

Swedish clinical guidelines—Prevention and management of metabolic risk in patients with severe psychiatric disorders

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Individuals with severe psychiatric disorders are more likely than the population at large to develop metabolic derangements such as overweight and diabetes. Cardiovascular disease is also more frequently seen in this group. Contributing factors may include inappropriate diet or lack of physical activity, but antipsychotic medication may also play a role. Seven Swedish specialist medical societies have collaborated in formulating a set of concise clinically applicable guidelines—reproduced here in modified form—for the prevention and management of metabolic risk in this patient group. The importance of implementation is emphasized.

• *Severe mental illness; Severe mental disorder; Schizophrenia; Bipolar disorder; Physical health; Weight gain; Diabetes; Cardiovascular disease; Guidelines; Clinical practice guidelines*

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Severe psychiatric disorders including bipolar disorder, schizophrenia and other psychotic conditions can exert a devastating influence on the life of the sufferer. When treatment is lacking or inadequate, these conditions result in long-term psychological suffering and a greatly increased risk of social isolation and suicide. Appropriate treatment of these conditions includes many avenues of approach. Antipsychotic medication is generally an important and necessary element in treatment, for either a short period or more continuously.

Individuals with bipolar disorder or schizophrenia are more likely than others to develop metabolic derangements—overweight, diabetes and lipid disorders—as well as increased mortality related to cardiovascular disease (1–8). Unhealthy lifestyle factors including lack of physical activity or inappropriate diet may play a role. Medication can also be a contributing factor, since antipsychotics can induce or exacerbate metabolic derangements (3, 4, 9–17). Some of these medications show less of an effect, while others can contribute to more serious metabolic derangement (Table 2). Young people or individuals with no prior exposure to antipsychotic medication can be especially prone to this side-effect (11). Pronounced weight gain after initiating treatment with antipsychotic

medication is a sign of metabolic derangement. Pronounced weight gain can result in increased social stigmatization, and is a risk factor for type 2 diabetes and cardiovascular disease. Weight gain and other metabolic derangements during treatment with antipsychotics can be combated.

The object for these guidelines has been to formulate concrete and practically useful principles for the prevention, detection and management of metabolic derangements by any mental healthcare provider. This document provides a concise summary of the state of the art in this field, as well as references for further study. Medications other than antipsychotics can also contribute to weight gain and are cause for increased vigilance, but these are not considered here. Finally, individuals with severe psychiatric disorders are at increased lifetime risk of a number of other physical ailments (2, 5, 6, 18–20), but these are not considered in these guidelines either.

Method

These guidelines were composed in collaboration between representatives of the Swedish Psychiatric Association, the Swedish Association of Child and Adolescent Psychiatry,

the Swedish Association of Family Medicine, the Swedish Association of Diabetology, the Swedish Society of Internal Medicine, the Swedish Society of Cardiology, and the Swedish Association for the Study of Obesity. Representatives of each of the seven specialist medical societies contributed to this document with the support of pertinent literature. In order to facilitate a broad national consensus, a first draft of the document was circulated in a comprehensive consultation round to all members of the executive committees of the seven specialist medical societies, several user organizations, a number of nursing societies, as well as to all chiefs of staff of the country's psychiatric as well as child and adolescent psychiatric clinics, among others. Viewpoints garnered from the consultation round contributed to the final disposition of the document.

The guidelines, which were drawn up in 2009, can be found together with links and other relevant material on the website of the Swedish Psychiatric Association: www.svenskpsykiatri.se.

Metabolic risk in the population

Overweight (body mass index, BMI 25–29.9; Table 1) and *obesity* (BMI 30 or more) are signs of metabolic derangement, and are a growing problem in Sweden; 10% of Swedish men and women suffer from obesity (21). Genetics, lifestyle and socioeconomic conditions are contributing factors (22). Obesity, a condition that is difficult to treat (23, 24), is associated with an increased risk of a number of physical ailments (25–27), and preventive treatment is thus crucial. Healthy eating habits and regular physical activity are among the most important factors for good health (81). Further information including dietary recommendations can be found in the links provided in these guidelines.

Diabetes mellitus is a group of disorders with varying etiology in which chronic hyperglycemia (raised blood sugar) is the common denominator. Hyperglycemia is associated with other metabolic derangements, and gives rise in the long run to changes in small and large vessels resulting in organ damage, primarily affecting the eyes, kidneys, nerves, heart and brain.

Type 1 diabetes is characterized by a progressive lack of insulin related to damage to insulin-producing cells in

the pancreas. Typical symptoms are weight loss, increased thirst and increased urinary production. This is the most common form of diabetes in onset prior to 35 years of age, but onset can take place at any age and even in overweight individuals.

