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THERAPY IN PRACTICE

Pharmacological Management of Glucose Dysregulation in Patients Treated with Second-Generation Antipsychotics

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Abstract
Fasting hyperglycemia, impaired glucose tolerance, prediabetes, and diabetes are frequently present in patients treated with second-generation antipsychotics (SGAPs) for schizophrenia, bipolar disorder, and other severe mental illnesses. These drugs are known to produce weight gain, which may lead to insulin resistance, glucose intolerance, and metabolic syndrome, which constitute important risk factors for the emergence of diabetes. The aim of this review was to formulate therapeutic guidelines for the management of diabetes in patients treated with SGAPs, based on the association between SGAP-induced weight gain and glucose dysregulation. A systematic search in PubMed from inception to March 2020 for randomized controlled trials (RCTs) of diabetes or prediabetes in patients treated with SGAPs was performed. PubMed was also searched for the most recent clinical practice guidelines of interventions for co-morbid conditions associated with diabetes mellitus (DM) (arterial hypertension and dyslipidemia), lifestyle interventions and switching from high metabolic liability SGAPs to safer SGAPs. The search identified 14 RCTs in patients treated with SGAPs. Drug therapy using metformin as first-line therapy and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or perhaps sodium–glucose cotransporter-2 (SGLT2) inhibitors as add-on therapy, might be preferred in these patients as well, as they favorably influence glucose metabolism and body mass index, and provide cardio-renal benefits in general to the DM population, although for the SGLT-2 inhibitors there are no RCTs in this specific patient category so far. Metformin is also useful for treatment of prediabetes. Arterial hypertension should be treated with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, and statins should be used for correction of dyslipidemia. The outcome of lifestyle-changing interventions has been disappointing. Switching from clozapine, olanzapine, or quetiapine to lower cardiometabolic-risk SGAPs, like aripiprazole, brexpiprazole, cariprazine, lurasidone, or ziprasidone, has been recommended.

1 Introduction

People with severe mental disorders have a 10- to 25-year lower life expectancy [1–3]. Reasons for this increased mortality include the underlying psychiatric illness, unhealthy lifestyle behaviors, but also medication side effects, and suboptimal monitoring and management of both disease- and medication-related cardiovascular risk factors and morbidity [4, 5]. Fasting hyperglycemia, impaired glucose tolerance, prediabetes and diabetes mellitus (DM) are frequently present in patients treated with second-generation antipsychotics (SGAPs) for schizophrenia, bipolar disorder, and other severe mental illnesses [6–9]. Patients treated with first- and second-generation antipsychotics (Aps) are at risk of rapid and considerable weight accrual, which leads to insulin resistance, and in turn, may promote the development of glucose intolerance and metabolic syndrome [10]. Weight-gain-associated metabolic dysfunctions are the key to understanding the mechanisms and management of AP-induced glucose dysregulation, but some APs also seem to affect glucose homeostasis via weight-independent mechanisms [5, 7, 10, 11].

2 Epidemiology

The first large-scale, cross-sectional study of glucose metabolism in patients treated with APs evaluated a consecutive cohort of 783 subjects without a history of diabetes or exposure to antihyperglycemic drugs [6]. Most patients had been diagnosed with schizophrenia (66.9%) or schizoaffective disorder (12.6%), and were treated (in descending order of frequency) with olanzapine, risperidone, quetiapine,

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Key Points

When treating patients with severe mental illness with an SGAP, the first choice of therapy should be an antipsychotic (AP) with low risk of metabolic disturbances, if adequate to control the psychiatric disorder.

Lifestyle support and counseling should also be provided to all AP-treated patients. If prediabetes or diabetes mellitus (DM) develop, the appropriate change in AP regimen would be a switch to a medication with lower adverse cardiometabolic effects to improve glucose control, if adequate for the psychiatric condition.

Along with lifestyle intervention, metformin should also be implemented as first-line therapy for DM, both for glycemic and weight control, as soon as possible. Metformin can also be considered in case of prediabetes, mainly if additional conditions are present (obesity, previous gestational diabetes).

As second-line therapy, a GLP-1RA (especially liraglutide or once-weekly exenatide) or an SGLT2 inhibitor should be chosen for the management of DM, as they confer additional advantages (weight control, cardiorenal protection, low risk of hypoglycemia), although for SGLT2 inhibitors no specific RCTs are available so far.

clozapine, amisulpride, first-generation Aps, and aripiprazole. The study identified diabetes in 80 (10.2%) and prediabetes in 290 (37.0%) patients. The prevalence of diabetes was greatest in patients treated with olanzapine (32.5%) and lowest in those receiving aripiprazole or amisulpride (2.5%). A significant intergroup gradient from normal glucose tolerance to prediabetes to diabetes was observed for waist circumference (94.4 vs. 97.2 vs. 105.7 cm in males, and 88.5 vs. 93.7 vs. 101.8 cm in females), homeostatic model assessment of insulin resistance (2.1 vs. 2.8 vs. 6.3) and frequency of metabolic syndrome (16.2% vs. 41.0% and 68.8%). The insulin secretion during and post-challenge with a glucose load correlated with waist circumference, triglyceride levels, younger age, and treatment with clozapine [12].

The prevalence data were later confirmed by a meta-analysis of 25 studies that included 145,718 schizophrenia patients treated with various APs and 4,343,407 control subjects [13]. Using recognized criteria, the pooled prevalence of type 2 diabetes mellitus (T2DM) was 10.8%. The relative risk (RR) of diabetes was almost double (pooled RR: 1.82) compared with general population control subjects. Age and family history of diabetes correlated with the increased risk of T2DM in the pooled data [13, 14].

3 Pathobiology

A recent network meta-analysis assessed the metabolic liability of APs reported in 100 randomized controlled trials (RCTs) of acute treatment of schizophrenia conducted over a median 6-week period [8]. Data regarding fasting glucose were available in 37 studies comparing 3032 patients receiving placebo with 10,681 patients treated with 16 different APs. Blood glucose levels decreased in patients on lurasidone and increased in patients treated with clozapine, olanzapine, and zotepine [8]. Compared with placebo, no significant changes in fasting glycemia were reported with several APs (quetiapine, risperidone, paliperidone, iloperidone, aripiprazole, brexpiprazole, ziprasidone, amisulpride, asenapine, sertindole, cariprazine, and haloperidol). At the extremes of this evaluation were a mean of 5.2 mg/dL decrease with lurasidone and 18.9 mg/dL increase with clozapine after 6 weeks of AP exposure [8]. These data parallel, to some extent, those obtained for weight gain, which was noted for clozapine, olanzapine, and zotepine, but also for quetiapine, risperidone, paliperidone, iloperidone, sertindole, and brexpiprazole. The 6-week weight changes ranged from − 0.28 kg for ziprasidone to 3.01 kg for clozapine [8]. Overall, taking into account also the changes in lipid concentrations, clozapine and olanzapine had the worst metabolic profiles, while aripiprazole, brexpiprazole, lurasidone, ziprasidone, and cariprazine appeared to be metabolically the safest [8]. The risk of developing metabolic changes correlated with the amount of weight gained, male sex, and non-White ethnicity [8]. Thus, there seem to be important differences between APs in terms of their metabolic side effects. Although the median treatment duration of the available studies was relatively short, the review provided important information on newer APs with safer metabolic profiles, while confirming existing data, which pointed to clozapine and olanzapine as having the highest risk for both glucose metabolism disturbances and weight gain [8, 15, 16] (Table 1).

