 2.28, 95% CI 1.67-3.11) [54].

Common side effects include nausea, restlessness, and abnormal/vivid dreams. (See 'Safety' below.)

Varenicline can be started at 0.5 mg once daily for days 1 to 3, then increased to 0.5 mg twice daily for days 4 to 7, then increased to 1 mg twice daily for the remainder of treatment, 12 weeks total. Patients are advised to start varenicline one week prior to a target smoking quit date.

For patients who are unwilling or unable to abruptly quit smoking, they should target 50 percent smoking reduction by four weeks after starting varenicline, then reduce smoking by another 50 percent by eight weeks with a goal of stopping smoking by 12 weeks. For this group, varenicline should be continued for an additional 12 weeks.

Nicotine replacement treatment — Overall, the balance of evidence suggests that NRT is efficacious for smoking cessation patients with mood disorders, but unclear in patients with psychotic disorders. Seven small trials using heterogeneous study designs to test NRT for patients with SMI were negative for the primary outcome of smoking cessation [52,56].

A large 2016 clinical trial randomly assigned 2051 patients with mood, anxiety, and psychotic disorders to receive NRT (21 mg per day, transdermal patch) or placebo [58]. Patients assigned to NRT were more likely to achieve continuous abstinence during the trial compared with placebo (odds ratio 1.65, 95% CI 1.24-2.20). Subgroup analyses found that the 721 patients with mood disorders were more likely to achieve continuous abstinence on NRT compared with placebo, but no difference was seen in the 99 patients with psychotic disorders [54].

In our clinical experience, NRT has contributed to successful smoking cessation in motivated patients with schizophrenia spectrum disorders.

Common side effects of NRT include abnormal or vivid dreams and insomnia. Long-acting NRT may need to be removed at night to minimize these side effects. Some side effects such as tachycardia, nausea and dizziness may occur because the dose of NRT is too high for the patient. Ensure that the patient's prior cigarette use is carefully assessed in order to find their optimal NRT dose.

Also consider symptoms of nicotine withdrawal in patients for whom nicotine is underdosed. Common side effects of withdrawal include insomnia, restlessness, irritability, and cravings. Consider the use of short-acting NRT in combination with long-acting NRT for patients who were heavy smokers and experience severe withdrawal.

Dosing and administration of NRT in patients with SMI follows guidelines for NRT treatment the general population. These are reviewed in detail separately. (See "Pharmacotherapy for smoking cessation in adults", section on 'Administration'.)

Safety — Concern that varenicline and bupropion might be associated with exacerbation of psychiatric symptoms in the treatment of patients with psychiatric disorders have not been supported by subsequent analyses. The US Food and Drug Administration issued a black box warning for varenicline and bupropion in 2009 for risks of depression and suicidal thoughts/behavior based on analysis of postmarketing surveillance data. Subsequent study has not supported the associations [58,62,63], leading to the withdrawal of the warning in 2016 [64]. As examples:

- A clinical trial of 8144 smokers motivated to quit, half of whom had stable psychiatric disorders (eg, major depressive, bipolar, anxiety or psychotic disorders) compared treatment with varenicline, bupropion, NRT, or placebo [58]. After 12 weeks, rates of neuropsychiatric adverse events did not differ by treatment assignment. Patients with psychiatric comorbidity had a higher rate of neuropsychiatric symptoms compared with patients without the comorbidity, but rates were low for both groups.

- A systematic review and meta-analysis of 39 randomized trials including over 10,000 participants with and without psychiatric illness also found that varenicline did not increase the risk of suicide or suicide attempts, suicidal ideation, depression, aggression, or death compared with placebo [63].

Psychosocial interventions — In contrast to clinical trials in the general population, clinical trials in SMI patients do not consistently demonstrate efficacy for any particular psychosocial intervention for smoking cessation [41]. (See "Behavioral approaches to smoking cessation".)