Type 2 diabetes is characterized by reduced effect of insulin on cells in the body—so-called insulin resistance—combined with a relative lack of insulin. This is the most common presentation upon diagnosis after 35 years of age, and incidence increases with age. Onset can take place earlier, and overweight is a contributing factor in earlier onset. Onset is often slow and symptoms often vague. Weight loss is uncommon unless blood sugar is very high (>15–20 mmol/l or 270–360 mg/dl). Classical symptoms of diabetes can thus be lacking when glucose levels are marginally elevated. The symptom-free period in type 2 diabetes can last several years even though organ damage is ongoing. Screening, detection and treatment of type 2 diabetes in individuals at increased risk are thus crucial.

Dyslipidemia—deranged blood lipids—is in certain cases associated with an increased risk of *cardiovascular disease*. Dyslipidemia can be secondary to overweight, hypothyroidism, kidney disease and overconsumption of alcohol, which all should be considered and if necessary treated prior to treatment of the lipid derangement. Treatment of symptom-free individuals should not be initiated simply because of elevated lipid levels, but rather only after a complete risk evaluation has shown that significant utility for the patient is reasonable to expect. Evaluating indications for the treatment of dyslipidemia is a complex call, which should be made in consultation with a primary care physician, internist or pediatrician.

The term *metabolic syndrome* indicates that several of the above-mentioned metabolic derangements are found together, often accompanied by hypertension. The metabolic syndrome is associated with a substantially increased risk of cardiovascular disease.

Antipsychotic medication increases metabolic risk

Children and adolescents

Well performed studies have shown favorable symptomatic effects of antipsychotics in children and adolescents with schizophrenia and psychosis (28), bipolar disorder (29), autism (30) and aggressiveness (31). Young individuals are at increased risk of developing hormonal, motor as well as metabolic side-effects (32, 33). Accelerated weight gain in young patients is a particularly serious side-effect posing substantial health risks later in life (32–36). Pre-pubertal children run the greatest risk of alarmingly rapid weight gain (35, 37). All antipsychotics including traditional low-dose drugs (38, 39) as well as ziprasidone and aripiprazole (11, 40) can induce weight gain in young patients. The association between weight gain in the young and deleterious blood lipids and insulin

Table 1. Body mass index (BMI) calculation.

BMI = weight (kg)/height ² (m)
Underweight, adult: BMI < 18.5
Normal weight, adult: BMI 18.5–24.9
Overweight, adult: BMI 25–29.9
Obesity, adult: BMI 30 and above

Age-adjusted BMI-values in children are provided as BMI-percentile-for-age values or standard deviations (sd). Please see <http://www.bcm.edu/cnrc/bodycomp/bmiz2.html>.

resistance has been shown especially with regard to olanzapine (11, 41–43).

Adults

Under-diagnosis and under-treatment of somatic disease are still a problem for individuals with severe psychiatric disorders, a situation that does not appear to have improved during the last few decades (2, 44–47). It is well known that medication with antipsychotics contributes to overweight even in adults (1, 48). Patients treated with antipsychotics show an increased incidence of risk factors for cardiovascular disease (49). Increased insulin resistance usually coincides with weight gain, but has also been demonstrated in patients with normal weight treated with olanzapine and clozapine (50–53). The weight gain engendering effects of various antipsychotics is shown in Table 2.

Prevention and management of metabolic risk

Primary prevention

The term *primary prevention* refers to measures taken to prevent or delay the onset of illness in healthy individuals, for example preventing the onset of diabetes and cardiovascular disease. Most patients who start treatment with antipsychotics are young and without complicating physical illness. Primary prevention should receive highest priority in order to prevent suffering, because preventive measures have the greatest potential for success, and effective primary prevention is cost-effective. It is crucial to *prevent overweight/obesity*, a condition that is difficult to treat and entails an increased risk of diabetes and cardiovascular disease. Care providers in psychiatry are responsible for this effort, either through in-house measures or in collaboration with other care providers.

Successful primary prevention requires well devised strategies and a methodical approach. The psychiatric nurse has a key role in this task.

Table 2. Weight gain related to antipsychotic medication (70–74).

Clozapine	+++
Olanzapine	+++
Risperidone	++
Quetiapine	++
Perphenazine	+/++
Haloperidol	+/++
Aripiprazole	+
Fluphenazine	+
Ziprasidone	+/0

Clinically relevant weight gain: adults: $\geq 7\%$; children: $\geq 5\%$ during the first 3 months and subsequently 0.5 standard deviation in age-adjusted body mass index. Weight gain usually appears early on in treatment. Rapid initial weight gain is predictive of marked ultimate weight effect.