The exact molecular mechanisms of AP-induced glycemic dysregulation are not known. It has been hypothesized that most of the effects of APs on carbohydrate metabolism are secondary to increased adiposity and subsequent insulin resistance [17]. APs have been shown to significantly increase body weight and waist circumference, and it is well known that overweight/obesity play a central role in developing insulin resistance, a crucial metabolic dysfunction of T2DM [6, 8, 18]. However, there is evidence that patients treated with SGAPs may develop new-onset DM, or even diabetic ketoacidosis, in the absence of relevant changes in body weight, suggesting that independent effects on carbohydrate metabolism may occur, possibly by direct effects on insulin secretion [19–21]. Additionally, glucose abnormalities induced by olanzapine and clozapine that appear

within a short time of treatment initiation are incompletely explained by weight gain [7, 22].

The available evidence from animal and human studies can be integrated into three main hypothetical mechanisms to explain the pathobiology of AP-induced glucose dysregulations: obesity-associated insulin resistance, weight gain-independent insulin resistance, and AP-induced β pancreatic cell dysfunction and apoptosis [11].

The link between weight gain/obesity, intra-abdominal adiposity, insulin resistance and T2DM is well established in the general population. The AP-associated weight accrual appears to occur in stages, with rapid weight gain after AP initiation, and a high-weight plateau maintained thereafter [11]. The central role for the weight gain effects of APs probably involves increased appetite and caloric intake following congruent effects of serotoninergic 5-HT_{2C}, histaminergic H_1, or dopaminergic D2 receptor blockade, while a drug effect on resting energy expenditure and a hypometabolic state may have an adjuvant role [12, 17]. Neocortical 5-HT2A receptors might also play a role [23]. The differences in the affinity of SGAPs to these receptors might explain the differences in the propensity for drugs to induce weight gain [24]. Different effects on weight and metabolism also point towards overlapping and distinct mechanisms [25]. Genetic predisposition and lifestyle factors (dietary overload, physical inactivity) may further modulate the risk of weight increase during AP treatment [24, 26].

Histaminergic H_1-receptor antagonism was found to be best correlated with AP-induced weight gain by increasing food intake, and with DM [27–29]. Data from animal studies have confirmed and strengthened this explanation, with findings that linked H_1-receptor antagonism by olanzapine, and consecutive activation of hypothalamic 5' AMP-activated protein kinase (AMPK), leading to appetite stimulation [30]. Animal studies have shown that the blockade of 5-HT_{2C} receptors by olanzapine is involved in weight gain and hyperphagia in rats, probably following the decrease of the anorexigenic pro-opiomelanocortin (POMC) expression in the arcuate nucleus [31, 32]. Moreover, 5-HT_{2C} receptor agonists were found to promote reduced caloric intake through activation of melanocortin 4 receptors (MCR4), while the antagonism of the receptors has the opposite effects, i.e. increasing food intake by impairing satiety [25, 33, 34]. The antagonism of D2 receptors following AP treatment can increase appetite through their involvement in the reward system/feeding behavior [29, 35].

Various neuropeptides related to energy homeostasis and appetite are also implicated in AP-induced weight gain, i.e. orexigenic/anorexigenic hypothalamus-related and adiposity-related signals, but also digestive system-related signals [26]. For example, increased appetite can result from increased orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) expression in the hypothalamus, found to be induced by APs, and partially mediated by H_1-receptor blockade [36]. Other neuropeptides like leptin or ghrelin might be involved in the weight gain and T2DM induced by APs [37]. Animal studies have shown an increased expression of leptin receptor gene with olanzapine, while clinical data indicated higher leptin levels in patients treated with APs, even after adjustment for body weight [38, 39]. However, the findings were not consistent across all studies [40]. It has been suggested that leptin signaling is disturbed in patients taking APs, resulting in leptin resistance and improper control of food intake and energy expenditure [41]. Treatment with clozapine and olanzapine, but, interestingly, not with risperidone, an AP with a lower liability for metabolic disturbances, was associated with decreased adiponectin levels in clinical studies [42–44].

Importantly, insulin resistance may be induced by SGAPs in the absence of weight gain. Abnormalities in glucose metabolism, including DM, were reported within the first months of SGAPs administration without changes in body weight or body mass index (BMI) [45]. In skeletal muscle the SGAPs seem to impair insulin signaling, glucose transport, and glycogen content [46]. Data from animal studies suggest that this would be possible through direct inhibition of Akt activity and insulin receptor substrate (IRS)-1 phosphorylation by APs [11, 47]. Both effects would result in reduced glucose transporter type 4 (GLUT4) translocation to the membrane for glucose transport, with consequent impaired glucose uptake by skeletal muscle cells, and insulin resistance [47]. The SGAP-induced molecular mechanisms causing disruption of glucose metabolism in hepatocytes are less well understood, but this seems to occur by inhibiting 5-HT2 receptor-mediated glycogen synthesis [46].

Table 1 Risk of weight gain associated with second-generation antipsychotics [8, 15, 16]

Antipsychotic	Risk of weight gain
Aripiprazole	Low
Brexpiprazole	Low
Cariprazine	Low
Lurasidone	Low
Ziprasidone	Low
Amisulpride	Intermediate
Asenapine	Intermediate
Quetiapine	Intermediate
Risperidone	Intermediate
Paliperidone	Intermediate
Iloperidone	Intermediate
Sertindole	High
Zotepine	High
Clozapine	High
Olanzapine	High

While insulin resistance is an important preliminary stage, altered mass and/or function of β cells is necessary for the emergence of DM [48]. APs have been found to alter the insulin secretory capacity, although not all studies replicated that finding [40], but have also been associated with increased apoptosis in β cells [11]. Blockade of 5-HT_{2A} and muscarinic M3 receptors seem to be associated with decreased insulin response to glucose, while antagonism of D2 and 5-HT_{2C} receptors increased insulin secretion [46, 49]. Affinity for the cholinergic muscarinic M3 receptor subtype was proposed as the best predictor for risk for AP-induced DM, given the fact that clozapine and olanzapine, which have the highest liability for metabolic effects, also have the highest affinity for M3 receptors [50]. In fact, the AP-induced disturbance of M3 receptor-mediated glucose-dependent parasympathetic regulation of β-cell insulin secretion has been suggested to be a significant mechanism in this context [46]. Decreased insulin secretion could also be mediated through decreased ATP production, known to regulate insulin secretion, an effect that was found to be induced by clozapine in insulin-responsive cells [51]. However, the molecular mechanisms through which APs impair β-cell insulin secretion are less clear, and possibly depend on receptor binding, dose, and duration of therapy [46]. Apart from their direct effects on β cells, APs apparently also stimulate glucagon secretion in the pancreatic α cells [52].

We performed a review of publications retrieved from PubMed from inception to March 2020. The database was searched using the search terms "diabetes" AND "schizophrenia" and "randomized controlled trials." We retrieved 149 articles, and identified six adequately powered trials. Changing the search term "schizophrenia" to "antipsychotics" retrieved 198 articles, but did not change the number of RCTs. Additionally, we manually searched meta-analyses and identified eight additional RCTs. PubMed was also searched for the most recent clinical practice guidelines of pharmacological interventions for co-morbid conditions associated with diabetes (obesity, arterial hypertension, and dyslipidemia), lifestyle interventions, and switching from high metabolic liability APs to safer drugs. Within these sources, we manually searched their references for additional articles, and selected those with the most impact on the experts' decisions.

