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Diagnosis and management of hyperglycaemia in patients treated with antipsychotic drugs

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Abstract

Research results indicate the presence of an association between mental disorders, certain antipsychotics, and the risk of developing prediabetes (preDM) and specific type diabetes mellitus (DM). However, there are no precise recommendations for their diagnosis and treatment. The obtained data suggest the necessity to perform diagnostics of carbohydrate disorders at the onset of the first symptoms of psychosis, even before the implementation of antipsychotic drugs, and the oral glucose tolerance test (OGTT) seems to be the optimal tool. There is a lot of controversy regarding the timing of control tests addressing the development of dysglycaemia during the use of antipsychotic drugs. We suggest that it should be carried out during the first 4-8 weeks, and in the absence of disorders it should be repeated once a year or with a change in antipsychotic treatment. The diagnostic regimen should then include the need for OGTT supported by routine determination of the percentage of glycated haemoglobin. If dysglycaemia is diagnosed, the therapeutic management should include non-pharmacological management and hypoglycaemic agents. These recommendations should be individually tailored to each patient and take into account the presence of obesity, which is often found in this group of patients. Weight reduction can be achieved with a properly balanced diet, physical effort, and in justified situations also with drugs effectively reducing body weight. For this reason, drugs are recommended that, if preDM and DM are diagnosed, simultaneously lower glucose levels and reduce body weight. So far, effectiveness in this area has been demonstrated for 2 incretinomimetics: exenatide and liraglutide. Due to the mechanism of preDM/DM development in patients using antipsychotics, the usefulness of other hypoglycaemic drugs with insulin-sensitizing potential — metformin and pioglitazone — has also been suggested. To date, there has been no research on the benefits of other hypoglycaemic drugs in this group of patients. **(Endokrynol Pol 2022; 73 (5): 872–884)**

Key words: *diabetes; prediabetes; antipsychotic drugs; diagnostic; treatment*

Introduction

The studies published to date indicate the presence of an association between the use of certain antipsychotic drugs and the risk of development of carbohydrate metabolism disorders. These disorders include both prediabetes (preDM), including impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes (DM) classified as specific types of diabetes due to other causes [1–3]. In 2021, it is estimated that 537 million people have DM, and this number is projected to reach 643 million by 2030, and 783 million by 2045. In addition, 541 million people are estimated to have impaired glucose tolerance in 2021 [4]. The incidence of the disorder varies across places and migrant groups, as do symptoms, course, and treatment response across individuals. The evidence comes from a wide variety of studies using different methods, each with strengths and weaknesses that may contribute to some of the patterns observed.

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 reported that mental disorders accounted for 654.8 million estimated cases in 1990 and 970.1 million cases in 2019 (an increase of 48.1%) [5]. A review and meta-analysis perform by Jongsma et al. showed that the prevalence of all psychotic disorders was 26.6 per 100,000 person-years [6]. It is estimated that DM can affect 8.7% with major depressive disorders, 6.2% with bipolar disorders, and 12% of patients with severe mental illnesses (schizophrenia, depression, bipolar and psychotic disorders). A high (19%) incidence of "prediabetic conditions" in patients with various types of psychoses has also been observed [7]. A recent study by Liu et al. indicates that patients with bipolar disorders have nearly 1.6 times greater risk of developing DM [8]. These data may be underestimate to the real risk of antipsychotic drugs. This is because they often do not take into account the presence of undiagnosed type 2 diabetes before using antipsychotic drugs.

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Drugs with relatively high pro-diabetic potential include chlorpromazine, clozapine, and olanzapine. A slightly lower risk of developing these disorders has been observed in patients using quetiapine and risperidone, and the lowest during therapy with haloperidol, perphenazine, ziprasidone, aripiprazole, paliperidone, and lurasidone [1]. When analysing the above data, it should be considered that most studies assessing the diabetogenic potential of antipsychotic drugs do not take into account their daily dose. For example, Højlund et al. revealed that low-dose (25 250 mg) quetiapine was not associated with higher risk of DM [9]. The use of antipsychotics such as aripiprazole, risperidone, haloperidol, and olanzapine has also been shown to be associated with the risk of IGT, and in the case of clozapine, haloperidol, and olanzapine — also of IFG development [10–12]. However, there are no data on the differences between the individual antipsychotics with respect to the risk of developing preDM. Based on assessment of the insulin sensitivity index (SI), homeostatic model assessment for insulin resistance (HOMA-IR), and glucose effectiveness (SG), a similarly strong pro-prediabetic effect of clozapine and olanzapine and a lower effect of risperidone has been suggested [13]. In Table 1 we present a diabetogenic profile of antipsychotic drugs depending of weight gain [1, 14].