- All patients who begin treatment with antipsychotic medication should be informed regarding the risk of weight gain and how it can be prevented. Provided patient consent, inform the family and ancillary personnel as well.
- All patients taking antipsychotic medication should be offered a health-profile interview or consultation, in which the focus is on establishing a dialogue concerning lifestyle habits. This will also provide an overview of risk factors. A health-profile interview takes about an hour, and is preferably administered by a psychiatric nurse. A standardized and evidence-based profile form should be used, for instance “Hälsokurvan” (Sw: Health curve). Links to the Hälsokurvan profile form and to information on training in its use can be found in the Swedish language version of these guidelines.
- Follow-up should be carried out at least once yearly. For many patients, more frequent contact will in all likelihood be required in order to have any effect on lifestyle factors. An instructive profile form is filled out by the patient at home and brought along to the visit, which can facilitate documentation and discussion regarding lifestyle factors. One such profile form can be found on the website of the Swedish Psychiatric Association. There is evidence that questions regarding lifestyle habits administered during short counseling sessions can facilitate changes in lifestyle habits in the wider population (54–57). There is also evidence that preventive measures can be effective even among patients with psychotic disorders (58).
- Smoking cessation treatment should be accorded top priority in this group, especially for individuals with other risk factors for cardiovascular disease.

Secondary prevention through screening for metabolic risk

Secondary prevention refers to measures for early detection of metabolic derangements in order to prevent or delay disease progression and thus avoid significant weight gain or progression to diabetes. Available knowledge indicates that even small improvements with regard to risk factors decrease the risk of future cardiovascular disease (17).

The attending psychiatrist is the one responsible for the detection of and initiation of measures to deal with metabolic derangements in this patient group. Each psychiatric clinic should have a routine for screening for metabolic risk factors in this patient group, and a protocol is suggested in Table 3. Indications for intervention as well as reference values for the parameters monitored

Table 3. Systematic monitoring of physical health, main focus on metabolic risk.

	Quarterly, all patients	Yearly, all patients	Temporarily intensified monitoring upon initiating or switching antipsychotics			
			Initial values	4 weeks	8 weeks	12 weeks
History and physical examination. Family history of or known cardiovascular disease, diabetes. Actively inquire as to symptoms of diabetes, cardiovascular disease, perhaps also symptoms of thyroid conditions, chronic obstructive lung disease, prolactin disorder. Assessment: smoking, diet, physical activity, subjective health. Physical examination including dental status.		X	X			
Weight (and height for children/adolescents)	X		X	X	X	X
Waist circumference (a)		X	X			X
Blood pressure (b)		X	X			X
FPG (fasting plasma glucose) (c), possibly HbA1c		X (young patients twice/year)	X			X
Blood lipids (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) (d)		X (young patients twice/year)	X			X
Consider routine screening of thyroid status, liver function, renal assays, as well as electrolytes, prolactin, complete blood count and EKG		X				

(a) Reference values for waist circumference: Women >88 cm significantly increased risk, men >102 cm significantly increased risk (75). Reference values for young patients are lower and age-related (76). Waist circumference to be measured at the level of the navel after a normal exhalation.

(b) Goal blood pressure <140/90. In diabetes and kidney disease <130/80 (77).

(c) Fasting plasma glucose (FPG) ≥ 7.0 mmol/l (approx. 126 mg/dl) on two separate days is diagnostic for diabetes. "Fasting" means no food or drink after 22:00 the night before, FPG tested in the morning. Slightly elevated level, so called impaired fasting glucose IFG = FPG 6.1–6.9 mmol/l (approx. 110–125 mg/dl) is a relative indication for an oral glucose tolerance test (OGTT) for increased diagnostic sensitivity. An OGTT is not difficult to perform and can easily be offered by the psychiatric care provider for this patient group. The fasting patient consumes 75g of glucose dissolved in water (can be ordered from the local pharmacy). Capillary P-glucose ≥ 12.2 mmol/l (approx. 220 mg/dl) or venous P-glucose ≥ 11.1 mmol/l (approx. 200 mg/dl) after 2 h is diagnostic for diabetes (78). These values apply as well for non-fasting glucose if there are symptoms of high blood sugar (fatigue, increased thirst, increased urine volume). Non-fasting P-glucose 7.8–11 mmol/l (approx. 140–198 mg/dl) indicates impaired glucose tolerance (IGT).