4 Management of Antipsychotic (AP)-Induced Metabolic Dysregulations

4.1 Lifestyle Changes

The dietary intake of patients with severe mental illness has been recently evaluated in a meta-analysis of 58 studies with 35,481 psychiatric patients and 5465 non-psychiatric control subjects [53]. The main psychiatric diagnoses within this sample were schizophrenia (47%), bipolar disorder (12%), and first-episode psychosis (7%). Overall, the mean energy intake was 1332 kJ/day higher among patients with severe mental illness versus controls [53]. A diagnosis of schizophrenia-spectrum disorder was associated with a 1695 kJ/day difference versus controls, while patients with bipolar disorder had an excess of only 827 kJ/day, but the difference between the two subgroups did not reach statistical significance [53]. A diet high in bread, rice, and baker's confectionery correlated with schizophrenia. Low protein intake and excess refined sugar were associated with psychosis in patients experiencing significant life stressors. Severe mental illness was also associated with decreased intake of fish, nuts, vegetable oils, fruit, and vegetables, but higher amounts of salt, sweetened beverages, and hydrogenated oils [53].

The effect of dietary interventions in patients treated with APs is modest and the findings must be cautiously interpreted due to large variations in the primary outcomes and length of observation. As assessed by a recent meta-analysis of 26 studies that included 18 trials in patients with schizophrenia, the interventions led to an average decrease of 2.7 kg in weight, 0.87 kg/m^2 in BMI, and 2.3 cm in waist circumference [54]. For all three parameters, the effect was somewhat greater if the intervention was started at AP initiation than subsequent to AP use (− 2.95 vs. − 2.64 kg for weight loss, − 0.95 vs. − 0.84 kg/m^2 for BMI, and − 4.82 vs. − 1.86 cm for waist circumference) [54].

Consensus exists that nutrition therapy is a cornerstone of the management of DM, with the caveat that a variety of eating patterns are acceptable, as long as they support reaching weight, glycemic, lipids and blood pressure individualized goals, and address individual preferences [55].

In addition, patients with schizophrenia are known to have reduced physical activity, with 9–10 h daily of sedentary behavior [56]. A meta-review of the evidence regarding physical activity as a treatment for severe mental illness indicates that aerobic exercise can reduce psychiatric symptoms, improve cognition and cardiorespiratory fitness, and have an inconsistent impact on anthropometric measures in patients with schizophrenia-spectrum disorders [57]. The Guidance of the European Psychiatric Association endorses the use of physical activity in routine clinical care to help improve psychiatric and medical outcomes in these patients [57].

The outcome of lifestyle-changing interventions in patients with schizophrenia-spectrum disorders has been disappointing. In the CHANGE trial, 428 patients with abdominal obesity were randomized to usual care or to 12 months of lifestyle coaching, care coordination, and treatment as prescribed by their primary-care physician [58]. Coaching involved home visits by trained professionals

(physical therapy technicians, occupational therapists, or dietitians) to encourage realistic and attractive physical activities and dietary changes. In the intervention group the patients received an average of 24.6 visits. At the conclusion of the study, there were no differences in glycated hemoglobin (HbA1c), weight, waist circumference, or time spent performing moderate or vigorous physical activity [58]. A replication study (STEPWISE RCT), using group rather than individual coaching, evaluated 414 patients with schizophrenia, schizoaffective disorder, or first-episode psychosis [59]. After 12 months, there were no differences in glycemic control, assessed by fasting blood glucose and HbA1c, lipid levels, energy intake, and weight [59].

The most up-to-date meta-analysis of lifestyle interventions for body weight reduction in people with severe mental illness included 41 RCTs ($n = 4267$, 73% with schizophrenia, mean baseline BMI = 32 kg/m^2) lasting 8–52 weeks (mean = 22), and found statistically significant, but likely not clinically relevant, reductions in BMI versus controls ($-$ 0.63 kg/m^2, 95% confidence interval [CI]: $-$ 1.02 to $-$ 0.23; $p = 0.002$) [60]. At post-intervention follow-up (17 RCTs), the effect on BMI remained similar but was no longer statistically significant ($-$ 0.63 kg/m^2, 95% CI: $-$ 1.30 to 0.04; $p = 0.07$) [60]. The risk ratio for losing $\geq$ 5% of baseline weight was 1.51 (95% CI: 1.07–2.13; $p = 0.02$) versus the control groups. However, glucose ($p = 0.70$), total cholesterol ($p = 0.12$), blood pressure ($p = 0.58$), and quality of life ($p = 0.66$) did not differ between lifestyle interventions and control groups [60].

4.2 Pharmacological Interventions for Patients with Diabetes Mellitus Receiving Second-Generation APs

When approaching a patient with severe mental illness who develops DM while on an AP, the first approach is to re-evaluate if a certain AP is mandatorily required for psychiatric symptoms control, and whether the current AP could possibly be switched to an alternative drug with less diabetogenic and/or weight gain potential [8, 61]. When AP cessation or switching is not possible or unsuccessful, and other pharmacological interventions need to be considered, the augmenting medication should concomitantly aim at controlling hyperglycemia and other components of the metabolic syndrome, mainly overweight/obesity. There are several antihyperglycemic drug classes available now that have proven additional benefits, apart from controlling hyperglycemia (i.e., cardiovascular and renal protection, weight loss, low risk of hypoglycemia, etc.).

The classes of oral and injectable antidiabetic drugs and their effect on body weight and glycemic control are summarized in Tables 2 and 3, respectively.

4.2.1 Switching APs

APs have a clearly demonstrated heterogeneous range of metabolic liability profiles, which justifies switching among APs to reduce the risk [5, 8, 25, 61, 62]. However, this should be performed with care, as switching APs might be associated with a higher risk of relapse [63]. Research in this area, summarized below, has been limited in scope and sample size [64].

A first controlled trial assigned 173 olanzapine-treated patients with schizophrenia or schizoaffective disorder to switch to aripiprazole or to stay on olanzapine [19]. After 16 weeks, more patients treated with aripiprazole lost $\geq$ 7% of their baseline weight (11.1% vs. 2.6%) and improved their lipid profiles, but changes in the glycemic parameters were not significant and did not differ from the olanzapine group [19].

A larger and more comprehensive investigation enrolled 215 patients with schizophrenia or schizoaffective disorder, with BMI $\geq$ 27 kg/m^2 and dyslipidemia in a "behaviorally oriented" exercise and diet program, and were treated with stable dosages of risperidone, quetiapine, or olanzapine [65]. Subjects were randomly assigned to continue their current regimen or switch to aripiprazole, and were followed up for 24 weeks. Switchers lost significantly more weight (2.9 kg) than patients continuing their baseline AP treatment, but there were no significant changes in fasting glucose and insulin, HbA1c, or in glucose levels 2 h after the ingestion of 75 g of glucose [65].