The diabetogenic properties of antipsychotic drugs are very diverse and associated with various mechanisms of action, the main one being the development of insulin resistance (IR). This mechanism is directly related to inhibition of insulin-signalling pathways at different levels in the muscles, hepatocytes, and adipose tissue (olanzapine and clozapine), or indirectly connected with weight gain and obesity (mechanism related to antagonistic effect on the serotonin 5-HT2C, histamine H1, and dopamine D2 receptors and changes in the gut microbiome, locomotor activities and reduction of thermogenesis of brown adipose tissue, for exaple olanzapine, clozapine and risperidone) [6]. These mechanisms are known as the main factors in the development of type 2 diabetes (T2DM), which poses a risk of misdiagnosing a particular type of diabetes. It should be emphasized, however, that the onset of carbohydrate metabolism disorders, regardless of the type of diabetes, is associated with dangerous consequences for health, independent of the severity of hyperglycaemia. Some of them, such as ketoacidosis, appear suddenly in patients using antipsychotics and pose a direct threat to the patient's life [15], while others manifest themselves after a long time in the form of micro- and macrovascular complications [16, 17]. Other mechanisms of development of hyperglycaemia include an antagonistic effect on M3 muscarinic receptors (olanzapine and clozapine), a direct apoptotic effect on pancreatic β-cells due to the mitochondrial route (olanzapine and clozapine), or an indirect effect related to the impact on the dopaminergic, histaminergic, serotonergic, adrenergic, and muscarinic receptors and the consequent inhibition of insulin secretion, increase in glucagon secretion (lithium), genetic abnormalities (polymorphism of cytochrome P450 gene CYP1A2 responsible for the metabolism of clozapine, polymorphisms apoE for risperidone), and increase in leptin levels (risperidone, the highest increase in leptin occurs during olanzapine treatment, lower after clozapine, and the lowest after quetiapine and aripiprazole) [2]. There is still a lack of precise guidelines for the diagnosis and treatment of carbohydrate metabolism disorders in patients with various types of psychoses and using antipsychotic drugs. For this reason, it seems justifiable to establish such an algorithm, and the purpose of this paper is to point out the important issues and problems associated with the development of such an algorithm.

Table 1. ***Diabetogenic potential of anti-psychotic drugs depending on weight gain***

Antipsychotic	Risk of diabetes	Weight gain
Clozapine	+++	+++
Chlorpromazine	+++	+++
Olanzapine	+++	+++
Risperidone	++	++
Quetiapine	++	++
Amisulpride	++	++
Asenapine	++	+
Lurasidone	+/++	+
Ziprasidone	++	+
Aripiprazole	+/++	+
Haloperidol	+	++
Perphenazine	+	+
Paliperidone	+	++

Values are reported as high (+++), moderate (++), low/moderate (+/++), low (+), very low (+)

Diagnostics of carbohydrate metabolism disorders

The current Diabetes Poland guidelines do not include the need to perform non-standard diagnostics drug-induced DM, including those related to antipsychotic drugs. They accept fasting blood glucose (FG), blood glucose level at 120 minutes of an oral glucose load test (OGTT), and glycosylated haemoglobin (HbA_{1c}) as equivalent tools for diagnostic purposes. They also pay particular attention to OGTT to identify a higher

number of individuals with DM and preDM [3]. It should be emphasized that for many years European guidelines (EASD — European Association for the Study of Diabetes) have clearly indicated antipsychotic drugs as one of the main risk factors for this disease, and they indicate the need to look for disturbances in the carbohydrate metabolism in this group of patients [18]. They also do not include the standards of diagnostic procedures in this group of patients. Standards for dysglycaemia tests in patients using antipsychotic drugs should take into account both the appropriate moment of their performance and the selection of a specific diagnostic tool. When creating such guidelines, one should first remember about the individual approach to patients with various degrees of mental disorders, often preventing the implementation of appropriate diagnostics and pharmacotherapy [19].

The available publications suggest the need to perform tests for carbohydrate metabolism disorders at the time of the first symptoms of psychosis, before the institution of antipsychotic medication, and the optimal tool at this time should be OGTT. These suggestions are supported by the results of 2 meta-analyses. In the first of them conducted by Perry et al., subjects with the first episode of these disorders were demonstrated to have no significant differences in FG levels compared to healthy people. In contrast, these patients had significantly higher glucose values measured after 2 hours in OGTT and a higher IR value measured by HOMA-IR [20]. In the second meta-analysis, Yang et al. showed that patients at the time of the first episode of schizophrenia, compared to healthy patients, had both higher FG and two-hour values in OGTT, higher fasting insulin activity, and HOMA-IR. It is noteworthy that there were no significant differences in the proportion of HbA_{1c} [21].

It has also been suggested that tests for DM should be performed before the institution of antipsychotics in populations of patients more likely to develop dysglycaemia. Low high-density lipoprotein cholesterol (HDL-C) values (below 28 mg/dL), as well as age ≥ 58 years in the situation when high-density lipoprotein cholesterol (HDL-C) concentration is ≥ 28 mg/dL and FG ≥ 92 mg/dL are also indicated as the main predictors of DM [22].

There is some controversy concerning the need to perform control tests for carbohydrate metabolism disorders in patients who receive antipsychotic medications, especially those with hyperglycaemic potential. Epidemiological studies indicate the necessity to perform such tests in specific groups of patients. The risk factors for dysglycaemia include aging, rapid (within 8 weeks) increase in triglycerides (TG) (for DM ≥ 145 mg/dL and for prediabetes ≥ 59 mg/dL), and weight gain (≥ 6.1 kg over 2 weeks in people with TG increase < 145 mg/dL). However, it has not been confirmed that a family history of DM plays a significant role in the estimation of such a risk in patients using antipsychotics, as is the case in patients not yet treated [22, 23]. Additionally, the problem of the risk of DM development during treatment with typical and atypical antipsychotic drugs has been demonstrated to affects not only adults, but also children and adolescents, mainly females. It is associated with the need to perform screening tests also in that group of patients [24]. It should be emphasized that a recent study conducted by Wang et al. [25] does not support the suggested association between the continuation of antipsychotics in pregnancy and the risk of developing gestational diabetes mellitus (GDM) [26].