(d) Blood lipids: indication for treatment and treatment goals are dependent on compounding risk factors (79, 80), and consultation with a primary care physician, internist or pediatrician is recommended.

in metabolic screening are a complex subject, and collaboration with primary care physicians, internists or pediatricians is recommended.

It is the responsibility of the attending psychiatrist to monitor metabolic status upon initiating or switching antipsychotic medication. A schedule for this monitoring is also to be found in Table 3, and includes the recording of relevant values prior to treatment with a new medication. When prescribing is being carried out by a specialist other than a psychiatrist, then monitoring for metabolic risk is the responsibility of that physician. A characteristic first symptom of metabolic derangement is weight gain, which in its turn is a risk factor for lipid derangement, type 2 diabetes and hypertension. It is believed that abdominal obesity in particular entails a higher level of risk (10, 12–14, 27, 59, 60). If metabolic effects of antipsychotic medication appear, often they do so relatively soon after a drug switch, and so monitoring of metabolic parameters should be especially rigorous during the first weeks/months after initiating treatment with a new antipsychotic drug. Pathological fasting

glucose values are ordinarily a late sign of metabolic derangement, and should not be used exclusively in screening for metabolic risk. Still, for several of the antipsychotics, there are infrequent cases in which rapid progression to diabetes has been described soon after the initiation of treatment.

Managing weight gain and increases in lipids and blood sugar

When a patient's metabolic status is compromised upon initiation or change of antipsychotic medication, it is possible to switch to a drug with less potential for metabolic effects (Table 2). There is support for the understanding that a drug switch of this nature can influence metabolic risk factors favorably (1, 4, 10). A more offensive strategy for influencing other risk factors may be indicated, including smoking cessation treatment, change of diet or regular physical activity. There is a certain amount of scientific support for the understanding that such interventions can have effects on metabolic risk factors in this patient group (58).

Advice regarding lifestyle does not always have the desired effect, and switching to another antipsychotic is for some patients inappropriate from a psychiatric point of view. Pharmacological treatment of metabolic derangement has been tried in several studies, both in children and in adults. Especially for children (from 10 years) and adolescents with pronounced weight gain after initiating treatment with an antipsychotic, short-term studies have shown that addition of metformin has a positive effect on weight gain and insulin resistance (61,62). Metformin was given to patients who had not been diagnosed with diabetes and was well tolerated. Metformin without other blood sugar lowering medication does not give rise to hypoglycemia. In adults, addition of metformin to antipsychotic medication has both shown favorable metabolic effects (63–65) or no effect (66). Note that there is no indication for metformin treatment of patients without diabetes. If treatment with metformin is nonetheless being considered for patients with pronounced weight gain but without diabetes (67–69), it is advisable to consult a primary care physician, internist or pediatrician.

Keep in mind contraindications to metformin such as kidney failure, hepatic insufficiency or acute dehydration with risk for lactic acidosis. Keep in mind pharmacological interactions, which can influence kidney function including interactions during radiological procedures using iodinated contrast media.

Further issues in secondary prevention

The risk of developing diabetes and cardiovascular disease is increased for patients with psychotic disorders or bipolar disorder. These individuals are sometimes less observant of early signs of cardiovascular disease and therefore do not seek care in time. For patients over 50 years of age, the attending psychiatrist should inquire at least once yearly for symptoms of angina pectoris and when required refer the patient to a primary care physician for further investigation.

These patients sometimes show a pronounced inability to fend for themselves, including establishing timely contact with providers of appropriate somatic care when needed. Simply informing a patient that primary care might be appropriate is insufficient. The individual with a psychotic disorder may need concrete support by his or her mental health aide or human service assistant from the psychiatric clinic or social services, in order actually to go to his or her community clinic or hospital. Support can be required for the visit itself, for noting the date and time of the next visit, and for working out methods for remembering to take prescribed medications regularly.

Patients with risk factors for cardiovascular disease should be urged to alert emergency services immediately

upon noticing symptoms that could indicate heart attack, for ambulance transportation to the hospital. Patients with psychotic disorders often arrive at the hospital rather late after symptom onset and as a result suffer extensive infarctions with risk of subsequent heart failure. During postinfarction follow-up, patients can be offered smoking cessation treatment.

Take responsibility for functioning collaboration with other specialties

At an organizational level, circumstances vary from one locality to another. Each psychiatric care provider should initiate a dialogue or enter into a formal agreement with local primary care providers with regard to the management of these patients, detailing who is responsible for what. Do not forget to include patients in municipal assisted living facilities or homes for care and housing. In some places, the best solution for a psychiatric clinic may be to retain the regular services of a consultant in internal medicine, family medicine or pediatrics, possibly at the same time enlisting a specially interested psychiatric nurse whose tasks will entail supervising routines for regular blood tests and health interviews for this group—similar to lithium clinics. Ultimate responsibility for establishing functioning collaborative routines for the care of these patients falls on the shoulders of each psychiatric care provider's chief of staff.