Switching APs has been compared with add-on metformin in a group of 127 overweight/obese children and adolescents who had evidence of substantial weight gain after being started on APs drugs [66]. Patients were allocated to continuation of current treatment, or add-on metformin in incremental dosing from 500 to 2000 mg/day, or switching to aripiprazole, molindone, or perphenazine. After 24 weeks, patients in the switch group showed a significant decrease in the BMI z-score, but had no changes in fasting glucose and insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), or in HbA1c levels. The glucose metabolism parameters were not significantly different in a comparison of the add-on metformin and switch groups [66].

The meta-review by Vancampfort et al. indicated that switching from olanzapine to quetiapine or aripiprazole had a non-significant effect on body weight (standardized mean difference (SMD): $-$ 0.11 kg, 95% CI: $-$ 0.23 to 0.03; two trials; $n = 287$), but a medium size effect on glucose levels reduction (SMD: $-$ 0.71, 95% CI: $-$ 0.85 to $-$ 0.58; two trials; $n = 280$) [64]. Therefore, if glucose intolerance develops, the appropriate change in AP regimen would be a switch to an AP with lower

Table 2 Mechanism of action and effect on body weight of oral antidiabetic agents in patients with type 2 diabetes [102, 118, 165–167]

Antidiabetic drug class	Mechanism of action	Effect on body weight (change in kg)	Effect on glycemic control (change in HbA1c)
Associated with weight loss			
Metformin	Activates AMP-kinase Decreases hepatic gluconeogenesis Inhibits lipid synthesis	+ 1.5 to − 2.9 Mean change in body weight in studies of metformin in treatment-naïve patients	~ − 1% vs. placebo
SGLT2 inhibitors: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	Inhibit SGLT2 in the proximal tubule of the nephron and block glucose reabsorption in the kidney, resulting in glucosuria	− 0.9 to − 2.5	~ − 0.8%
α-Glucosidase inhibitors: acarbose, miglitol	Inhibit intestinal α-glucosidase activity	− 0.43 to − 1.80	~ − 0.8%
GLP-1 RA: semaglutide	Stimulate GLP-1 receptors increase insulin secretion in response to glucose Decrease glucagon secretion in response to glucose Slow gastric emptying Increase satiety	− 0.2 to − 2.6	− 0.6 to − 1.1% placebo-adjusted
Weight neutral			
DPP-4 inhibitors: sitagliptin, saxagliptin, linagliptin, alogliptin, vildagliptin	Inhibit DPP-4 activity, increasing postprandial incretin (GLP-1, GIP) concentration Increase insulin secretion (glucose dependent) Decrease glucagon secretion (glucose dependent)	− 0.09 to + 1.11	− 0.6 to − 0.9% versus placebo
Associated with weight gain			
Meglitinides: repaglinide, nateglinide	Close K^+ATP channels on β-cell plasma membrane Increase insulin secretion	+ 0.91 to + 2.67	~ − 0.75% versus placebo
Sulfonylureas: glyburide, glipizide, glimepiride	Close K^+ATP channels on β-cell plasma membrane Increase insulin secretion	+ 2.01 to + 2.6	− 1.25% versus placebo
Thiazolidinediones: pioglitazone, rosiglitazone	Activate nuclear transcription factor PPAR-γ Increase insulin sensitivity	+ 2.30 to + 4.25	~ − 1.25% versus placebo

HbA1c glycated hemoglobin, *DPP-4* dipeptidyl peptidase 4, *GIP* gastric inhibitor polypeptide, *GLP-1 RA* glucagon-like peptide-1 receptor agonist, *K^+ATP* ATP-sensitive potassium channels, *PPAR-γ* peroxisome proliferator-activated receptor γ, *SGLT2* sodium glucose co-transporter 2

cardiometabolic liability. For example, patients treated with clozapine, olanzapine, or quetiapine may benefit from switching to aripiprazole [67]. Other lower-liability options include ziprasidone, brexpiprazole, cariprazine, and lurasidone [68]. The cardiometabolic risk appears to be similar for oral and long-acting injectable preparations [67]. When switching to the newest APs, such as brexpiprazole and cariprazine, clinicians should be aware that data regarding their long-term use are not yet available [68].

4.2.2 Oral Antihyperglycemic Drugs

4.2.2.1 Metformin Metformin is the cornerstone drug for the pharmacological intervention for T2DM, unless there are contraindications to its use, such as renal dysfunction with glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2, metabolic acidosis (including diabetic ketoacidosis), and hypersensitivity [69]. Proven long-time benefits of metformin treatment in the general T2DM population are its effects on glucose control, the good tolerability and the

Table 3 Mechanism of action and effect on body weight of injectable antidiabetic agents in patients with type 2 diabetes [102, 165, 168, 169]

Antidiabetic drug class	Mechanism of action	Effect on body weight (change in kg)	Effect on glycemic control (change in HbA1c)
Associated with weight loss			
GLP-1 RA Short-acting: exenatide, lixisenatide Long-acting: liraglutide, exenatide - extended release albiglutide dulaglutide, semaglutide	Stimulate GLP-1 receptors increase insulin secretion in response to glucose Decrease glucagon secretion in response to glucose Slow gastric emptying (short-acting agents) Increase satiety	− 0.14 to − 6.9 with variations depending on specific agent	− 0.8 to − 1.8%
Associated with weight gain			
Insulins: basal, rapid-acting, short-acting, intermediate-acting, premix	Stimulate insulin receptors Increase glucose disposal Decrease hepatic glucose production Suppress ketogenesis	+ 1.56 to + 5.75	~ − 1.0% or more, depending on dose and regimens

HbA1c glycated hemoglobin, *GLP-1 RA* glucagon-like peptide-1 receptor agonist

advantage of low cost, making it a first-choice therapy in AP-induced DM as for the general DM population [70].

Metformin produces a decrease of hepatic gluconeogenesis, and increases insulin-stimulated systemic glucose disposal [71, 72]. During chronic administration, metformin inhibits gluconeogenesis in an AMPK-ACC (acetyl-CoA carboxylase)-dependent and independent manner [73, 74]. In addition, the drug promotes the inhibition of lipid synthesis, and stimulates fatty acid oxidation, thus lowering free fatty acid levels [75, 76]. Other beneficial effects include the inhibition of intestinal absorption of glucose, possibly through redistribution of GLUT2 transporters, an increase in plasma levels of glucagon-like peptide (GLP)-1, and sensitivity to incretins, but these are not essential mechanisms for the glucose-lowering effect of metformin. Additionally, alterations of the intestinal microbiota and gut-mediated mechanisms also seem to be implicated [75, 77–82].

However, the mechanisms by which metformin exhibits its benefits in AP-induced metabolic disturbances are not entirely clear. Animal studies indicated that metformin attenuates olanzapine-associated hepatic (but not peripheral) insulin resistance [83]. In addition, it has been suggested that metformin has anorectic effects and counteracts AP-induced weight gain, possibly through modulation of orexigenic/anorexigenic peptides and alteration of feeding behavior [84, 85]. It was also shown in several clinical studies that metformin increased serum growth differentiation factor 15 (GDF15), and this correlated with changes in body weight [86, 87]. GDF15 is a peptide produced in response to stress and acts through a receptor complex (glial-derived neurotrophic factor receptor alpha-like (GFRAL)), predominantly found in small hindbrain regions (area postrema and nucleus of the solitary tract), through which it diminishes food intake [88, 89]. Additional to the central mechanism of food intake reduction, GDF15 may reduce gastric motility by binding to neuronal structures in the gastrointestinal tract and increase energy expenditure [90, 91]. Metformin administration augments GDF15 expression mainly in the small intestine, colon, and kidneys, and this may mediate its beneficial effects on energy balance [86].

