

Metabolic syndrome in patients with schizophrenia: Underlying mechanisms and therapeutic approaches (Review)

ASPASIA MANTA¹, ANASTASIA GEORGANTA², AFRODITI ROUMPOU¹, VASSILIS ZOUMPOURLIS³,
DEMETRIOS A. SPANDIDOS⁴, EMMANOUIL RIZOS⁵ and MELPOMENI PEPPA^{1,2}

¹Endocrine Unit, Second Propaedeutic Department of Internal Medicine, Research Institute and Diabetes Center, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, 12462 Athens, Greece; ²Third Department of Internal Medicine, Sotiria General Hospital for Chest Diseases, School of Medicine, National and Kapodistrian University of Athens, 11527 Athens, Greece; ³Biomedical Applications Unit, Institute of Chemical Biology, National Hellenic Research Foundation (NHRF), 11635 Athens, Greece; ⁴Laboratory of Clinical Virology, Medical School, University of Crete, 71003 Heraklion, Greece; ⁵Second Department of Psychiatry, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, 12641 Athens, Greece

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Abstract. Schizophrenia (SCZ) represents a considerable health concern, not only due to its impact on cognitive and psychiatric domains, but also because of its association with metabolic abnormalities. Individuals with SCZ face an increased risk of developing metabolic syndrome (MS), which contributes to the increased cardiovascular burden and reduced life expectancy observed in this population. Metabolic alterations are associated with both the SCZ condition itself and extrinsic factors, particularly the use of antipsychotic medications. Additionally, the link between SCZ and MS seems to be guided by distinct genetic parameters. The present narrative review summarizes the relationship between SCZ and MS and emphasizes the various therapeutic approaches for managing its components in patients with these conditions. Recommended therapeutic approaches include lifestyle modifications as the primary strategy, with a focus on behavioral lifestyle programs, addressing dietary patterns and physical activity. Pharmacological interventions include administering common antidiabetic medications and the selection of less metabolically harmful antipsychotics. Alternative interventions with limited clinical application are also discussed.

Ultimately, a personalized therapeutic approach encompassing both the psychological and metabolic aspects is essential for the effective management of MS in patients with SCZ.

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1. Introduction

Schizophrenia (SCZ) is a severe mental disorder characterized by disruptions in thought, emotion and behavior that affect millions of individuals worldwide, constituting a considerable public health challenge (1). SCZ has a median incidence of 15.2 per 100,000 individuals, with substantial variation across geographic regions, and a preponderance in males (2).

Beyond cognitive impairment and psychiatric symptoms, SCZ is associated with increased comorbidity throughout the lifespan of an individual (3). Substantial evidence indicates that individuals with SCZ have a reduced life expectancy of 15–20 years compared with the general population, primarily due to suicide, accidents, and the significantly increased risk for cardiovascular disease (CVD) (4–6). SCZ has also been associated with an increased risk of developing chronic kidney disease (CKD), and, even though patients with SCZ present a lower incidence of end-stage renal disease, these patients exhibit increased mortality rates once on dialysis (7,8).

Metabolic syndrome (MS) is a cluster of interrelated metabolic abnormalities that are associated with an elevated risk of CVD (9). According to the diagnostic criteria set by the American Heart Association and the National Heart, Lung and Blood Institute, the diagnosis of MS requires the presence

Correspondence to: Professor Melpomeni Peppa, Endocrine Unit, Second Propaedeutic Department of Internal Medicine, Research Institute and Diabetes Center, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Rimini 1, 12462 Athens, Greece
E-mail: moly6592@yahoo.com

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of three or more of the specific criteria presented in Table I, which include central obesity, hyperglycemia, low high-density lipoprotein (HDL) cholesterol, hypertriglyceridemia and hypertension (10). MS has a high global prevalence, affecting 25-33% of the population (11). Data suggests a bidirectional association between SCZ and MS, which may partially explain the increased risk, morbidity and mortality from CVD in this population (12). Individuals with SCZ exhibit an increased prevalence of MS, 2-3-fold higher compared with that of the general population affecting approximately 41% of patients depending on the diagnostic criteria and medications (13). Extensive research has shown that patients with SCZ have a considerably elevated risk for abdominal obesity, hypertension, low HDL cholesterol, hypertriglyceridemia and overall MS (14,15), which gradually increases with illness duration (16) and advancing age (17).

