

Metabolic risk reduction in patients with schizophrenia treated with antipsychotics: recommendations of the Polish Psychiatric Association

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Summary

Patients with schizophrenia are susceptible to physical illnesses, which reduces their life expectancy by an average of 20 years compared with the general population. The most common physical illnesses amongst patients with schizophrenia are metabolic disorders and cardiovascular diseases. The aim of this paper is to present recommendations on metabolic risk reduction in patients with schizophrenia treated with antipsychotics, accepted as a position statement of the Polish Psychiatric Association for use in the management of persons suffering from schizophrenia in Poland. A routine assessment of metabolic risk is recommended for the early detection of metabolic disorders and to monitor the safety of the antipsychotic treatment. It includes: medical history, physical examination, laboratory tests. Each patient should undergo this assessment before the initiation of treatment, after 6 and 12 weeks of treatment, and at least once a year thereafter. In men and women suffering from schizophrenia who are over the age of 40 and 50 years, respectively, a cardiovascular risk assessment using the SCORE charts is also recommended. (1) Antipsychotics with a low potential to cause metabolic disorders should be preferred and administered at the appropriate dose in order to reduce metabolic risk. (2) If other agents found to cause metabolic disorders are used, the treatment should be modified by augmentation or by switching to another antipsychotic with a lower potential to cause metabolic disorders. (3) Consultation by an internal medicine

specialist and medical treatment should be recommended. (4) Patients should be assisted in developing healthy eating habits, encouraged to pursue regular physical activity and (5) to quit smoking, drinking alcohol and using psychoactive substances.

Key words: schizophrenia, metabolic disorders, risk factors, antipsychotics, management, recommendations

Introduction

Patients with schizophrenia require chronic treatment over multiple years and over their lifetimes they tend to develop other health problems in addition to their underlying mental illness, which in some cases can be quite serious. Patients diagnosed with schizophrenia are particularly susceptible to physical illness. Several analyses have shown that 35–70% of patients with schizophrenia also suffer from a serious physical illness [1]. According to the Patient Outcomes Research Team (PORT) study of 719 persons, 36% of the subjects could be diagnosed with more than one physical illness, and in 48%, a physical illness was currently present and active [2]. Life expectancy in patients with schizophrenia is 20 years shorter than that in the general population [3], which is largely due to physical illness. The profile of health problems amongst patients has changed over the past several decades. While tuberculosis and gastrointestinal tract infections prevailed in the past, cardiovascular disease, diabetes mellitus, obesity, and metabolic syndrome have emerged in the 1990s as the predominant problems [4]. Metabolic syndrome and its components – visceral obesity, hypertension, diabetes mellitus, and dyslipidemia – are of particular importance amongst patients with schizophrenia [5, 6]. This is directly related to the increased risk of cardiovascular death compared to the general population [7]. It is worth noting that obesity and metabolic syndrome in psychiatric patients are not only associated with a higher risk of physical illness but also impact the quality of life, cognitive functions, compliance with pharmacological treatment, and additionally stigmatize the patients, lower their self-esteem, contribute to social withdrawal, and interfere with finding employment and building a satisfactory relationship with a partner. Therefore, obesity and metabolic syndrome exacerbate the serious psychological and social problems already carried by the diagnosis of schizophrenia. Right from the very start of the antipsychotic treatment, consideration should be given not only to its effectiveness but also to its tolerability and the possible physical complications, particularly obesity and metabolic syndrome, and strategies to prevent and minimize these complications should also be implemented right from the very beginning of treatment. The aim of the paper is to present recommendations on metabolic risk reduction in patients with schizophrenia who are treated with antipsychotics.

Methods

The recommendations have been based on the presentations prepared and given by a panel of experts during a work meeting which took place in June 2019. The expert panel consisted of psychiatrists experienced in the treatment of schizophrenia (DD, JH, JS, AS, AW), a physician, psychopharmacologist (PB) involved in basic research and clinical studies of antipsychotics, and internal medicine specialists (AKC, AM) experienced in the treatment of metabolic disorders and cardiovascular disease. The resulting presentations provided the current recommendations of scientific societies and literature reviews on the following topics:

- the causes of increased risk of metabolic disorders in patients with schizophrenia, broken down into non-pharmacological and disease-specific factors, and factors related to pharmacological treatment;
- diagnostic recommendations aimed to enable the early detection of metabolic disorders in patients with schizophrenia and to monitor metabolic parameters during antipsychotic treatment;
- treatment recommendations aimed to reduce the risk of metabolic disorders and counteract them in patients with schizophrenia, including pharmacological, non-pharmacological and general medical interventions.

Each of the presentations was discussed and critically evaluated and based on that each of the authors prepared their respective part of the recommendations in writing. After the recommendations had been discussed amongst the experts and accepted, they were submitted in the form of a manuscript to the Board of the Polish Psychiatric Association and, after taking into account the Board's comments, they were adopted as a position statement of the Association with the recommendation that these be used in the management of persons suffering from schizophrenia in Poland.

Non-pharmacological and disease-specific factors that increase the risk of metabolic disorders in patients with schizophrenia

The increased risk of morbidity in patients with schizophrenia, especially in terms of metabolic syndrome and cardiovascular disease, has very complex determinants. It is not only affected by factors specific to the mental illness and its treatment, the patient's lifestyle and behavior, and sociocultural settings, but also by the problems faced by the healthcare system [8, 9].

Metabolic disorders have been found to occur in antipsychotic-naive patients with schizophrenia. These patients also tended to display insulin resistance, which can lead to dyslipidemia and weight gain [10]. Ryan et al. [11] showed that patients with first-episode psychosis, before they started the antipsychotic treatment, had three times as much visceral fat as healthy volunteers matched for BMI (body mass index). It was

also found that normal-weight patients with schizophrenia had more visceral fat than BMI-matched healthy volunteers, with both groups exhibiting similar quantities of subcutaneous fat [12].

The increased insulin levels and/or insulin resistance observed in treatment-naive patients with schizophrenia may be related to the specific etiology and pathogenesis of their psychosis, through direct effect on the brain or indirectly via the hypothalamic-pituitary-adrenal axis [13, 14]. Patients with the first episode of schizophrenia have elevated markers of inflammation (C-reactive protein, interleukin-6, interleukin-1 receptor antagonist, TNF), which are also present in metabolic syndrome, type 2 diabetes mellitus, and atherosclerosis [15].

The increased risk of metabolic syndrome does not only apply to patients with schizophrenia but also to their first-degree relatives [16], which points to the contributory role of genetic determinants. Studies have also demonstrated pleiotropy between schizophrenia and dyslipidemia [17] and a genetic association of schizophrenia with autoimmune disorders, cardiovascular disease and type 2 diabetes mellitus [15].