The selection of a diagnostic tool should also take into account the potency of the hyperglycaemic antipsychotic drug. The data are also ambiguous in this regard. This is clearly indicated by the meta-analysis and regression carried out by Carnovaled et al. The rank order of the drugs in terms of changes in glucose mean levels (largest reduction to largest increase) was as follows: aripiprazole, iloperidone, ziprasidone, quetiapine, lurasidone, risperidone, brexpiprazole, clozapine, paliperidone, sertindole, olanzapine, haloperidol, and cariprazine. The mixed comparisons showed a smaller increase of glucose mean concentrations after aripiprazole as compared with risperidone, paliperidone, haloperidol, cariprazine, and no treatment, and a greater increase after olanzapine as compared with aripiprazole, ziprasidone, quetiapine, and placebo/no treatment. The drug ranking from the largest reduction to largest increase of HbA_{1c} was found to be haloperidol, ziprasidone, risperidone, placebo/no treatment, olanzapine, quetiapine, and lurasidone. The mixed comparisons showed a smaller increase of HbA_{1c} mean levels after haloperidol or ziprasidone as compared with risperidone, olanzapine, quetiapine, lurasidone, and placebo/no treatment [27]. Table 2 presents the impact of antipsychotic drugs on the markers (FG, HBA_{1c}, OGTT) of glucose homeostasis [7, 27–29]. Another problem related to diagnostics in patients with mental disorders concerns the determination of the optimal moment to perform control tests for the development of carbohydrate metabolism disorders during treatment with antipsychotic drugs. When determining that time, it should be borne in mind that the use of some of these drugs increases the risk of an acute complication of hyperglycaemia, which is ketoacidosis. According to clinical data, this complication may occur predominantly with olanzapine, used both as monotherapy and in combination with other antipsychotics. The use of clozapine, risperidone, quetiapine, and aripiprazole is also associated with

Table 2. *The impact of antipsychotic drugs on markers of glucose homeostasis*

Antipsychotic	FG	2-h PG	HbA_{1c}
Olanzapine	↓/↑ (mostly ↑)	↑	↑
Haloperidol	↓/↑ (mostly ↑)	⇔/↑	↓
Risperidone	↓/↑	↑	↓/↑ (mostly ↓)
Ziprasidone	↓/↑ (mostly ↓)	⇔	↓
Aripiprazole	↓/↑ (mostly ↓)	↑	N/A
Quetiapine	↓/↑ (mostly ↑)	↑	↓/↑ (mostly ↑)
Lurasidone	↓/↑ (mostly ↓)	N/A	↓/↑ (mostly ↑)
Clozapine	↑	⇔	N/A
Zotepine	↑	N/A	N/A
Paliperidone	↑	N/A	N/A
Bexpiprazol	↑	N/A	N/A
Carpirazine	↑	N/A	N/A
Iloperidone	↓/↑	N/A	↓
Sertindole	↑	N/A	N/A
Asenapine	↓	N/A	N/A
Amisulpride	↓	N/A	N/A
Chlorpromazine	N/A	⇔	N/A

FG — fasting glycaemia; HbA_{1c} — glycated haemoglobin; 2-h PG — glycaemia determined after 2 hours in the oral glucose tolerance test (OGTT). Values are reported as increase (↑), decrease (↓), neutral (⇔), N/A — data not available

the development of that complication. However, no such situations have been reported when using ziprasidone, paliperidone, haloperidol, or amisulpride alone. Prodromes (such as polydipsia, polyuria, and weakness) were reported only in 30 patients, and lasted from one day to 4 weeks. It should be emphasized that the main risk factors for the development of this complication were polypharmacy, average age younger than in the general population of patients with T2DM, gender imbalance with predominance of males, absence of autoimmune markers of DM, as well as the absence of significant weight gain [15].

The research conducted so far, assessing the risk of carbohydrate metabolism disorders developing during antipsychotic therapy, includes very different patient follow-up times, usually ranging from 48 weeks to 20 years [30, 31]. In the study by Lee et al., the mean time from the diagnosis of psychosis to the diagnosis of DM was demonstrated to approximate 2 years (683 ± 482 days for the non-treated group and 689 ± 485 days for the antipsychotic treatment group) [32].

In the study by Chun-Hsin et al., assessing the effect of quetiapine on carbohydrate homeostasis as measured by an intravenous glucose tolerance test (IGTT) over 2, 4, and 8 weeks, higher insulin and HOMA-IR values were found at week 8 of the therapy only. It should be emphasized that insulin secretion was found to be significantly decreased at week 2, returning to baseline at week 4, and increasing significantly at week 8 in olanzapine-treated schizophrenic subjects [33]. In turn, in the study by Chiu et al., after 14 days of olanzapine or risperidone administration in patients with schizophrenia, there were no statistically significant changes in FG concentration, glucose disappearance rate, or in insulin sensitivity assessed by homeostasis model assessment, the insulin/glucose ratio, and quantitative insulin sensitivity check index. In response to a glucose load, the insulin secretion decreased significantly in the olanzapine group [34]. In contrast, the results of the study by Smith et al., comparing five-month olanzapine and risperidone treatment indicate the emergence of significantly adverse changes in glucose and insulin metabolism after one month of olanzapine administration [35].