Metformin is generally well tolerated and can be safely used in patients with GFR ≥ 30 mL/min/1.73 m^2, but kidney function should be checked at baseline and at least yearly during metformin therapy [69, 70]. For people with kidney function impairment (GFR: 30–44 ml/min/1.73 m^2) dose reduction and closer monitoring is needed [69]. Furthermore, chronic administration of metformin has been associated with vitamin B12 deficiency and worsening of neuropathy symptoms, so that monitoring of vitamin B12 is advised [92].

A meta-review that summarized and compared meta-analyses of pharmacological and non-pharmacological interventions in people with schizophrenia spectrum disorders without current T2DM, reported that metformin therapy was associated with a small reduction of HbA1c (SMD: − 0.385 [− 0.69 to − 0.07], $p = 0.016$; four trials, $n = 383$, I2 = 0%, $Q = 0$) and medium fasting glucose level lowering effect (SMD: − 0.65 [− 0.94 to − 0.35], $p < 0.001$; 17 trials, $n = 1281$, I2 = 0%, $Q = 0$) [64]. The same study reported that metformin (as well as switching the AP from olanzapine to quetiapine or aripiprazole) was found to be the best evidence-based intervention for glucose level reductions (followed by GLP1 RAs), and for improving insulin resistance (followed by rosiglitazone) [64]. One of the meta-analyses

found that longer intervention treatments were associated with greater improvements in fasting glucose level [93]. In the Improving Metabolic Parameters in Antipsychotic Child Treatment (IMPACT) study of non-diabetic, overweight/obese SGAPs-treated youth, which is currently the only RCT that compared metformin and SGAPs switch directly, and both against healthy lifestyle instructions provided to all three treatment arms, weight-related benefits versus the control condition were similar for metformin (effect size at week 24 = 0.99) and AP switch (effect size at week 24 = 0.91), but only metformin was associated with a significant decrease in fasting blood sugar (effect size at week 24 = 0.12 (non-significant)) [66].

Metformin is the most studied antihyperglycemic agent for AP-induced weight gain, with proven evidence of a medium-size effect [94–96]. Metformin is generally viewed as having modest weight-loss potential, possibly due to an anorectic effect [64, 97]. A meta-analysis in patients without DM treated with clozapine (eight studies, $n = 478$) demonstrated the superiority of metformin versus placebo in reducing weight (− 3.12 kg, 95% CI: − 4.88 to − 1.37, $p = 0.0005$) and BMI (− 1.18 kg/m^2, 95% CI: − 1.76 to − 0.61, $p < 0.0001$) [95]. The mean daily metformin dose was 750–1500 mg/day, except for one study that used 250–500 mg/day, and treatment duration was 3–6 months [95]. A second meta-analysis in clozapine-treated patients with schizophrenia that analyzed data from six RCTs (treatment-group: $n = 207$, control-group: $n = 207$) has found that under metformin therapy 500–1500 mg/day for 6–24 weeks, there were significantly greater reductions in body weight (mean difference (MD): − 2.89 kg, 95% CI: − 4.20 to − 1.59) and BMI (MD: − 0.81 kg/m^2, 95% CI: − 1.16 to − 0.45) [98]. Similarly, a meta-analysis of four RCTs with 105 olanzapine-treated participants with schizophrenia and bipolar disorder showed that concomitant administration of metformin 750–2550 mg/day for 12 weeks was associated with a significant decrease in body weight (MD: 5.02 kg, 95% CI: 3.93–6.10) compared with placebo [99]. Moreover, a systematic review and meta-analysis that evaluated several pharmacological interventions to counteract AP-induced weight gain in patients with schizophrenia, including ten metformin studies, showed a significant decrease in body weight (MD: − 3.17 kg, 95% CI: − 4.44 to − 1.90) with metformin 500–2000 mg/day for 12–24 weeks versus placebo, but the results were heterogeneous ($I^2 = 88\%$) [100]. Metformin was one of the therapies effective for prevention of clinically relevant ≥ 7% weight gain [100]. Metformin appeared to be more effective in preventing AP-induced weight gain in first-episode patients (MD: − 5.94 kg, 95% CI: 6.75 to − 5.12) versus chronically treated patients (MD: − 2.06 kg, 95% CI: − 2.71 to − 1.41), suggesting that early intervention might be advantageous [94]. Another meta-analysis of five studies in adults treated with atypical APs found that the effect of metformin was more pronounced in patients with a manifest (> 10%) body weight increase prior to randomization (reduction by 7.5%, 95% CI: 2.9–12.0 vs. by 4.8%, 95% CI: 1.60–8.0 in the overall group) [101].

A similar effect was seen in youth with severe mental illness. The above-mentioned IMPACT trial, which included 127 overweight/obese, psychiatrically stable youth (most on aripiprazole or risperidone), reported that patients receiving metformin 1000 mg twice a day (bid) (up-titrated over 4 weeks from 500 mg/day) experienced a significant decrease in the primary outcome BMI z-score (effect size at week 24 = 0.68) and all other weight-related outcomes [66]. Another 16-week RCT in children and adolescents ($n = 39$, age 10–17 years), treated with olanzapine, risperidone, or quetiapine showed that the weight gain was stabilized in subjects receiving metformin, while it continued to increase (0.31 kg/week) in the placebo arm [84].

4.2.2.2 Dipeptidyl-peptidase (DPP)-4 Inhibitors DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin) prevent the enzymatic degradation of incretin hormones, increasing the postprandial circulating levels of GLP-1 and glucose-dependent insulinotropic peptide (GIP) [102]. This effect stimulates glucose-dependent insulin secretion by pancreatic β cells [103]. Increased levels of GLP-1 regulate glucose homeostasis by several other mechanisms, such as inhibiting production of glucagon by pancreatic α cells, delaying gastric emptying, and suppressing appetite [103].

The DPP-4 inhibitors are generally well tolerated and have a good safety profile. A higher risk for hospitalization for heart failure (HHF) was reported with saxagliptin, but this finding was not confirmed by subsequent observational studies [104–106]. The DPP-4 inhibitors can be safely administered in patients with mildly or moderately impaired kidney function, although dose reductions might be needed. An exception is linagliptin, which is excreted in the bile and is not affected by renal function [103, 107].

Clinical trials in T2DM patients showed that treatment with DPP-4 inhibitors is associated with reductions of HbA1c of low–moderate magnitude (about 0.6–0.9% vs. placebo) [102, 108]. To date, no RCTs have been performed in psychiatric populations or AP-treated patients.

4.2.2.3 Sodium-Glucose Co-Transporter (SGLT) 2 Inhibitors The SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, ertugliflozin) reduce blood glucose by inhibiting tubular glucose reabsorption, which results in increased glucose urinary excretion [109]. Additionally, SGLT2 inhibition results in multiple cardiovascular and renal benefits at least in part induced by glucosuria and natriuresis, which includes a decrease in plasma volume and blood pressure, plasma uric acid levels, and decreased weight, partially to

due to a negative caloric balance [110]. SGLT-2 inhibitors are preferred in patients with a compelling need to minimize weight gain or promote weight loss [97].