When examining the increased metabolic risk consideration should be given to the neurodevelopmental hypothesis of schizophrenia, according to which certain adverse prenatal factors are involved in the etiology and pathogenesis of the illness, e.g., infection, malnutrition, growth limitation, hypoxia, dysregulation of the maternal hypothalamic-pituitary-adrenal axis, increased levels of glucocorticoids, and the triggering of inflammatory response. These factors also play an important role in the development of physical illnesses later in life and can therefore be considered as shared risk factors, already present in the fetal period. Intrauterine malnutrition, for instance, can permanently alter the metabolism, while affecting at the same time the development of the central nervous system [15].

The above data on the potential biological associations between schizophrenia and physical illness do not exhaust the subject of disease-specific risk factors of metabolic syndrome. The patient's physical health is equally affected by the severity of psychosis as it is by its positive symptoms (e.g., distrustful attitude towards doctors, delayed diagnosis due to the bizarre and delusional account of the symptoms of physical illness), negative symptoms (e.g., avolition, lack of motivation, withdrawal, overlap of nonspecific symptoms of the physical illness with psychopathological symptoms), cognitive deficits (impulsivity, emotional dysregulation) [8].

The course and severity of schizophrenia are directly related to the patient's lifestyle and behaviors. Compared to the general population, patients with schizophrenia are less physically active, spend more time in bed [18, 19], live a more sedentary lifestyle, consume more foods but of poorer quality, and smoke considerable amounts of cigarettes [9]. The economic situation of the patients is often difficult and their possibilities to receive support from friends and relatives are limited. An increasing problem is the

so-called dual diagnosis, which refers to the coexistence of disorders associated with harmful use of substances.

Prevention and treatment always take place in the interaction between the patient and the healthcare system. It turns out that despite the increased somatic risk, patients with schizophrenia have poorer access to diagnostic evaluation and therapeutic interventions than patients in the general population [20, 21]. In many cases, physical illnesses remain undiagnosed and untreated. For example, analysis of data from the CATIE study showed that the rates of non-treatment were 30.2% for diabetes mellitus, 62.4% for hypertension, and 88.9% for dyslipidemia [22]. Despite regular contacts with mental health professionals, patients – compared to the general population – undergo fewer prophylactic and follow-up tests, less frequently receive adequate and timely treatment for cardiovascular disease, e.g., revascularization procedures as part of interventional cardiology, bypass surgeries, treatment with beta-blockers or statins) [23, 24].

Factors negatively affecting physical health also include those directly related to the organization of healthcare. Mental health facilities can be far away from hospitals or general clinics, which implies a limited access to psychiatric consultations. Insufficient communication between psychiatrists and general practitioners or other specialists is a big problem. It is sometimes the case that a psychiatrist does not have full access to the patient’s medical record and that a patient (and his relatives), when seeing a non-psychiatrist doctor, do not mention the patient’s mental illness. This is due to the fear of stigmatization and the negative beliefs and attitudes, still widespread in our society, towards persons with schizophrenia. Despite the considerable progress in postgraduate education, non-psychiatrist physicians are still insufficiently prepared for providing comprehensive medical care to patients with mental disorders, while psychiatrists lack competence in modern non-psychiatric medicine. Finally, limited expenditure on psychiatric care leads to limited ordering of diagnostic tests pertaining to physical health and ancillary studies. The non-pharmacological factors that increase the risk of metabolic syndrome in patients with schizophrenia are listed in Table 1.

Table 1. Non-pharmacological risk factors of metabolic syndrome in patients with schizophrenia

Related to the course of schizophrenia
Severity of symptoms
Diagnostic delay
Overlap of mental illness symptoms and non-specific symptoms of physical illness
Poor compliance
Shared biological, genetic, developmental, inflammatory, endocrine mechanisms

table continued on the next page

Related to lifestyle
Smoking
Stimulants
Low physical activity
Poor diet
Lack of care about follow-up tests
Related to socioeconomic and cultural circumstances
Poor financial situation
Lack of support
Stigmatization and discrimination
Related to healthcare system
Low expenditure on psychiatry
Distance to mental health facilities
Poor communication between physicians and lack of coordination of treatment activities
Insufficient postgraduate education

Factors related to pharmacological treatment that increase the risk of metabolic disorders in patients with schizophrenia

The purpose of this subchapter is to discuss the pharmacological mechanisms inherent to the action of second-generation neuroleptics which, in clinical practice, can translate into increased appetite (and/or decreased satiety), weight gain, deterioration of glucose tolerance, and unfavorable changes in the lipid profile, or – in a broader sense – into increased cardiometabolic risk. Many statements in this subchapter also apply to first-generation neuroleptics [25, 26].

The use of the term ‘neuroleptics’ is fully intended. In clinical practice, this term is often used interchangeably with the term ‘antipsychotics’. However, we would like to point out that neuroleptics are also used for the treatment of non-psychotic conditions. The psychotropic profile of a neuroleptic agent may, by definition, include desirable effects (psychomotor retardation, sedation, somnolence) and undesirable effects (loss of interest, dysphoria, anhedonia), which may indirectly contribute to the changes in food preferences and to metabolic disorders [25, 27].

In terms of pharmacology, second-generation antipsychotics are mainly antagonists (blockers) of receptors for central and peripheral nervous system transmitters, including selected receptors for monoamines (dopamine, serotonin, noradrenaline, histamine) and muscarinic receptors for acetylcholine. In light of the ample evidence of the central, anorexic effects of such transmitters as dopamine, histamine, serotonin or noradrenaline, opposite effects, i.e., the increasing feeling of hunger and increasing weight, should

be expected with blockers of the D2 dopaminergic receptors, histamine H1 receptors, 5-HT_{2A} and 5-HT_{2C} serotonergic receptors or α ₁-adrenergic receptors. Central anticholinergic action, the blockade of the muscarinic receptors (most commonly M1 and M3) by neuroleptics, is an additional mechanism that contributes to the increased feeling of hunger, or the orexigenic effect [28]. Preclinical and clinical studies confirm that neuroleptic-mediated disinhibition of hunger and inhibition of satiety mainly occur in the hypothalamus and other limbic structures [29]. The very principal mechanism of action of neuroleptics, i.e., the blockade of dopamine D2 receptors, may lead to increased appetite and weight gain. For this reason, these problems occur, although less frequently, even with the most selective first – and second-generation agents (haloperidol and amisulpride, respectively) [25, 29].