Data obtained from studies conducted by American researchers indicate that a screening test for DM is ordered within a year in approximately 75% of patients using antipsychotics, but it is actually performed in only 55% of them. Within 2 years of observation, these numbers increase slightly (to 87 and 73%, respectively). The group of patients in whom such diagnostics is performed less frequently includes young adults (18–29 years of age), black, smoking, and suffering from affective disorders (depression, bipolar disorders). The group of people who are more likely to be diagnosed for DM include

Asians, patients with schizophrenia, with excess body weight, with a history of preDM, and people who use mental health and primary care health services more often. Most frequently, the diagnostics is performed by primary care physicians (54.3%) and psychiatrists (7.6%) [36].

Holt et al. proposed that the diagnosis for DM should be repeated within 3–4 months, to detect patients who quickly develop carbohydrate metabolism disorders. They also postulated that these tests should be repeated every year [1]. In view of the significant risk of developing carbohydrate metabolism disorders, including their acute complications, the question arises whether such diagnostics should be carried out earlier. The authors of this paper suggest performing diagnostic tests in the first 4-8 weeks. In the absence of disorders, such diagnostics should be repeated annually or in the case of any change in the antipsychotic treatment.

According to the recommendations of international societies, the proposed diagnostic tools for carbohydrate metabolism disorders include determination of the FG concentration twice, OGTT, and determination of the percentage of HbA_{1c} [8]. Studies assessing the risk of developing prediabetes and DM in people using antipsychotics take into account many markers of carbohydrate metabolism disorders (including C peptide concentration, fasting insulin level) and that level and after 2 hours in OGTT, HOMA-IR, and other IR markers, showing large discrepancies between the evaluated diagnostic tests. Therefore, the question arises whether, in the group of patients with psychotic disorders, including those using antipsychotics, the standard principles of diagnosis of carbohydrate disorders should be used, as is the case in other types of DM.

Studies assessing the risk of dysglycaemia in this group of patients indicate that OGTT, during which various degrees of carbohydrate metabolism disorders can be diagnosed, should be the preferred diagnostic tool [37]. The above suggestion is supported by studies demonstrating significant differences in FG and glucose after 2 hours in OGTT between patients using various types of antipsychotics, such as olanzapine, risperidone, or haloperidol [38]. In turn, in the meta-analysis carried out by Rotella et al., olanzapine was associated with higher FG than haloperidol and ziprasidone used for more than 52 weeks, whereas patients treated with risperidone showed significantly higher FG than those on haloperidol and ziprasidone. In addition, variation of FG from baseline was significantly greater for amisulpride, olanzapine, and quetiapine than for ziprasidone and for haloperidol as compared to risperidone. It should be emphasized that, according to the standard criteria for DM diagnosis, quetiapine was associated with a risk of DM significantly greater than placebo and smaller than olanzapine [39]. However, it should be stressed that there are considerable doubts concerning the use of psychiatric drugs before OGTT related to their pharmacokinetic properties. For example, it was found that taking a tablet containing 10 mg of olanzapine significantly decreased glucose effectiveness and raised FG over 4.25 hours as compared to placebo [40]. Such observations reduce slightly the sensitivity and diagnostic specificity of OGTT.

Therefore, the authors of this paper suggest the need to employ an additional diagnostic test that would reinforce the strength of OGTT. The observations of Romain et al. indicate the equivalence of HbA_{1c}, FG, and OGTT in the diagnostics of DM and only FG and HbA_{1c} in the diagnostics of prediabetes. They also found that the HbA_{1c} value seems to identify different individuals, or individuals with different profiles compared to FG and 2-h OGTT, and that obesity could lower the consistency between HbA_{1c} and 2-h OGTT in the detection of glucose abnormalities. In view of the above observations, it has been suggested that the FG test should be used along with HbA_{1c} for the first screening test when OGTT is not possible. Because of the complexity of administration, the OGTT could be used as a 2nd step or for more compliant individuals [41]. The above observations apply to a study conducted by Steylen et al., who demonstrated that the majority of patients using antipsychotics were diagnosed with DM or prediabetes using the FG criterion, with HbA_{1c} determination significantly contributing to an increase in the number of patients with a prediabetic condition [42].

Some studies indicate the usefulness of insulin and HOMA-IR concentration in the diagnosis of carbohydrate metabolism disorders, due to the strong correlation with the OGTT results. Research by De Hert et al. confirmed that people using antipsychotics for IGT often have normal FG levels and elevated insulin levels [43]. A three-year follow-up of patients treated with haloperidol, olanzapine, and risperidone showed no significant differences between either the duration of therapy or the increase in glucose and HOMA-IR, with the highest upward trend noted within the first year after initiation of the therapy [44]. Taking into account the research conducted so far, the authors of this paper point to the need to perform primarily OGTT as the main diagnostic tool supported by routine determination of the HbA_{1c} percentage. They do not recommend increasing the costs of diagnostic methods by determining the concentration of insulin, C peptide, and other advanced methods of insulin sensitivity determination.