The SGLT2 inhibitors demonstrated clear cardiovascular and renal benefits [111]. Three cardiovascular outcome trials (CVOTs) have been completed and another one is still ongoing and led to US Food and Drug Administration (FDA) approval of empagliflozin for reducing cardiovascular mortality in patients with T2DM, and of dapagliflozin for reducing the risk of HHF in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors [107, 112–115].

The RCTs in patients with T2DM have demonstrated significant reductions in HbA1c and fasting plasma glucose with a similar glucose-lowering capacity to metformin or DPP-4 inhibitors [109]. The SGLT2 inhibitors lower HbA1c by about 0.7–0.9% [116–118].

Treatment with the SGLT2 inhibitors is associated with caloric loss/energy deficit related to glucosuria, and generally accompanied by a weight loss of about 1–3 kg, which was observed in RCTs and real-world studies lasting 12–104 weeks [119, 120]. A small body composition study in T2DM patients ($n = 27$) indicated that the SGLT 2 inhibitor-associated weight loss is due to reduction of adipose tissue mass and transient loss of extracellular fluid [121].

So far there are no studies of SGLT2 inhibitors in patients on AP therapy evaluating their effect on weight or other components of the metabolic syndrome. However, given their propensity to control hyperglycemia and body weight and exert cardio-renal protection, this drug class might be a preferred option in this patient category as well, perhaps in combination with metformin.

4.2.2.4 Other Oral Antihyperglycemic Drugs Sulfonylureas, meglitinides, and thiazolidinediones are associated with weight gain and its consequences (Table 2), and the first two with a higher risk of hypoglycemia, which makes them rather a less desirable option for treatment of hyperglycemia in these patients. Moreover, there are no specific trials with sulfonylureas, meglitinides, or α glucosidase inhibitors in patients on APs, and their use is basically guided by data in general T2DM populations. A small double-blind, placebo-controlled study in patients treated with APs and with impaired glucose metabolism has shown that treatment with pioglitazone for 3 months prevented the deterioration of fasting glucose and improvement of HDL-cholesterol [122]. Rosiglitazone slightly improved insulin sensitivity after 8 weeks in a small double-blind, placebo-controlled trial in patients with schizophrenia with clozapine-associated glucose dysregulation, but it is now withdrawn from the market [123]. In addition, caution should be exerted with use of thiazolidinediones due to increased risk of heart failure [69].

4.2.3 Injectable Antihyperglycemic Drugs

4.2.3.1 GLP-1 Receptor Agonists (GLP-1RAs) GLP-1RAs (liraglutide, semaglutide, albiglutide, dulaglutide, lixisenatide, exenatide) are used as second- and third-line therapy, and act by increasing glucose-dependent insulin secretion, decreasing glucagon secretion, and decelerating gastric emptying, and thus have an important impact on glucose control, while minimizing the risk of hypoglycemia [102, 124]. Overall, in T2DM patients GLP-1RAs reduce HbA1c by about 0.8–1.8% [102]. In experimental models of diabetes, GLP-1RAs inhibit β cell death and promote β cell-mass expansion [124–126]. Preclinical data also suggest that GLP-1RAs modulate intestinal and systemic inflammatory responses, and support the role of gut microbial dysbiosis in modifying GLP-1 secretion, but there are limited data in human T2DM models to support similar findings [124].

So far, there have been three published RCTs in patients with severe mental illness that evaluated the effect of a GLP-1RAs on weight and other cardiometabolic features. One randomized placebo-controlled trial of adjunctive treatment with once-weekly exenatide in AP-treated patients with schizophrenia-spectrum disorders ($n = 45$) showed no significant reductions in fasting plasma glucose (time $p = 0.001$) in both groups after 3 months of treatment, despite significant weight loss in each group at the end of treatment (without between-group differences) [127]. The CODEX trial, an open-label RCT, evaluated once-weekly exenatide in clozapine-treated obese adults with schizophrenia, with or without T2DM ($n = 28$), and demonstrated that compared to usual care, patients receiving exenatide presented greater reduction of fasting glucose (− 0.34 vs. 0.39 mmol/L, $p = 0.036$) and HbA1c levels (− 0.21% vs. 0.03%, $p = 0.004$) [128]. At follow-up, however, the group formerly treated with exenatide presented an increase in HbA1c at 12 months after trial endpoint compared with the former usual-care group (MD: 0.81%, $p = 0.009$) [129]. In the third RCT that randomized 103 patients with prediabetes and schizophrenia-spectrum disorders treated with clozapine/olanzapine to receive 1.8 mg liraglutide daily or placebo, liraglutide-treated patients presented significantly improved glucose tolerance after 16 weeks (63.8% vs. 16.0% returned to normal glucose tolerance, $p < 0.001$) [130]. The liraglutide-treated group had significantly lower HbA1c levels (− 0.2%, 95% CI: − 0.3 to − 0.1%, $p < 0.001$) and fasting plasma glucose (− 0.90 mg/dL, 95% CI: 0.88–0.95, $p < 0.001$) versus placebo [124]. 1 year after completion of the intervention, however, the HbA1c and fasting glucose returned to baseline levels [131].

The meta-analysis of the three trials ($n = 164$, age: 40.0 ± 11.1 years; with and without T2DM) indicated that, overall, HbA1c and fasting blood glucose were each significantly reduced on GLP-1RA therapy (MD: − 3.25 (SE = 0.66), p

< 0.001, and − 0.45 (SE: 0.09) mmol/L, $p < 0.001$, respectively) [132]. There was also a higher proportion of patients with impaired glucose tolerance that shifted the glycemic status to normoglycemia at the end of interventions (68.4% vs. 23.7%) [132].

In addition to the glucose-lowering effect, GLP-1RAs regulate feeding behavior by enhancing satiety/suppressing appetite and inhibiting caloric intake, which results in weight loss [102]. Overall, in T2DM patients GLP-1RAs reduce weight by about 2–3 kg, depending on the agent, dosage, and combination [133]. The main mechanisms through which the GLP-1RAs associate with weight loss have been explained, but in this context it should also be noted that neurons in the human brain (parietal cortex, hypothalamus, and medulla) express GLP-1 receptors, and some GLP-1RAs have been shown to cross the blood-brain barrier in animal models [134, 135]. GLP-1RAs seem to activate GLP-1 receptors on afferent vagal fibers and subsequently engage CNS processing through the gut-brain axis [136]. Also, the central GLP-1 receptor activation, specifically within the nucleus tractus solitarius in the caudal brainstem, plays a critical role in controlling food intake [137]. Thus, both peripheral and central mechanisms of energy intake/balance are involved [138]. A relatively recent study in 21 T2DM patients undergoing functional magnetic resonance imaging (fMRI) has demonstrated that liraglutide altered parietal cortex activity related to highly desirable food cues, pointing to a central mechanism responsible at least in part for the effects of liraglutide on metabolism and weight loss [132]. Additionally, in animal models liraglutide and other GLP-1RAs have proven neuroprotective effects, by improving neurogenesis, normalizing synaptic plasticity, and exerting anti-inflammatory, anti-oxidant, and anti-apoptotic effects [137, 138].