It is worth noting that the etiological and pathogenetic associations between the mechanisms of action of second-generation neuroleptics and weight gain on the one hand and the metabolic risk on the other are not accidental. The shifting of the pharmacological profile towards the blockade of serotonin receptors that was planned many years ago and included the 5-HT_{2A} subtype and also the 5-HT_{2C} subtype considerably improved the safety profile of these agents in terms of the symptoms of parkinsonism. Unfortunately, the blockade of serotonin receptors disturbs the physiological anorexic effect of this monoamine in the hypothalamus, resulting in an increased preference for high-calorie foods, including sweet snacks [29, 30].

Many authors emphasize the key role for the development of metabolic complications of second-generation neuroleptic treatment played by the blockade of 5-HT_{2C} receptors and by the pathological ‘synergy’ between the effects on various receptor systems (e.g., simultaneous blockade of D2 and H1 receptors or of D2 and 5-HT_{2C} receptors). It is these mechanisms that are most likely responsible for the markedly higher risk of metabolic complications attributed to clozapine and olanzapine, two non-selective neuroleptics with a high affinity for 5-HT_{2C} and H1 receptors [25, 29].

Many pharmacological effects typical of second-generation neuroleptics (e.g., antagonism for D2, α ₁, H1 receptors) may lead to weight gain in an indirect manner, i.e., unrelated to the effects on the mechanisms of hunger and satiety [25]. Neuroleptics, by definition, cause sedation and decrease psychomotor activity, which apart from its therapeutic advantage may rapidly decrease the body’s energy requirement and exacerbate metabolic complications that result from the increased sensation of hunger and the peripheral hormonal changes [27].

Hyperprolactinemia is a relatively typical adverse reaction to neuroleptics with strong inhibitory effects on D2 receptors. Independently of its many other effects, prolactin is a hormone that increases the risk of obesity, which at least partially explains the weight gain observed with such second-generation neuroleptics as amisulpride or risperidone [28, 29].

A discussion of the increased metabolic risk secondary to the neuroleptic treatment should also address strictly peripheral mechanisms. Many of the receptors mentioned above play a key role in the activity of the peripheral nervous system, including the autonomic nerve endings that regulate the secretion of hormones, e.g., insulin. Clozapine and olanzapine are likely the most potent inhibitors of insulin secretion by anticholinergic action, i.e., the blockade of muscarinic M3 receptors localized on the surface of pancreatic beta cells [26, 30]. Most neuroleptics are able to decrease insulin secretion by blocking serotonin receptors, e.g., 5-HT_{2A} receptors. Other receptor-mediated effects of these agents, including antihistamine effects, are associated with the inhibition of glucose uptake by skeletal muscles or abnormal metabolism of fats in the liver. In this manner, not only the central but also the peripheral effects of neuroleptics increase the risk of diabetes mellitus and other metabolic syndrome components [29, 30].

When conducting the antipsychotic treatment, irrespective of the generation or profile of the neuroleptic used, one should expect an increased feeling of hunger and appetite for high-calorie foods, weight gain, and cardiometabolic complications. Importantly, as no complete correlation between weight gain and an increased metabolic risk has been demonstrated, every patient treated with antipsychotics should be monitored for weight gain, evidence of dyslipidemia, hyperglycemia, and – in a broader sense – metabolic syndrome [25, 31]. From a practical standpoint, of critical importance is the knowledge of pharmacological strategies that could limit the development of metabolic complications accompanying the antipsychotic treatment [31]. In the clinical setting, at least two such strategies can be considered important and feasible. The first strategy is based on ago-antagonist (partially agonist) action on D₂ and D₃ dopamine receptors. This mechanism characterizes the effects of aripiprazole and cariprazine, which are available in Poland, and may translate into a smaller increase in appetite and a smaller weight gain [32]. The other strategy involves the use of D₂ receptor blockers devoid, at least partially, of the so-called additional receptor-mediated effects (amisulpride, ziprasidone, lurasidone). In the case of amisulpride and lurasidone, the essential point is the nearly complete elimination of the orexigenic receptor-mediated effects – the antihistaminic and anticholinergic effects [26, 29, 30].

In summary, second-generation neuroleptics are psychotropic medications whose pharmacological actions can lead to rapid, unfavorable changes in the regulation of hunger and satiety, in the control of energy expenditure and body weight, and in the peripheral release of insulin, and in glucose tolerance. The metabolic disorders resulting from these changes may be independent of the principal clinical effect (i.e., antipsychotic effect) but better correlated with the sedative effect or the induction of somnolence. Just as importantly, the peripheral receptor-mediated effects of second-generation neuroleptics, including insulin release suppression, may impair glucose

tolerance independently of weight gain [29, 30]. It follows from the above that in each patient treated with a second-generation neuroleptic, basic vigilance for the metabolic complications of the treatment is needed, and screening tests should not be delayed even if no significant changes in the patient's weight are observed [25, 26, 30]. The choice of the agent alone can be an element of prevention of antipsychotic treatment complications. In patients with high metabolic risk, an agent should be considered whose risk of metabolic complications is at least partially reduced by its mechanism of action (e.g., partial agonist action on D2 receptors) or its receptor selectivity (no effect on histamine and cholinergic receptors). As mentioned above, these agents include lurasidone, aripiprazole, ziprasidone, and amisulpride [28, 29].

The above conclusions are elaborated on in the subsequent subchapters on clinical practice. Interested readers are referred to the recently published review papers for a more extensive, theoretical discussion of the associations between the mechanisms of action of antipsychotics and the metabolic complications of the antipsychotic treatment [26, 29–31].

Diagnostic recommendations

A routine assessment of metabolic risk in patients with schizophrenia is recommended in order to enable the early detection of metabolic disorders in these patients and to monitor the safety of the antipsychotic treatment in terms of metabolic complications.

The assessment of the risk includes:

- (1) medical history – presence of risk factors of or clinically overt cardiovascular disease (CVD) and/or diabetes mellitus, family history, smoking status, eating habits, level of physical activity;
- (2) physical examination – body weight and height with calculated body mass index (BMI), waist circumference, blood pressure (mean value of at least 2 measurements during a single visit);
- (3) laboratory tests – fasting glucose, lipid profile, serum creatinine with estimated glomerular filtration rate (GFR), uric acid level [33, 34].

The frequency of laboratory testing depends on the patient's individual risk, co-morbidities, and current treatment. The published recommendations indicate that metabolic risk assessment in each patient with schizophrenia should be carried out before the initiation of the antipsychotic treatment, several weeks and a few months into the treatment, and at least once a year thereafter [33, 35–37]. The recommended schedule of metabolic risk assessment is provided in Table 2.