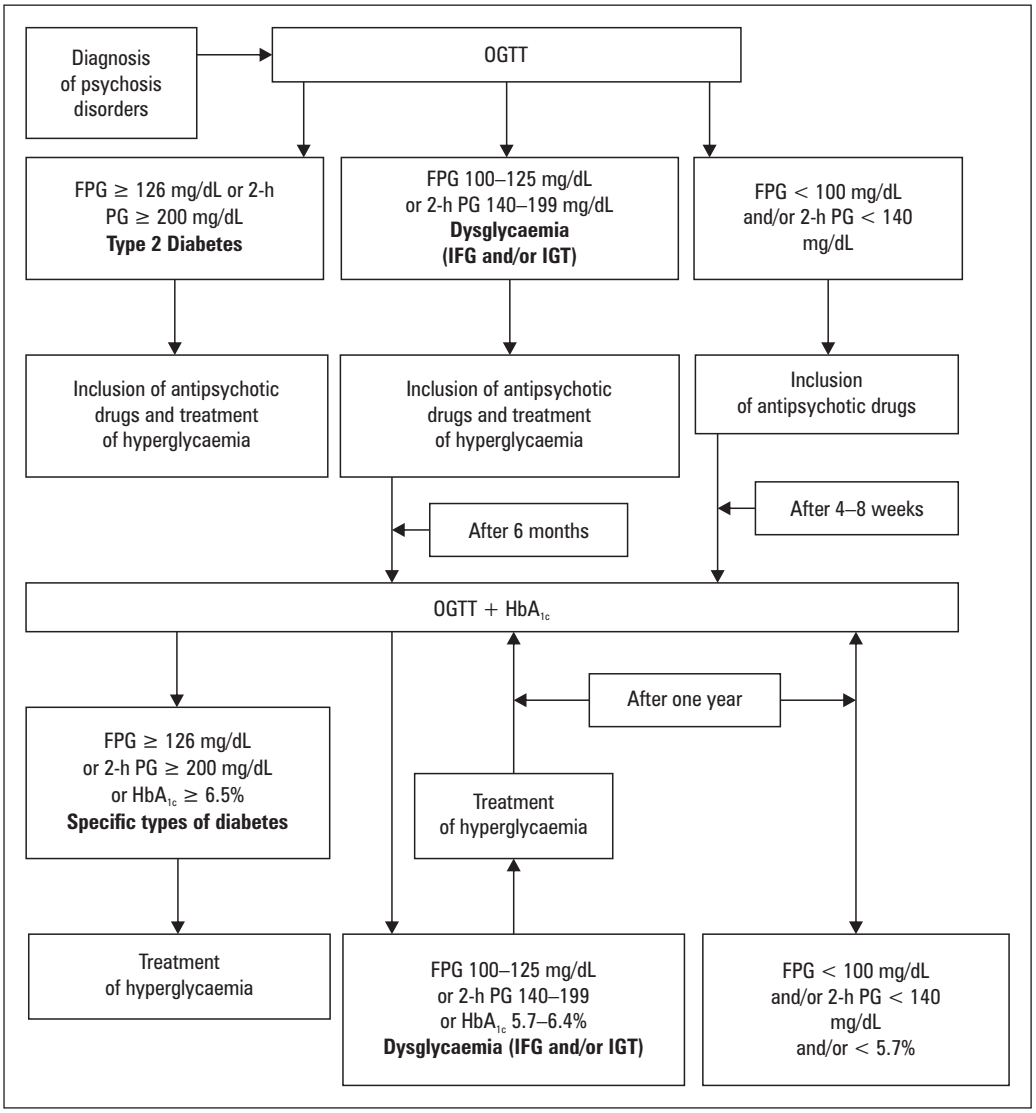

Figure 1. *Diagnostic regimen for diabetes and prediabetes in patients using antipsychotics. FPG — fasting plasma glucose; IFG — impaired fasting glucose; IGT — impaired glucose tolerance; HbA_{1c} — glycated haemoglobin; OGTT — oral glucose tolerance test; 2-h PG — 2-h plasma glucose value during a 75-g oral glucose tolerance test*

In Figure 1 we present our proposition of a diagnostic regimen for DM and preDM in patients using antipsychotics.

Optimal hypoglycaemic therapy

Non-pharmacological therapy

According to global recommendations, the basis of preDM and DM therapy should be an appropriately selected diet and physical effort for the patient. Such management is also recommended for patients with dysglycaemia associated with antipsychotic treatment. It should be remembered that the selection of the right diet should be individual for each patient and take into account many factors, including body weight, BMI, total cholesterol (TCH), LDL-C, HDL-C, TG, glucose concentrations, and the administered antipsychotic medication. In a recently published study by Pillinger et al., it was observed that olanzapine and clozapine exhibited the worst and aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone the most benign metabolic profiles [45]. In view of such frequent occurrence of excess body weight in patients with serious mental illnesses, it is suggested in the first place to use therapy aimed at reduction of body weight, regardless of the coexistence of carbohydrate metabolism disorders [46]. Such a goal can be achieved with a proper qualitatively and quantitatively balanced diet, physical exercise, and in justified situations also medications with a proven reducing effect on body weight. In the STRIDE study conducted on a group of patients treated with olanzapine, without carbohydrate metabolism disorders, it was demonstrated that therapy consisting of reduction of the calorie content

of meals, the DASH diet (Dietary Approaches to Stop Hypertension), and regular physical exercise used for 12 months is associated with a significant reduction in body weight and BMI, with this effect concerning the first 6 months of the therapy. In the further period of 6–12 months, such management was not observed to bring significant results. No significant effect on fasting insulin, Framingham Diabetes Risk Score, or HOMA-IR was observed throughout the treatment period. It is noteworthy that there was a significant reduction in FG, and this effect was also maintained throughout the study period [47]. It has also been suggested that various types of exercise programs are useful to reduce the risk of developing DM in patients using olanzapine [48]. However, the usefulness of educational programs such as STEPWISE, a theory-based group education in the field of health-promoting lifestyle, which at 12 months demonstrated neither clinical nor financial benefits for patients with schizophrenia [49], is questioned. Despite the presence of controversy related to the difference in the risk of developing carbohydrate metabolism disorders between patients using typical and atypical antipsychotics [50], it should be borne in mind that sertinodl, zotepine, clozapine, and olanzapine are associated with a high risk of weight gain, while amisulpiride, asenapine, quetiapine, risperidone, paliperidone, and iloperidone — with moderate, and aripirazole, brexiprazole, cariprazole, and ziprasidone — with low risk. Therefore, taking into account also the aforementioned diabetogenic potential, a switch to another antipsychotic medication is suggested, if possible [51].