Implementation strategy

To facilitate implementation these guidelines have been laid out in concise form, with the core message summarized in tables and info boxes, serving as decision support tools for dealing with early signs of metabolic derangement. A broad consensus has been actively sought in order to increase the likelihood of implementation, representatives for seven specialist medical societies have collaborated, and each society has formally approved the guidelines. The final version of the guidelines will be presented in various Swedish medical journals and meetings. Chiefs of staff at psychiatric and child and adolescent psychiatric clinics have been involved, firstly by having been kept informed ahead of time regarding this undertaking, and secondly during the consultative phase by contributing viewpoints on the first draft. The final version of the guidelines has been forwarded directly to each chief of staff. User organizations as well as several nursing societies have taken part in the consultative phase of the work. A collaborative effort toward implementation is being planned together with user organizations and the *Psykiatriska Riksföreningen*, a society of psychiatric nurses. Work is being done to incorporate perspectives on the implementation of these guidelines in relevant psychiatric quality registers.

Info Box 1. Summary.

Background

- Metabolic derangement—such as weight gain, elevated blood lipids, progression to diabetes—are common among individuals with bipolar syndrome, schizophrenia and other psychotic disorders. Metabolic derangements increase the risk of future cardiovascular disease.
- Antipsychotic medication can contribute to metabolic derangement.
- Weight gain is an early sign of metabolic derangement. Established overweight is difficult to treat and should therefore be prevented. If weight gain nonetheless should occur, for instance upon initiating antipsychotic medication, then this should be detected early on and steps should be taken to prevent further weight gain.
- The prescribing physician is responsible for detection and management of any metabolic derangement that occurs upon initiating antipsychotic medication or consequent to a drug switch. The chief of staff of a psychiatric care provider is responsible for establishing means and methods for collaborative efforts with representatives of other medical specialties whose assistance may be required in the treatment of metabolic derangement.

Steps for preventing weight gain

- Educate the patient regarding the importance for future health of lifestyle habits including nutrition, smoking cessation and physical activity. It is suggested that this take place in the context of a structured health interview with the psychiatric nurse, who makes an assessment regarding the presence of risk factors for cardiovascular disease, and who provides follow-up lifestyle counseling. Educate family and human service assistants as well.
- Repeat this interview and counseling at least once yearly.
- Upon initiating treatment with an antipsychotic or when switching from one drug to another, the risk of metabolic repercussions should be carefully considered in choosing a medication, aside from other criteria for drug choice (Table 2). This is especially important for patients with a family history of or already established metabolic derangement or cardiovascular disease, as well as patients who can be expected to be particularly vulnerable to metabolic effects, such as adolescents.

Steps to take when weight gain has occurred or elevated blood lipids are detected

- More frequent blood testing:
 - FPG once monthly
 - Weight and waist circumference once monthly
 - Blood lipids quarterly
- Intensify educative efforts regarding lifestyle change and weight-reduction (nutrition, physical activity, smoking cessation)
- Consider switching to another antipsychotic (Table 2).
- Consult with a primary care physician/internist/pediatrician; consider medication against weight gain or elevated blood lipids. Consider making a referral.

Steps to take when raised blood sugar levels are detected

- If impaired fasting glucose/IFG (FPG 6.1–6.9 mmol/l, approx 110–125 mg/dl) is detected, or non-fasting glucose is 7.8–11 mmol/l, (approx. 140–198 mg/dl)
 - repeat assay, if still IFG offer an OGTT. Consultation with primary care physician/internist/pediatrician. Establish contact with a diabetes nurse.
 - Intensify educative efforts regarding lifestyle change and weight-reduction (nutrition, physical activity, smoking cessation)
 - Consider switching to another antipsychotic (Table 2).
- If diabetes: consultation with or referral to primary care physician/internist/pediatrician regarding pharmacological interventions. Make sure that contact is actually established and that follow-up actually takes place!

Info Box 2. For the patient/patient's family—questions to pose to the physician upon starting or switching antipsychotic medication:

- What is the risk of developing a metabolic derangement and other side-effects with this particular drug? Are the expected results of treatment worth this risk?
- What advice is to be had for preventive measures with regard to weight gain?
- How will care be planned and organized so as to detect any early signs of metabolic derangement?

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Conflicts of interest:

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