Table 2. Recommended schedule of metabolic risk assessment in patients with schizophrenia (based on [35–37])

Parameters	Before treatment	At 6 weeks	At 3 months	Every 12 months
Family history	X			
Medical history, including smoking, physical activity, eating habits	X	X	X	X
Body weight (BMI)	X	X	X	X
Waist circumference (measured at the level of the umbilicus)	X	X	X	X
Blood pressure	X	X	X	X
Fasting glucose	X	X	X	X
Fasting lipid profile	X		X	X
Serum creatinine and GFR	X			X
Uric acid	X			X
ECG *	X			
Prolactin **	X		X	X
Dentition and oral hygiene	X			X

* Performed for the evaluation of cardiovascular risk category (assessment of, e.g., signs of left ventricular hypertrophy or of previous myocardial infarction). Irrespectively, in patients receiving antipsychotics, ECG should also be performed after treatment initiation, as well as after dose up-titration to monitor the QT interval.

** Determination of prolactin level is recommended in patients with menstrual disorders or sexual dysfunction

GFR – glomerular filtration rate

In addition, given that about half of Polish patients with schizophrenia without overt CVD have a high or very high global cardiovascular risk, in men and women suffering from schizophrenia who are over the age of 40 and 50 years, respectively, it is also recommended that the cardiovascular risk be assessed using the SCORE (Systematic COronary Risk Evaluation) chart calibrated for the Polish population (Pol-SCORE, Figure 1) together with cardiovascular risk classification (Table 3) [34, 38, 39].

Table 3. Cardiovascular risk categories (based on [40])

Very high risk	Documented CVD DM with target-organ damage* or ≥ 3 major risk factors** Severe CKD (GFR < 30 ml/min/1.73 m ²) SCORE $\geq 10\%$
High risk	Markedly increased single risk factor*** DM with 1–2 additional risk factors** or disease duration of ≥ 10 years, without target-organ damage* Moderate CKD (GFR 30–59 ml/min/1.73 m ²) SCORE 5–9%
Moderate risk	DM: young patients (< 50 years in the case of type 2 DM, < 35 in the case of type 1 DM) with DM duration of < 10 years, without other risk factors SCORE 1–4%
Low risk	SCORE $< 1\%$

* microalbuminuria, retinopathy, neuropathy or left ventricular hypertrophy

** e.g., smoking, hypertension, dyslipidemia or obesity

*** e.g., familial hypercholesterolemia or grade 3 hypertension (blood pressure values $\geq 180/110$ mm Hg)

CVD – cardiovascular disease; DM – diabetes mellitus; CKD – chronic kidney disease; GFR – glomerular filtration rate; SCORE – result in the SCORE chart allowing the assessment of 10-year risk of cardiovascular death

It should be stressed that patients with schizophrenia may be at a higher cardiovascular risk than might be suggested by the assessment using the SCORE chart, which is why in cases of borderline results, a higher level of risk should be assumed to be present [34, 40]. In younger patients, assessment of the relative risk or of the cardiovascular risk age (the so-called vascular age) is recommended [34].

Pharmacological treatment

As mentioned on multiple occasions, assessment of the risk of obesity and/or metabolic syndrome in persons with schizophrenia is comprehensive and includes various factors. One of these factors are the adverse reactions to certain psychotropic medications, including antipsychotics [41]. Certain antipsychotics are associated with a higher risk of adverse reactions related to weight gain and, consequently, physical symptoms.

Below are the most recent recommendations on pharmacological interventions aimed to reduce metabolic risk in patients with schizophrenia that can be found in the literature:

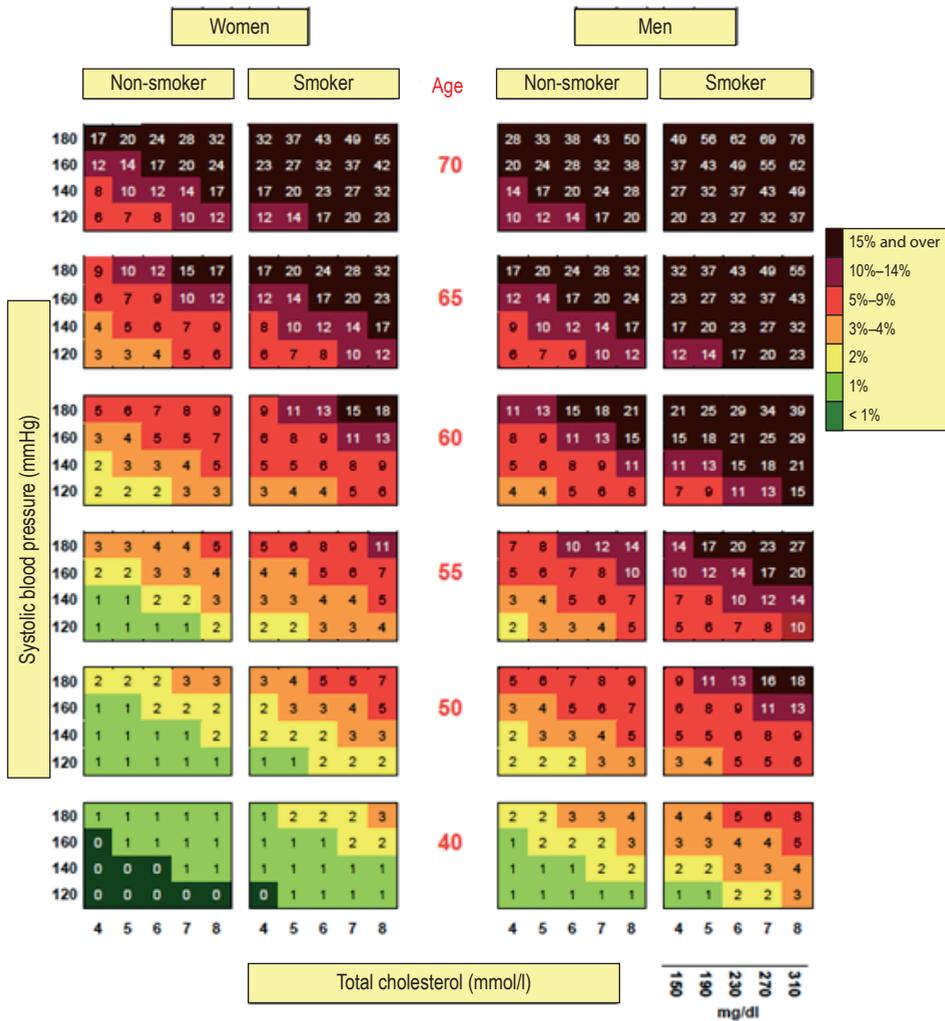


Figure 1. A SCORE risk chart calibrated for the population of Poland (Pol-SCORE [39]) allowing the assessment of 10-year risk of cardiovascular death in persons without the diagnosis of cardiovascular disease or diabetes mellitus

1. Choosing a specific antipsychotic medication at an appropriate dose depending on the presence of metabolic risk in the patient.
2. Modifying the antipsychotic treatment: adjusting the dose of the medication, augmenting the treatment with another antipsychotic medication characterized by a low risk of weight gain.
3. Switching to another antipsychotic medication (as above).
4. Treating the physical illnesses (metformin, statins etc.).