Somewhat surprisingly, the study by Ishøy et al. showed that both once-weekly exenatide and placebo groups experienced similar weight loss (− 2.24 ± 3.3 and − 2.23 ± 4.4 kg, respectively, $p_{interaction} = 0.98$) after 3 months of treatment in 45 AP-treated patients with schizophrenia-spectrum disorders [127]. In the CODEX trial, however, more clozapine-treated obese participants treated with once-weekly exenatide achieved ≥ 5% weight loss ($p = 0.029$) after 24 weeks versus usual care [128]. In addition, patients receiving exenatide had greater reduction of mean weight (− 5.29 vs. − 1.12 kg, $p = 0.015$), and BMI (− 1.78 vs. − 0.39 kg/m^2, $p = 0.019$) [128]. Nevertheless, at 12 weeks' follow-up, patients in the former exenatide group presented greater weight gain (8.28 kg, $p < 0.001$) compared with those in the usual-care group [129].

In the study by Larsen et al. in patients with prediabetes and schizophrenia-spectrum disorders, participants receiving liraglutide had a significant placebo-subtracted body weight loss (5.3 kg, 95% CI: − 7.0 to − 3.7), BMI decrease (− 1.8 kg/m^2, 95% CI: 2.4 to − 1.3]) and waist circumference reduction (− 4.1 cm, 95% CI: − 6.0 to − 2.3) ($p < 0.001$ for all) [130]. After 1 year of follow-up, body weight increased in the liraglutide-treated group, but the placebo-subtracted weight loss still remained significant compared to baseline (− 3.8 kg, 95% CI: − 7.3 to − 0.2, $p = 0.04$) [131].

The recent meta-review indicated a small but significant effect of GLP1-RAs on weight reduction (SMD: − 0.44, 95% CI: − 0.60 to − 0.28, $p < 0.001$; three trials, $n = 168$, $I^2 = 0\%$,) and BMI reduction (SMD: − 0.41, 95% CI: − 0.57 to − 0.26, $p < 0.001$; three trials, $n = 168$, $I^2 = 0\%$), but no significant effect on waist circumference (SMD: 0.03, 95% CI: − 0.13 to 0.18, $p = 0.39$; three trials, $n = 163$, $I^2 = 0\%$) [64]. The meta-analysis by Siskind et al. [132] suggested that the body weight loss with GLP-1RAs was greater in patients treated with clozapine/olanzapine than with other APs (4.70 kg, 95% CI: 3.13 to − 6.27 vs. 1.50 kg, 95% CI: − 1.47 to − 4.47, $p < 0.001$).

4.2.3.2 Insulin As for the general T2DM population, insulin can be used in AP-treated T2DM patients in case of symptomatic hyperglycemia, when other pharmacological interventions fail or are not tolerated, or in case of an acute medical event with actual or potential glycemic decompensation [37, 139]. Although insulin has the highest efficacy in decreasing HbA1c, it is also generally associated with weight gain, possibly due, at least in part, to resolution of glucosuria after its initiation, or possibly also due to increased caloric intake caused by the fear or experience of hypoglycemia [69, 140]. Insulin therapy in patients with severe mental illness is problematic, given the expected problems with adherence to the complex treatment plan, self-monitoring of blood glucose levels, and recognition and treatment of hypoglycemia.

So far, no specific trial with insulin therapy in AP-induced DM has been published.

4.2.4 Pharmacological Management of Common Co-Morbid Conditions

4.2.4.1 Dyslipidemia The aggressive pharmacological approach to dyslipidemia in patients with T2DM has been justified by the results of several RCTs in patients with and without coronary heart disease. The Heart Protection Study ($n = 5963$ DM patients, 40–90 years old) has shown that treatment with 40 mg simvastatin daily for 5 years resulted in significantly less frequent new cardiovascular events (coronary death, non-fatal myocardial infarction (MI), coronary revascularization, or stroke), equivalent to a net reduction of 22% compared to placebo [141]. Low-density lipoproteins (LDL)-cholesterol decreased on average by 39 mg/dL (1.0 mmol/L) during the study [141]. The subgroups of diabetic patients with the most substantial risk reductions were those

without occlusive arterial disease (33% event rate reduction) and those with LDL-cholesterol < 116 mg/dL (3.0 mmol/L) at baseline (27% event rate reduction) [141]. In the Collaborative Atorvastatin Diabetes Study, 2838 DM patients aged 40–75 years without a history of cardiovascular disease (but with cardiovascular risk factors) were randomly assigned to 120 mg atorvastatin daily or placebo [142]. After a median follow-up duration of 3.9 years, a 37% risk reduction in the cardiovascular events (48% for strokes, 36% for acute coronary events, and 31% for coronary revascularizations) was recorded in patients treated with atorvastatin [142]. The risk reduction of cardiovascular events was apparent as early as 6 months after initiating atorvastatin and was fully expressed at 1 year [143].

The American Diabetes Association (ADA) advocates statin therapy in patients with T2DM based on cardiovascular risk status and age: for secondary prevention, a high-intensity statin therapy (or maximum tolerated dose) is recommended; for primary prevention in adults older than 40 years, a moderate- or high-intensity statin therapy is recommended, based on the presence of cardiovascular risk factors and estimated cardiovascular risk [144]. When statins alone cannot achieve an LDL-cholesterol target < 70 mg/dL, add-on treatment with ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may be considered [144]. For patients with significant triglyceride elevation (≥ 500 mg/dL), a fibrate might be added to reduce the risk of pancreatitis [144].

We are not aware of any statin trial specifically in patients with T2DM who also are treated with APs. However, in non-diabetic patients with mental illness and APs treatment, statin therapy had a similar effect to that expected in the general population [10, 145, 146]. Patients treated with APs may develop dyslipidemia as a side effect of specific therapy, but other factors like unhealthy lifestyle might contribute [147]. Several studies have shown that in patients with severe mental illness treated with APs, statins significantly reduced the total and LDL-cholesterol levels even after short-term therapy (1 or 3 months) [10, 145]. Additionally, the meta-analyses that evaluated the statin add-on therapy in this patient category have found that they may also have the potential to improve psychiatric symptoms [148, 149].

Limited data, however, indicate that that lipid-lowering agents are infrequently prescribed to patients treated with APs. In a large pharmaco-epidemiologic study using the Norwegian prescription database for adults starting AP treatment in 2004–2012, only 5.3% of the population were co-prescribed a lipid-lowering medication [150]. After adjustment for age and sex, the co-prescribing rates were similar in patients treated with clozapine or olanzapine, other SGAPs, or first-generation drugs. In the general population control sample, the proportion of individuals receiving lipid-lowering drugs was 34%. Data are missing regarding the use of lipid-lowering agents in patients with concomitant diabetes and dyslipidemia.

4.2.4.2 Arterial Hypertension Arterial hypertension is highly prevalent in individuals with T2DM and represents a major risk factor for cardiovascular morbidity [151]. The mechanism of the association has not been completely elucidated, but the main current mechanistic theories highlight the role of insulin resistance with regard to changes in the adrenergic, renin-angiotensin-aldosterone (RAA), and calcium-calmodulin systems [151, 152]. Insulin resistance and obesity tilt the balance between vasodilators (prostacyclin and nitric oxide) and vasoconstrictors (angiotensin II and endothelin) toward vasoconstriction and modify the incretin-mediated calibration of the RAA axis [151, 152]. Alterations of the calcium-calmodulin system lead to an increase in the intracellular calcium levels, which is followed by increased peripheral resistance and extracellular fluid volume [152].