Incretinomimetics

In the absence of effects of non-pharmacological therapy, it seems justified to include drugs with proven effectiveness in body weight reduction, which in the case of diagnosis of preDM and DM would simultaneously reduce the systemic levels of glucose. Such drugs include, first of all, incretinomimetics.

Exenatide administered once a week for 3 months has been demonstrated in patients treated with first-generation antipsychotics (perphenazine, zuclopenthixol, and chlorprothixene) and second-generation antipsychotics (clozapine, olanzapine, aripiprazole, risperidone, paliperidone, quetiapine, ziprasidone, amisulpride, and sertindole) to be associated not only with a significant reduction in body weight and BMI, but also with a decrease in HbA1c and FG concentration. It should be noted, however, that a statistically similar reduction was achieved in the placebo group. However, there were no new cases of DM while taking this drug, while one patient in the placebo group fell ill [52]. In turn, the CODEX study confirmed a similar, 24-week effect of once-weekly extended-release exenatide in a group of patients treated with clozapine on significant reduction of body weight, FG concentration, and HbA_{1c} percentage. It should be emphasized, however, that 12-month follow-up after completion of the therapy unfortunately showed a significant increase in body weight, BMI, and HbA_{1c} percentage. However, no significant changes in the mean FG values were noted [53, 54].

When liraglutide was used for 16 weeks in overweight and obese patients with schizophrenia, schizotypal disorders, or paranoid psychosis, treated for at least 6 months with clozapine or olanzapine, a significant improvement in anthropometric parameters (body weight, waist circumference, and BMI) and OGTT results was observed. It should be emphasized that as many as 30 out of 52 patients receiving the drug changed their status from preDM to normoglycaemia, which was associated not only with a significant reduction in HbA_{1c} and FG concentration, but also with an increase in C-peptide secretion, reduction of glucagon, TCH, and LDL-C concentrations, and increased beta cell function (calculated by HOMA-2). However, there was no significant effect of the therapy on the liver function, blood pressure values, quality of life, daily functioning, severity of psychiatric disorders, alcohol consumption, and the presence of side effects. Within a year of the end of this therapy, it was found that 12 patients taking liraglutide and 5 from the placebo group had developed DM. Of these, 4 and 3 patients, respectively, had been diagnosed before follow-up and had already initiated treatment with metformin. Compared to placebo, the liraglutide group developed poorer glycometabolic control — with increased HbA_{1c}, FG as well as a decrease in beta cell function. Comparing the entire period from the implementation of therapy to the end of the one-year follow-up period, the liraglutide group had a significant increase in body weight, BMI, and waist circumference. No difference in the number of patients developing DM was found between the 2 groups; 12 patients in the liraglutide group compared to 6 patients in the placebo group developed DM. No difference was found between the liraglutide group and the placebo group in FG, HbA_{1c}, C-peptide, HOMA -2 measurements, and waist circumference. Changes in the dose of clozapine and olanzapine were not statistically different between the 2 groups, nor was the switch from one type of antipsychotic medication to another [55, 56].

Sitagliptin

Although dipeptidyl peptidase-4 (DPP4) inhibitors are not associated with significant weight loss, they can also be used in the treatment of antipsychotic diabetes.

A study by Sarani et al. showed that 12 weeks of treatment with this drug in patients taking olanzapine for at least one month was associated with a significant reduction in HbA_{1c}. It should be emphasized that this observation concerned patients with normal BMI value and seven-year disease duration [57]. Another study revealed that sitagliptin treatment did not show any antipsychotic-like effect in an animal model study, unlike liraglutide [58].