Investigational treatment – augmentation with non-steroid anti-inflammatory drugs, N-acetylcysteine, drugs modifying the intestinal bacterial microflora [42, 43].

Optimizing the antipsychotic treatment in cases of alcohol abuse and smoking.

Selecting the right medication at the right dose

So far, in the case of patients with increased metabolic risk, the literature has focused on selecting a drug with the best tolerance profile, without this particular action. Recently published comparative meta-analysis of 32 antipsychotics found that drugs with the lowest risk of weight gain are ziprasidone, lurasidone, aripiprazole, haloperidol, brexpiprazole, and cariprazine [44]. The proposed division of antipsychotics based on their risk to cause weight gain and metabolic disturbances is presented in Table 4.

Table 4. **Division of antipsychotic drugs based on their risk to cause weight gain and metabolic disturbances (based on [9, 42–44, 74])**

Drug	Weight gain	Prediabetes and diabetes mellitus	Dyslipidemia
Second-generation antipsychotic drugs			
Amisulpride	+	-	-
Aripiprazole	-	-	-
Asenapine	++	+	+
Brexpiprazole	+	N	N
Cariprazine	+	N	N
Clozapine	+++	+++	+++
Iloperidone	++	+	+
Lurasidone	-	-	-
Olanzapine	+++	+++	+++
Paliperidone	++	+	+
Quetiapine	++	++	+++
Risperidone	++	+	+
Sertindole	++	+	+
Ziprasidone	-	-	-
First-generation antipsychotic drugs			
Chlorpromazine	+++	+++	+++
Flupentixol	++	+	+

table continued on the next page

Haloperidol	+	+	-
Perazine	++	+	+
Perphenazine	+	+	-
Promazine	++	+	+
Sulpiride	+	-	-
Zuclopenthixol	++	+	+

+++ high risk; ++ moderate risk; + low risk; – very low risk; N – available data indicate low risk, but a longer follow-up period is needed

Particular attention should, however, be paid to the doses used and to the phenomenon of polytherapy. According to research studies, using maximum doses of antipsychotics is not always effective and often leads to adverse reactions. This is also the case with combining two or more antipsychotics. However, in some cases augmentation of a drug that has a higher risk of weight gain with another antipsychotic agent that has a better tolerance profile is an effective strategy, especially in the case of treatment with clozapine in patients in whom clinical efficacy needs to be taken into account [43].

Switching or augmenting the antipsychotic treatment, providing treatment for physical illness

Pharmacological interventions include various agents, not only antipsychotics, used alone or as add-on therapy. A meta-analysis that compared a number of various interventions concluded that the most effective intervention in reducing weight was metformin (as add-on therapy), followed by treatment switch to aripiprazole, followed by augmentation with topiramate, and then, amongst others, antidepressant treatment (with reboxetine and fluoxetine). The 'main' treatment in these cases was in most cases olanzapine and clozapine [45, 46].

Another meta-analysis mentions non-pharmacological interventions as the most effective methods to improve physical health in persons with schizophrenia, followed by – in terms of weight reduction – treatment augmentation with aripiprazole, topiramate, d-fluphenazine, and metformin. The best results in terms of reducing waist circumference have been achieved by treatment augmentation with aripiprazole or topiramate, while switching the treatment from olanzapine to aripiprazole, including the use of metformin, proved to provide the best results in terms of reducing the risk of diabetes mellitus. Topiramate proved to be the most beneficial in terms of effects on lipid metabolism [9]. Metformin is the agent that is most commonly mentioned as beneficial in managing weight gain associated with antipsychotics [47].

In a literature review of patients switched from olanzapine to aripiprazole or quetiapine revealed weight reduction, BMI reduction, and improved glucose and

lipid profiles [48]. Treatment switch to aripiprazole or augmentation of olanzapine or clozapine treatment with aripiprazole is the most commonly reported strategy [45, 49, 50]. The current literature reports on using lurasidone as an agent having a beneficial profile in terms of potential metabolic risk, including weight gain [51].

Optimizing the antipsychotic treatment in cases of alcohol abuse and smoking

Persons with schizophrenia are undoubtedly at a higher risk of cardiovascular disease, diabetes mellitus and excessive weight gain, among other things, as a result of such risk factors as smoking and alcohol abuse. It is believed that cardiovascular disease – the direct factor responsible for the shortening of life expectancy by an average of 20 years – is negatively impacted by both alcohol abuse and smoking. Although according to some reports, mild to moderate alcohol consumption does not have such oppressive consequences for the development of cardiovascular disease, the prevailing opinion is that heavy alcohol consumption has a negative impact – affecting a considerable number of patients with schizophrenia – on the risk of coronary artery disease, hypertension, stroke, peripheral artery disease, cardiomyopathies, cardiac arrhythmias, hypercholesterolemia, and cancer in this population [52, 53].

Few studies have assessed the efficacy of pharmacological interventions in schizophrenia accompanied by serious alcohol abuse. In fact, older studies [54], with respect to first-generation antipsychotics, emphasize that these agents may not only fail to reduce the abuse and dependence but they may actually increase it. Few studies that assessed second-generation antipsychotics, namely olanzapine, risperidone and quetiapine, have shown the use of long-acting injectable (LAI) risperidone in particular and flupentixol to be more beneficial. Of the drugs that optimize the treatment of alcohol dependence in the course of schizophrenia, acamprosate and naltrexone are mentioned for the first-line treatment as options that are safe to use. Although disulfiram is mentioned as a second-line treatment, it should be borne in mind that disulfiram is contraindicated in schizophrenia due to its tendency for inhibiting dopamine beta-hydroxylase. However, it seems promising to use nalmefene that blocks the euphoric effect of alcohol and reduces craving [55–57].