As an example, a trial randomly assigned 45 patients with schizophrenia or schizoaffective disorder to 10 weeks of specialized smoking cessation group therapy or a standard manualized behavioral group therapy [65]. All subjects received treatment with transdermal nicotine patch 21 mg per day. The patients assigned to the specialized group therapy showed a trend toward a small advantage in smoking abstinence in the last four weeks of treatment (32.1 versus 23.5 percent) compared with the American Lung Association group. At six-month follow-up, however, smoking abstinence was higher in the American Lung Association group (17.6 versus 10.7 percent) compared with the specialized group therapy.

SUMMARY

- Metabolic syndrome is a constellation of risk factors for cardiovascular disease including abdominal obesity, insulin resistance, dyslipidemia (elevated triglycerides levels and low density lipoprotein-cholesterol), and hypertension. Metabolic syndrome is more common

in severely mentally ill (SMI) patients, and is also a side effect of many antipsychotic medications. (See "Metabolic syndrome in patients with severe mental illness: Epidemiology, contributing factors, pathogenesis, and clinical implications".)

- This topic reviews treatment options for metabolic abnormalities in patients with SMI. Our approach to selecting treatment among these options is described separately. (See "Approach to managing increased risk for cardiovascular disease in patients with severe mental illness".)

- Patients with SMI, at minimum, should be assessed annually for their personal and family history of diabetes, hypertension, and cardiovascular disease; fasting blood glucose or HbA1c; and lipid profile (table 2). Their smoking status, physical activity and diet, body weight, and blood pressure should be assessed quarterly. (See 'Monitoring' above.)

- Patients initiating treatment with an antipsychotic medication should be assessed with greater frequency during the first year (table 2) and then at least annually, but the frequency of monitoring should be tailored to the individual patient. (See 'Monitoring' above.)

- Estimates of the prevalence of obesity in SMI patients in the United States range from approximately 28 percent in patients with major depression or bipolar disorder to nearly 50 percent of patients with schizophrenia. (See 'Overweight and Obesity' above.)

- Metformin, topiramate, and adjunctive aripiprazole have shown efficacy in treating antipsychotic-induced weight gain in patients treated with antipsychotic drugs. Lifestyle interventions for obesity and overweight patients have been customized for the SMI population, and are reviewed separately. (See 'Adjunctive medications' above and "Lifestyle interventions for obesity and overweight patients with severe mental illness".)

- Individuals with SMI have a higher prevalence of tobacco smoking compared with the general population in the United States and internationally. (See 'Tobacco smoking' above.)

- Bupropion and varenicline have been found to be efficacious and safe in smoking cessation treatment in patients with schizophrenia (or psychotic disorders), bipolar disorder and depression (or mood disorders). Nicotine replacement therapy has been found to be efficacious in patients with bipolar disorder and depression (or mood disorders), but not in patients with schizophrenia (or psychotic disorders). (See 'Tobacco smoking' above.)

- Studies of people with schizophrenia, bipolar disorder, and schizoaffective disorder have found prevalences of type 2 diabetes two- to threefold higher compared with the general population. (See 'Diabetes' above.)

- Educational and self-management programs, and lifestyle interventions for diabetes care, have been customized for the SMI population; their availability varies widely. Initial management of hyperglycemia in SMI patients with type 2 diabetes, including glycemic control and pharmacotherapy are the same as in the general population; these are reviewed separately. (See 'Diabetes' above and "Initial management of hyperglycemia in adults with type 2 diabetes mellitus".)

- Hypertension is two to three times more frequent among people with schizophrenia and bipolar disorder compared with the general population. (See 'Hypertension' above.)

- The prevalence of dyslipidemia has been found to be higher in patients with schizophrenia compared with the general population. (See 'Dyslipidemia' above.)

- Treatment of hypertension and dyslipidemia in patients with SMI are generally the same as in the general population and are reviewed separately. However, treatment for dyslipidemia is recommended to be started at a lower threshold of abnormal lipid values compared with the general population. (See 'Hypertension' above and 'Dyslipidemia' above and "Overview of hypertension in adults" and "Low-density lipoprotein cholesterol-lowering therapy in the primary prevention of cardiovascular disease".)

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