Metformin

Despite the continuing controversy over the beneficial effects of metformin (MET) on body weight reduction, including patients with preDM and DM, a meta-analysis of randomized controlled trials (RCT) conducted in different age groups among patients using antipsychotics proved its significant beneficial effects on body weight and BMI [59]. A meta-analysis by Taylor et al. indicates comparable benefits from the non-pharmacological and pharmacological management in the group of patients with severe mental illnesses, with both of these therapies significantly affecting FG levels but not HbA_{1c}. It was further noted that the inclusion of MET or a change of antidepressant was associated with a reduction in HbA_{1c} [60]. MET is now the basis of T2DM therapy. A meta-analysis conducted by American researchers, including 62 studies involving patients using MET and antipsychotics, found that this drug, although it significantly reduced body weight, BMI, waist circumference, and HOMA-IR, did not reduce the risk of developing DM [61]. The results of the Diabetes Prevention Program and Diabetes Prevention Programs Outcomes Study, which showed that continuous use of antidepressants was associated with a significant risk of developing DM in a group of patients using placebo or intensive lifestyle modification, are also worth remembering. However, such a risk was not found in patients using MET 850 mg administered twice daily. It should be emphasized that this study involved patients at high risk of developing DM (age ≥ 25 years, BMI of ≥ 24 kg/m^2 or ≥ 22 kg/m^2 in Asian Americans, with FG of 95–125 mg/dL or ≤ 125 mg/dL in American Indians, 140–199 mg/dL 2 h in OGTT), including 10.3% of patients diagnosed with at least mild depression and 5.5% of patients who used antidepressants. Among the patients diagnosed with DM within a year, there was a significant improvement in the Beck Depression Inventory scale in the group of patients using MET or intensive lifestyle modification. However, elevated depressive symptoms or the use of antidepressants have not been found to be associated with subsequent significantly increased frequency of DM diagnoses [62, 63]. The benefits of MET 1500 mg/day for 4 months in patients taking antipsychotics and with early comorbid preDM and DM were confirmed in the study by Agarval et al. MET was shown to be associated with a significant decrease over time in the HOMA-IR and FG compared to people not using hypoglycaemic drugs. However, no differences between treatment groups in HbA_{1c}, the Matsuda index, and ISSI-2 (the Insulin Secretion Sensitivity Index-2) were observed. There was no difference in glucose tolerance (glucose excursion during 2-h OGTT) between groups [64]. The usefulness of MET in patients with schizophrenia treated with clozapine in preventing the development of DM and its beneficial effects on other components of metabolic syndrome (body weight, waist and hip circumference, triglycerides, HDL cholesterol and total cholesterol, and blood pressure), IR, and quality of life are currently being evaluated in the ongoing CoMET study [65].

Pioglitazone

Due to the mechanism of development of preDM and DM in patients using antipsychotics, the usefulness of other hypoglycaemic drugs with insulin-sensitizing potential has also been suggested. These drugs include PPAR-γ nuclear receptor antagonists, such as pioglitazone, available on the market. In the study by Smith et al. it was demonstrated that the use of this drug in 54 patients with schizophrenia during treatment with antipsychotics with IGT, TG concentration ≥ 120 mg/dL, and/or low HDL-C values for a period of 3 months at a dose of 30–45 mg was associated with a significant reduction of insulin, 2h glucose in OGTT and HOMA-IR tests. However, population-specific differences have been noted (USA *vs*. no effect on metabolic parameters among the Chinese population). It was further noted that the drug can also have a positive effect on the positive and negative syndrome scale (PANSS) depression factor score. It should be emphasized that at the end of the study, 52% of patients treated with pioglitazone, compared to 15% of those receiving placebo, had normal FG levels, and the use of pioglitazone did not increase their body weight or cause significant side effects [66].

Other hypoglycaemic agents

To date, there has been no research on the benefits of other hypoglycaemic drugs, such as SGLT2 inhibitors, sulfonylureas, meglitinides, or α glucosidase inhibitors, in the group of patients using antipsychotic drugs [51].

Clinical trials involving hyperglycaemic therapy in patients using antipsychotics are presented in Table 3.

Table 3. *Clinical trials involving hyperglycaemic therapy in patients using antipsychotics*

Study (trial name)	Type of study	Baseline sample	Hypoglycaemic agent (day dose in mg)	Antipsychotic [day dose in mg, mean (± SD)]	Durations	Change in glucose homeostasis after hypoglycaemic agent
Agarwal et al. [64]	RCT	30 overweight patients within 5 years of a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder, or under the age of 40 (regardless of illness duration), with comorbid preDM or DM (age 17–45)	MET 500, after 7 days 1000, after 14 days 1500	Quetiapine oral [341.88 (139.54)], aripiprazole [313.63 (88.69)], perphenazine [175.88 (NA)], risperidone [221.65 (95.47)], zuclopenthixol [600], clozapine [270.23 (99.23)], ziprasidone [159.68], paliperidone injectable [156], flupentixol oral [33.33], flupentixol injectable [200], olanzapine [219.54 (54.23)]	16 weeks	SR — HOMA-IR, FPG; NSR — Matsuda index, HbA_{1c}, ISSI-2
Wu et al. [72]	RCT	128 patients with a first psychotic episode of schizophrenia diagnosed (age 18–45)	MET 750 monotherapy or with lifestyle intervention	Clozapine: MET [106.8 (98.9–114.7)], MET + lifestyle intervention [122.5 (97.9-147.0)], Olanzapine: MET [5.6 (4.6-6.6)], MET + lifestyle intervention [6.3 (4.7-7.8)], Risperidone: MET [2.7 (2.3-3.2)], MET + lifestyle intervention [2.8 (2.3-3.3)], Sulpiride: MET [566.7 (512.5-620.9], MET + lifestyle intervention [542.8 (470.1–615.6)]	12 weeks	SR — FPG, insulin level, IRI (both MET and MET + lifestyle intervention)
Chen et al. [68]	Open-label, prospective, multi-centre	30 patients with schizophrenia who received olanzapine treatment for at least 3 months (age 18–60)	MET 1500	Olanzapine [11.5 (3.000]	8 weeks	SR — fasting insulin, FPG, HOMA-IR, HOMA-B; NSR — glucose disappearance rate (K_G)
Chiu et al. [70]	RCT	96 patients with schizophrenia (age 20–65)	MET 500 or 1000	Clozapine [269.6 (100.80)]	12 weeks	NSR — FPG
Jarskog et al. [71]	RCT	148 patients with schizophrenia (duration of illness ≥ 1 year) with BMI ≥ 27 kg/m^2 and were receiving one or a combination of 2 antipsychotics with no change in antipsychotic agents for 2 months and no change in dosage for one month prior to study entry (age 18–65)	MET 500	Higher-risk agents causing weight gain (clozapine, olanzapine, paliperidone, quetiapine, and risperidone), lower-risk agents causing weight gain (aripiprazole, fluphenazine, haloperidol, loxitane, perphenazine, thiothixene, and ziprasidone) or both higher- and lower-risk agents	16 weeks	SR — HbA_{1c}; NSR — FPG, fasting insulin
Smith et al. [66]	RCT	54 patients with schizophrenia and at least both a) impaired glucose and b) triglycerides ≥ 120 mg/dL and/or low HDL levels (age 18–70)	Pioglitazone 30 to 45	Antidepressants, antiparkinsonian, lithium (no data on the dose)	3 months	SR — fasting insulin, log C-peptide, FPG, 2-h PG, HOMA-IR; NSR — HbA_{1c}, 2-h insulin, HOMA-B