Data on the optimization of schizophrenia treatment along with smoking cessation suggest certain benefits when using bupropion and varenicline, both in terms of reducing the number of cigarettes smoked per day and alleviating the withdrawal symptoms. Studies investigating the replacement use of e-cigarettes are inconclusive. The use of nicotine patches (due to the content of substances which may increase the activity of cytochrome P450 1A2), on the other hand, while being able to reduce smoking, can also decrease serum levels of clozapine, olanzapine or haloperidol [58, 59].

Non-pharmacological treatment

Nutritional psychiatry and the modern diet

The ongoing urbanization, technological and cultural development, life under stress, the pursuit of self-actualization, and the resulting lack of time, altered eating habits, consumption of high-calorie and processed foods are all factors that undoubtedly affect mental health and promote the development of lifestyle diseases. Among these phenomena emerges nutritional psychiatry – a new field that explores the effects of the quality of nutrition and nutrients on mental health.

Overweight and obesity are certainly a social issue of our times. We consume increasing amounts of processed, high-calorie and nutritionally-poor food products, as a result of which we struggle with overweight and obesity coupled with nutrient deficiencies. Although our calorie intake increases, we do not consume the recommended amounts of micro – and macroelements that play vital roles in the proper functioning of the nervous system (such as the B vitamins, zinc or magnesium). We also consume less than recommended amounts of high-fibre and high-nutrient vegetables and cereal products. These eating habits – combined with smoking, reduced physical activity and harmful alcohol consumption – adversely affect our health, including mental health, and result in a growing incidence of lifestyle diseases, including mental disorders.

The gut-brain axis – effects of microbiota on mental well-being

Gut microbiota is estimated to form a complex ecosystem that consists of 10^{14} microorganisms (over a thousand different microorganism species [60]). With its 3.3 million genes, it exceeds the number of genes in the human genome by about 150-fold. The gut-brain axis involving a two-way relationship between the gastrointestinal tract and the central nervous system makes use of several communication mechanisms. Reciprocal exchange of information may take place via the autonomic nervous system, the vagus nerve or through humoral and hormonal factors. Many of the effects of probiotics on mental well-being were thought to be associated with the transmission of information via the vagus nerve. Studies on germ-free (GF) mice bred in sterile conditions, devoid of any detectable microorganisms, show the role of gut microbiota in the proper development and functioning of the endocrine system by affecting the development of the hypothalamic-pituitary-adrenal axis. It turns out that stress response, measured by glucocorticoid and adrenocorticotropin levels, was significantly increased in germ-free mice. It normalized after gastrointestinal tract colonization with a *Bifidobacterium infantis* strain. Stress also affects the development and diversity of gut microflora. Another link in the communication chain is the immune system. Microbiota is involved in the proper development of the immune system of the gastrointestinal mucosa, with bacterial antigens, such as polysaccharide

A, lipopolysaccharides and teichoic acids affecting its proper functioning. Microbiota also produces neurotransmitters such as gamma-aminobutyric acid, butyric acid, serotonin, dopamine, and short-chain fatty acids, which can directly affect the nervous system. Psychotropic medications, especially second-generation antipsychotics (olanzapine and risperidone), may adversely affect the composition and function of gut microbiota, which may contribute to metabolic disorders and weight gain in patients receiving these agents.

Prebiotics, probiotics, synbiotics, and psychobiotics

The term 'probiotics' refers to living organisms which positively affect the body's functioning when taken in appropriate amounts. Lactic acid bacteria are the most popular probiotics. Probiotics are mainly found in fermented dairy or pickled products. Prebiotics are non-digestible food ingredients whose fermentation in the gastrointestinal tract stimulates the growth or activity of bacteria, or affects both these factors, leading to the development of beneficial gut microbiota. Prebiotics include inulin and fructo-oligosaccharides. The beneficial effects of prebiotics may also involve the suppression of growth of pathogenic bacteria. Moreover, some studies have shown that by modifying the composition of microbiota, prebiotics can reduce inflammation [61]. Synbiotics are ingredients that contain both prebiotics and probiotics. This combination allows to take advantage of the synergistic effect of both these preparations. Psychobiotics are probiotic microorganisms which have a positive effect on human well-being. They often act by producing neurotransmitters, such as gamma-aminobutyric acid, serotonin or other substances affecting the nervous system cells, such as short-chain organic acids (acetic, propionic, butyric acids). Oral substitution of such probiotics as *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 for one month was associated with alleviation of symptoms of anxiety and depressive disorders and with decreased level of stress measured by cortisol levels in animal models [60]. Research to date gives hope that in the near future, the additional use of psychobiotics could improve the efficacy of antidepressants and antipsychotics, and reduce side effects, such as weight gain and metabolic disorders.

General recommendations on daily physical activity

Physical exercises includes aerobic and anaerobic activities. During aerobic exercise, energy for muscles is generated in reactions of combustion in the presence of oxygen. The most effective aerobic training is within 55–85% of maximum heart rate. Maximum heart rate is calculated from the following formula: 220 minus age. Anaerobic training is a process in which energy is generated in anaerobic processes, by exercising in the range of 80–90% of maximum heart rate. In 2007, Haskell et al. [62]

recommended aerobic activity of moderate intensity to be undertaken for a minimum of 30 minutes, 5 days a week, or high-intensity aerobic exercise for a minimum of 20 minutes 3 days a week. Combining different types of activity is allowable.

Given the confirmed beneficial effect of physical activity on cardiovascular and muscle function, on bone strength improvement and mortality reduction, the World Health Organization (WHO) published recommendations on the quantity and quality of physical activity [63]. The WHO recommends moderate-intensity aerobic exercise for at least 150 minutes a week or high-intensity aerobic exercise for at least 75 minutes a week. The activity should be performed in bouts of at least 10 minutes. For additional health benefits, the WHO recommends that aerobic physical activity should be increased to 300 minutes a week or that the total high-intensity physical activity should be performed for 150 minutes a week. In addition, physical activities that strengthen the large groups of muscles should be done 2 or more times a week. Universality is an important feature of these recommendations. They apply to all healthy adults aged 18–64 years, irrespective of age, gender, race or socioeconomic status. The aforementioned recommendations are also true for patients with hypertension or diabetes mellitus, the disorders frequently observed in patients with schizophrenia.

Research to date suggests that without proper psychoeducation and comprehensive support, exercise interventions alone are unlikely to cause weight loss in patients with serious mental illnesses (affective disorders, schizophrenia) [64]. Data from meta-analyses fail to show the effectiveness of aerobic exercise interventions on body weight or BMI in patients with bipolar affective disorder or schizophrenia [65].