The effect of intensive blood pressure control in general population patients with T2DM was comprehensively evaluated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [153]. The 4733 T2DM participants were randomly assigned to standard therapy with the goal of reaching a systolic blood pressure (BP) 130–140 mm Hg or intensive therapy targeting < 120 mm Hg [153]. The primary outcome was a 3-point MACE (cardiovascular death, MI, stroke). The therapeutic targets were achieved in both groups (133.5 mm Hg and 119.3 mm Hg). The annual rates of the 3-point MACE were 2.09% in the standard therapy group and 1.87% in the intensive therapy group, a statistically nonsignificant difference [153]. Compared with standard therapy, patients receiving intensive blood pressure control had a significantly higher incidence of serious adverse events (3.3% vs. 1.3%) caused by the antihypertensive medications.

The findings of the ACCORD study have been echoed in numerous other publications. A systematic review of RCTs evaluating a total of 61,772 patients with T2DM and 191,353 persons without diabetes found that achieving a target systolic BP of ≤ 140 mm Hg was correlated with a significantly greater reduction of cardiovascular risk in subjects with T2DM than in nondiabetic people [154]. The same therapeutic target (systolic BP < 140 mm Hg) was found to reduce end-stage renal disease in T2DM patients [154]. Achieving BP control to values of ≤ 140/90 mm Hg has been endorsed as the standard of medical care formulated by the ADA in 2020 for T2DM individuals with hypertension at lower risk of cardiovascular disease, while a target < 130/80 mm Hg might be appropriate for those at higher risk, if it can be safely achieved [144].

The mainstay of the pharmacological treatment of hypertension in patients with T2DM with or without renal impairment is either an angiotensin-converting enzyme inhibitor

or an angiotensin-receptor blocker drug. Only one type of these drugs should be used at any given time and both are contraindicated during pregnancy. Additional medications include thiazide diuretics and calcium channel blockers, which may also be used as first-line interventions in individuals who cannot tolerate renin-angiotensin modifying drugs or in those without albuminuria [144, 152, 155].

We are not aware of any antihypertensive medication trial in patients with T2DM who are also treated with APs. However, there is no reason to believe that the results would not extend from the general population to AP-treated individuals.

4.2.4.3 Obesity The FDA has approved four long-term pharmacological interventions for weight loss: phentermine-topiramate, naltrexone-bupropion, orlistat, and liraglutide. The approval was granted upon the demonstration of a safe and significantly greater yield of patients achieving a reduction of ≥ 5% of the baseline body weight than placebo, which is associated with a 10% decrease in fat mass, and a 9% reduction in the volume of the intra-abdominal adipose tissue in obese individuals with insulin resistance [156, 157]. The results are even more impressive in persons losing just over 10% of their body weight, as they have a 30% reduction in the intra-abdominal fat volume [157]. Moreover, a loss of 5–10% body weight in patients with T2DM is associated with a 0.5% decrease in HbA1c [158].

Phentermine-topiramate is the most effective intervention, while orlistat produces only modest sustained weight loss (Table 4). Overall, the incidence of adverse effects was higher in patients treated with phentermine-topiramate, naltrexone-bupropion, or liraglutide [159].

We are not aware of any RCTs of these medications approved for the treatment of obesity performed specifically in patients with T2DM who also are treated with APs.

5 Diabetes Prevention and Management of Prediabetes

Diabetes prevention remains the goal of lifestyle and pharmacological interventions in patients treated with APs, given their increased risk of developing insulin resistance and metabolic syndrome. The cornerstone of managing prediabetes is weight reduction of 5–7% of initial weight, 150 min/week of moderate exercise, and a diet with a calorie-restricted meal plan [160, 161]. A variety of eating patterns might be chosen for patients with prediabetes, including Mediterranean, low-calorie, and low-fat eating patterns [162].

Metformin has been investigated for its potential effect in diabetes prevention. The seminal study randomized 3,234 nondiabetic individuals (mean age: 51 years, mean BMI: 34.0 kg/m^2) with fasting and post-load hyperglycemia to metformin (850 mg twice daily), or to a lifestyle modification intervention aiming to decrease weight by ≥ 7%, or to placebo [162]. After an average follow-up of 2.8 years, the incidence of diabetes was 11 cases/100 person-years in the placebo group, 7.8 in the metformin group, and 4.8 in the lifestyle-modification group [162]. A later study compared the effect of combination metformin (500 mg twice daily) plus rosiglitazone (2 mg twice daily) versus placebo in 207 nondiabetic patients with impaired glucose tolerance [163]. After 3.9 years, incident diabetes was observed in 39% of patients receiving placebo, but only 14% of those treated with the metformin-rosiglitazone combination, translating into a relative risk reduction of 66%. Placebo-controlled clinical trials of DPP-4 inhibitors and GLP-1RAs have also been conducted, but they have not provided solid evidence of a significant effect on diabetes prevention [164].

The ADA has also supported the use of metformin for individuals with prediabetes, especially in those with a BMI ≥ 35 kg/m^2, those aged < 60 years, and women with prior gestational diabetes mellitus [160]. It might perhaps be considered in patients with prediabetes treated with olanzapine and clozapine [5]. More data are clearly needed to investigate the relative efficacy of diabetes prevention interventions in mentally ill patients treated with APs.

6 Conclusion

In summary, glucose dysregulation and cardiovascular risk factor accrual, morbidity, and mortality are common in people with severe mental illness and, especially, with schizophrenia.

Table 4 One-year weight loss after US Food and Drug Administration-approved pharmacological interventions [56]

Intervention	Average loss (kg) in excess of placebo	At least 5% of body weight (%)	At least 10% of body weight of body weight (%)
Phentermine-topiramate	8.8	75	54
Liraglutide	5.3	63	34
Naltrexone-bupropion	5.0	55	30
Orlistat	2.6	44	20

Reasons include the underlying psychiatric illness, unhealthy lifestyle behaviors, as well as medication-related adverse effects. Therefore, regular cardiovascular monitoring is imperative in these patients. When treating patients with severe mental illness with an AP, the first choice of therapy should be an AP with low risk of metabolic disturbances, if adequate to control the psychiatric disorder. Lifestyle support and counseling should also be provided to all AP-treated patients. If prediabetes or DM develop, the appropriate change in AP regimen would be a switch to a drug with lower metabolic liability to improve glucose control, if adequate for the psychiatric condition. Along with lifestyle intervention, metformin should also be implemented as first-line therapy for DM, for both glycemic and weight control, as soon as possible. Metformin might be considered also in case of prediabetes, mainly if additional conditions are present (obesity, previous gestational diabetes). As second-line therapy, a GLP-1RA (especially liraglutide or once-weekly exenatide) or an SGLT2 inhibitor should be chosen for the management of DM, as they confer additional advantages (weight control, cardio-renal protection, low risk of hypoglycemia), although for the latter group there are no specific RCTs available so far. Concomitant control of the other components of the metabolic syndrome (i.e., hypertension, dyslipidemia, obesity) should be implemented in order to improve cardiovascular health in people with severe mental illness.

Declarations

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