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Table 3. *Clinical trials involving hyperglycaemic therapy in patients using antipsychotics*

Study (trial name)	Type of study	Baseline sample	Hypoglycaemic agent (day dose in mg)	Antipsychotic [day dose in mg, mean (± SD)]	Durations	Change in glucose homeostasis after hypoglycaemic agent
Sarini et al. [57]	RCT	71 patients with schizophrenia (age 18–65)	sitagliptin 100	Olanzapine 10 to 30	12 weeks	SR — HbA_{1c}
Carrizo et al. [69]	RCT	61 patients (94.4% with schizophrenia)	Extended-release metformin 500 to 1000	Clozapine [180.3 (120.6)]	14 weeks	SR — HbA_{1c}, fasting insulin; NSR — FPG, HOMA-IR
Ishøy et al. [52]	RCT	80 antipsychotic-treated patients clinically stable schizophrenia (age 18–65)	Exenatide 2 (fixed dose) once weekly	Perphenazine, zuclopenthixol, chlorprothixene, clozapine, olanzapine, aripiprazole, risperidone, paliperidone, quetiapine, ziprasidone, amisulpirde, sertindole (no data on the dose)	3 months	NSR — HbA_{1c}, FPS, plasma glucagon and no debut of DM
Siskind et al., CODEX [53, 54]	RCT	28 patients with schizophrenia or schizoaffective disorder, taking oral clozapine for more than 18 weeks, BMI 30–45 kg/m^2, and with or without DM (age 18–64)	Exenatide 2	Clozapine (no data on the dose)	24 weeks	SR — FPG, HbA_{1c}; NSR — HOMA-IR, fasting insulin
Larsen et al. [56]	RCT	103 preDM patients with BMI ≥ 27 kg/m^2, diagnosed with a schizophrenia-spectrum disorder and on stabile treatment with either clozapine or olanzapine (age 18–65)	Liraglutide 0.6–1.8	Olanzapine [17.5 (17.5)] or clozapine [300.0 (200.0)]	16 weeks	SR — preDM status, FPG, IGT, 2h-PG, HbA_{1c}; NSR — HOMA-2
Whicher et al. [67]	RCT	47 patients with a diagnosis of schizophrenia, schizoaffective disorder, or first episode psychosis, and who had been prescribed antipsychotic medication for at least 1 month (age 18–75)	Liraglutide 3	Aripiprazole, aripiprazole intramuscular, clozpaine, flupentixol, olanzapine, paliperidone, quetiapine, risperidone, zuclopentixol decanoate, amisulpiride, or multiple antipsychotic medications (no data on the dose)	6 months	SR — HbA_{1c}; NSR — FPG
Svensson et al. [55]	RCT	103 patients overweight/obese patients with preDM, diagnosed with a schizophrenia spectrum disorder and treated with clozapine or olanzapine (age range no available)	Liraglutide 0.6 to 1.8	Clozapine, olanzapine (no data on the dose)	16 weeks and at the one-year follow up	After 16 weeks: SR — FPG, 2-h PG, HbA_{1c}, HOMA-2 After one-year follow up: 12 patients developed DM (*vs*. 5 on placebo); SR — HbA_{1c}, FPG, beta-cell function; NSR — C-peptide, HOMA-2

DM — diabetes; BMI — body mass index; FPG — fasting plasma glucose; HbA_{1c} — glycosylated haemoglobin A_{1c}; HOMA-IR — HOMA insulin resistance index; HOMA-B — HOMA beta cell function index; IRI — insulin resistance index; ISSI-2 — insulin secretion sensitivity index-2; MET — metformin; NSR — no significant reduction; preDM — prediabetes; RCT — randomized controlled trial; SR — statistical significant reduction

Conclusions

Carbohydrate metabolism disorders, including IFG, IGT, and DM, are a significant problem in patients using antipsychotic drugs due to the diverse hyperglycaemic potential of these drugs and the lack of adequate standards of diagnostic and therapeutic treatment of carbohydrate disorders. The available data indicate the need to perform such diagnostics even before the institution of antipsychotic medication and after 4-8 weeks of their administration, especially in patients at particularly high risk of developing dysglycaemia.

In the absence of carbohydrate metabolism disorders, such diagnostics should be repeated annually or when the antipsychotic treatment is changed. It has been suggested that the main diagnostic tool should be OGTT with additional determination of the percentage of HbA1c. The preDM or DM therapy combined with antipsychotic therapy is dependent on body weight. As in the case of T2DM, the use of MET in the first place is recommended in this group of patients. Its action can be supported by incretinomimetics, such as exenatide or liraglutide, especially in the case of concomitant overweight or obesity.

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REVIEW

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