Therefore, a promising approach to improving somatic parameters in patients with schizophrenia seems to be supplementing aerobic exercise programs with psychosocial and nutritional interventions. Study results suggest that increased physical activity (pedometer use) combined with psychological interventions in the form of motivational talks with obese patients with schizophrenia lead to weight loss after 12 weeks of the intervention [64]. Another study found a reduction in waist circumference, body weight and BMI, with no reduction in lipid and glucose levels, after a 3-month lifestyle-related intervention, including psychosocial interventions, behavioral therapy and aerobic exercise [64]. A new method of supporting therapy, especially in obese individuals, proposed due to the unsatisfactory effectiveness of aerobic exercise is high-intensity interval training. It is assumed that this form of physical exercise could have a positive effect on metabolic parameters in patients with schizophrenia, but this issue requires further research.

While changing the unhealthy habits that include sedentary lifestyle and low physical activity undoubtedly poses a therapeutic challenge in patients with schizophrenia, no clear and effective interventions are available that could significantly improve their current situation. There is evidence to support the use of physical

activity as an additional form of treatment for persons with schizophrenia spectrum disorders. A comprehensive approach to therapy could positively affect not only the reduction of symptoms and cognitive improvement, but also increase patients' quality of life.

It is generally recommended that patients engage in moderate or high-intensity physical activity for approximately 150 minutes a week [66], which is consistent with the general recommendations for physical activity in healthy adults which assume five 30-minute sessions of endurance training per week, or 20 minutes of high-intensity aerobic training 3 times a week. A walk can be an example of physical activity, which can be of low, moderate or high intensity, depending on the pace [64].

In addition, it is beneficial to include stretching exercises in the elderly, and in the case of persons at risk of falls, balance-improving exercises are also recommended [67]. According to WHO data, only less than a half of people with severe mental illnesses engage in any physical activity [68]. It is therefore necessary to raise the patients' awareness and encourage them to try to change their lifestyles to more active ones.

In contrast to healthy individuals, patients with schizophrenia are characterized by decreased motivation to engage in physical activity, for example, due to sedation, symptoms of schizophrenia, including anxiety and depression, lower level of education, lack of experience in performing physical exercises, social withdrawal or the negative symptoms of schizophrenia [69]. In order to increase the patients' motivation it is therefore important that aerobic physical exercises intended to affect cardiovascular capacity should be supervised by qualified staff [69]. The possibility to participate in classes coordinated by specially trained staff would undoubtedly be an advantage, so that the exercises can be adapted to the patients' physical condition, age, fitness level, and exercise capacity.

The EPA clinical practice recommendations on physical activity as a supportive therapy in the management of mentally ill patients are provided below [66].

1. Physical activity should be used in the management of mild depressive episodes to improve the symptoms and physical fitness.
2. Physical activity should be used as an adjunctive therapy (in addition to drug treatment) in the management of schizophrenia-spectrum disorders to improve the symptoms and to positively affect cognitive dysfunction and the quality of life.
3. Physical activity should be used to improve physical health in persons with serious mental illness.
4. People with serious mental illness should be screened for physical activity habits.

Treatment of physical illnesses

In all the patients with schizophrenia and co-existent modifiable cardiovascular risk factors, intensive measures to reduce these risk factors should be undertaken, ensuring in particular that patients follow the relevant recommendations on lifestyle and pharmacotherapy [70]. In addition, in patients with a high or very high cardiovascular risk (as assessed using the SCORE risk chart), intensive preventive measures should immediately be implemented, their antipsychotic treatment should be revised, and the patients should be referred to an internal medicine specialist, a diabetologist or a cardiologist, as in most cases patients will require initiation of an appropriate pharmacotherapy (e.g., antihypertensive, lipid-lowering or antidiabetic pharmacotherapy).

Smoking

Patients who are current smokers should be provided with smoking cessation advice at every appointment and offered assistance in the form of follow-up appointments and behavioral counseling, including the possibility of nicotine replacement therapy, varenicline or bupropion, which despite the initial concerns have proved effective and safe also in patients with schizophrenia [71]. However, with bupropion, the risk of drug interactions, e.g., with haloperidol or risperidone, should be taken into account [71]. Upon smoking cessation, patients treated with antipsychotic drugs that are metabolized mostly by cytochrome P450 isoenzyme 1A2 (e.g., olanzapine, clozapine) may require a reduction in the dosage of antipsychotics [72].

Overweight and obesity

Normal values of BMI ($< 25 \text{ kg/m}^2$) and waist circumference ($< 80 \text{ cm}$ in women and $< 94 \text{ cm}$ in men) should be aimed for using diet and physical activity [2]. The antipsychotic treatment should be reviewed in overweight or obese patients and in patients with initially normal weight who gained $> 7\%$ of baseline weight in the first 6 weeks after treatment initiation [33]. Overweight or obese patients should regularly be assessed for other cardiovascular risk factors, including the remaining components of metabolic syndrome. Some of the patients, especially those with co-existent additional metabolic risk factors, may be considered for metformin, which has been shown to reduce body weight, BMI and insulin resistance index in patients with schizophrenia receiving the antipsychotic treatment [33, 47]. This use of metformin is not, however, among the therapeutic indications listed in its *Summary of Product Characteristics* (SmPC).

Prediabetes and diabetes mellitus

Impaired fasting glucose and impaired glucose tolerance

Patients with impaired fasting glucose (IFG; defined as a fasting glucose of ≥ 100 mg/dl) should undergo the oral glucose tolerance test for the potential detection of diabetes mellitus or impaired glucose tolerance (IGT). In patients with IFG or IGT, weight reduction is recommended by appropriate dietary management and increased physical activity. Metformin should also be considered to stop the progression to type 2 diabetes mellitus (a therapeutic indication listed in the SmPC) [73]. Modification of the antipsychotic treatment should be considered.

Type 2 diabetes mellitus

The principles of managing patients with schizophrenia and type 2 diabetes mellitus are provided in Table 5.

Table 5. Principles of managing patients with schizophrenia and cardiovascular risk factors (based on [70, 73, 75, 76])

	Type 2 diabetes mellitus	Dyslipidemia		Hypertension
		Hypercholesterolemia	Atherogenic dyslipidemia	
Diagnostic criteria	Fasting glucose ≥ 126 mg/dl (2 measurements) or 2-hour glucose OGTT ≥ 200 mg/dl or Random glucose ≥ 200 mg/dl + symptoms of hyperglycemia	LDL recommended for the given cardiovascular risk group exceeded (see below: Treatment targets) and/or Total cholesterol ≥ 190 mg/dl ²	TG ≥ 150 mg/dl and HDL ≤ 40 mg/dl in men and ≤ 48 mg/dl in women and Presence of small dense LDL ⁴	SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg (a mean of ≥ 2 measurements taken during a single visit; measurements during ≥ 2 visits ³)
Management	Review of antipsychotic treatment			
	Referral to specialist care (internal medicine specialist, diabetologist, cardiologist)			
	Moderate, high or very high cardiovascular risk (see Table 3)	Cardiovascular risk assessment with the SCORE risk charts (Figure 1) and classification into the appropriate risk category (see Table 3)		

table continued on the next page

Management	<p>I. Lifestyle modification: diet (especially: frequent and regular consumption of meals, reduced caloric value of meals, and reduced consumption of monosaccharides) weight reduction increased physical activity</p> <p>II. Pharmacotherapy: metformin metformin + SGLT2 inhibitor¹ or GLP-1 receptor agonist¹ or another oral antidiabetic drug metformin + 2 oral drugs basal insulin + metformin and/or another oral drug combination insulin therapy</p>	<p>I. Lifestyle modification, including in particular: Reduced consumption of saturated and trans fats increased consumption of fibre weight reduction use of functional foods (phytosterols)</p> <p>II. Pharmacotherapy: in patients with high and very high cardiovascular risk – if target LDL values are exceeded in patients with low and moderate risk – pharmacotherapy to be considered if no control can be achieved with diet; mandatory when LDL \geq190 mg/dl statins as first-line treatment</p> <p>If failure to achieve the target LDL level despite treatment with a statin at the maximum tolerated dose – combination treatment (statin + ezetimibe as the first choice)</p>	<p>Hypertriglyceridemia</p> <p>I. Lifestyle modification, including in particular: weight reduction increased physical activity reduced alcohol consumption reduced consumption of carbohydrates, including monosaccharides supplementation of omega-3 fatty acids</p> <p>II. Pharmacotherapy: in patients with high and very high cardiovascular risk with TG >200 mg/dl, statin should be used as the first-line treatment to reduce the cardiovascular risk if elevated TG levels persist in these patients despite statin treatment, addition of omega-3 fatty acids should be considered in severe hypertriglyceridemia – a fibrate + omega-3 fatty acids as the first-line treatment to prevent acute pancreatitis Low HDL level Pharmacotherapy aimed to increase HDL levels is not recommended</p>	<p>I. Lifestyle modification: weight reduction diet (including reduced alcohol and salt consumption) smoking cessation increased physical activity</p> <p>II. Pharmacotherapy: in cases of SBP \geq160 mmHg and/or DBP \geq100 mmHg – pharmacotherapy right from the diagnosis of HT⁵ in grade 1 HT (SBP 140–159 mmHg and/or DBP 90–99 mmHg), without target-organ damage, diabetes mellitus or overt CVD: pharmacotherapy after 3-6 months of modified lifestyle (if SBP/DBP persists at \geq140/90 mmHg) and when HT is confirmed by ABPM or home measurements in most patients, first-line treatment should include an ACE-I/ARB in combination with a calcium channel blocker</p>
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table continued on the next page

Treatment targets	Overall goal: HbA _{1c} ≤7%	Target LDL levels depending on cardiovascular risk category: very high risk: <55 mg/dl ³ high risk: <70 mg/dl ³ moderate risk: <100 mg/dl low risk: <116 mg/dl	The primary goal of treatment is to achieve the target LDL level	<140/90 mmHg in all patients ≤130/80 mmHg in those patients who tolerate their antihypertensive treatment well
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¹ recommended especially in cases of co-existing CVD or chronic kidney disease; may also be preferable in the remaining patients with schizophrenia, diabetes mellitus and overweight/obesity, amongst other things, due to their beneficial effect on body weight

² LDL-cholesterol level is recommended as the main lipid parameter for the purposes of diagnosis and treatment; total cholesterol level is used for assessments with the SCORE risk chart

³and a reduction by ≥ 50% of the baseline value (in patients not receiving any LDL-lowering medication)

⁴ not assessed in the routine lipid profile

⁵ in grade 3 HT (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg) the diagnosis of HT and pharmacotherapy initiation already during the first visit

OGTT – oral glucose tolerance test; SGLT2 – sodium-glucose co-transporter 2; GLP-1 – glucagon-like peptide-1; HbA_{1c} – glycosylated hemoglobin; LDL – low-density lipoprotein; TG – triglycerides; HDL – high-density lipoprotein; HT – hypertension; SBP – systolic blood pressure; DBP – diastolic blood pressure; CVD – cardiovascular disease; ABPM – ambulatory blood pressure monitoring; ACE-I – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker

Dyslipidemia

Obesity is mainly associated with atherogenic dyslipidemia, a component of metabolic syndrome. Antipsychotics can increase the risk of atherogenic dyslipidemia and of hypercholesterolemia alike. Both these forms of dyslipidemia may co-exist (mixed dyslipidemia). The primary goal of treatment is to reduce the levels of low-density lipoprotein (LDL) cholesterol, which is the strongest lipid risk factor of CVD. The only exception are patients with severe hypertriglyceridemia due to the increased risk of acute pancreatitis with triglyceride levels exceeding 440 mg/dl, especially 880 mg/dl, as in these patients the primary goal is to reduce triglyceride levels. The detailed principles of managing patients with dyslipidemia are provided in Table 5.

Hypertension

The principles of managing patients with hypertension are provided in Table 5.

Recapitulation

The high prevalence of metabolic disorders and cardiovascular disease in patients with schizophrenia necessitates metabolic risk assessment and the monitoring of metabolic parameters in each patient. The following measures should be taken to reduce the risk of these disorders:

- antipsychotics with a low potential for causing metabolic disorders should be chosen and used;
- if an antipsychotic that increases the risk of metabolic disorders has to be used
 - the lowest effective dose should be prescribed (if metabolic disorders do develop, modification of pharmacotherapy is required by reducing the dose of the drug or augmentation with another antipsychotic that has a low risk of causing metabolic disorders. If this combination treatment proves effective, a complete discontinuation of the agent that increases the risk of metabolic disorders should be considered with continuation of treatment with the agent of low potential for metabolic abnormalities used alone);
- intensive efforts should be undertaken to reduce smoking, alcohol abuse and the use of psychoactive substances, and to correct lifestyle habits in terms of regular physical activity and healthy eating habits.

Patients at high metabolic and cardiovascular risk should be referred to an internal medicine specialist, a diabetologist or a cardiologist to have preventive measures implemented, and if a metabolic disorder or cardiovascular disease is already present, the patients should be referred to one of these specialists for appropriate pharmacotherapy.

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