Regarding glucose dysregulation specifically, patients with SCZ are 2-5-fold more likely to develop type 2 diabetes (T2DM) compared with the general population (18,19). This is attributable to some extent to lifestyle factors, as patients with SCZ frequently exhibit unhealthy eating habits, poor physical activity and high rates of smoking, all of which are classic risk factors for T2DM (18-20). An impaired glucose metabolism has been revealed in individuals with a first episode of SCZ, indicating that this abnormality appears from the early stages of the disease, increasing the chance of developing T2DM (21).

In addition, MS has a considerable role in cognitive deficits seen in patients with SCZ and can contribute to functional deterioration over the course of the disease (22). MS has been associated with abnormalities in thought processing, selective focus and memory, all of which can have a detrimental influence on treatment outcomes (22-24). In a study of 159 individuals diagnosed with SCZ, those with MS demonstrated markedly impaired performance across various cognitive domains, including processing speed, attention/vigilance, working memory and problem-solving skills. Specific components of MS, such as increased abdominal obesity and elevated triglyceride levels, were associated with worse cognitive scores. Conversely, higher HDL cholesterol levels were associated with improved attention and vigilance abilities (25).

The present narrative review discussed the existing literature and provides a comprehensive overview of the relationship between SCZ and MS, investigates the underlying mechanisms linking these two conditions, and discusses the optimal therapeutic approach for managing MS in this population.

2. Underlying mechanisms linking SCZ and MS

Extensive research has focused on the identification of the exact mechanisms that explain the relationship between SCZ and MS or its components. Even though these mechanisms have not yet been fully elucidated, both intrinsic factors related to SCZ itself, specific genetic factors and signaling pathways and extrinsic factors, particularly the use of antipsychotic agents (APAs), may be considerably involved (14,17,21,26-29).

Intrinsic factors

Inherent risk factors. SCZ appears to confer an inherent risk for metabolic abnormalities, even in the absence of medications and long-term behavioral modifications. These involve

abnormal glucose homeostasis (21), an increased waist-to-hip ratio, visceral fat accumulation (17), as well as hypertension and dyslipidemia (14).

Disruptions in inflammatory pathways, oxidative stress and adipose tissue dysfunction, may underlie the pathogenesis of MS in SCZ (26,30,31). These are mainly driven by insulin resistance (IR), which may explain their frequent co-occurrence (32). According to research, both APA-naïve and medicated patients with SCZ exhibit increased levels of IR compared with healthy individuals (33-35). Recent research has examined the role of the gut-brain axis and its key regulator, the gut microbiota, in the pathophysiology of MS in the general population and in patients with SCZ, in particular (36). The gut microbiome is essential for the metabolic and immunologic functions of the body, and its disturbance can induce metabolic alterations, including dysregulation of glucose and lipid metabolism, IR and low-grade inflammation (37). These metabolic abnormalities that patients with SCZ exhibit affect the gut microbiota (38), leading to an increase in pro-inflammatory bacteria and a decrease in anti-inflammatory organisms. These changes can trigger the brain inflammation and cognitive impairment due to the activation of microglia and the release of pro-inflammatory cytokines into the bloodstream, which can cross the blood-brain barrier (38-40).

An unbalanced gut microbiota is further associated with cognitive deficiencies due to the activation of the hypothalamic-pituitary-adrenal (HPA) axis, which increases cortisol levels and lowers brain-derived neurotrophic factor (40,41). Additionally, stress-induced dysregulation of the HPA axis exacerbates inflammation, altering the gut microbiota, a common feature in severe mental disorders (36). These metabolic abnormalities collectively affect cognitive functions in patients with SCZ, particularly processing speed and working memory, with more severe deficiencies seen in patients with MS (36). Endocrine abnormalities are also common in individuals with psychiatric disorders, including SCZ. These may include conditions such as hyperprolactinemia, androgen insensitivity syndrome and hyperandrogenism (42,43).

Genetic factors.

Substantial evidence indicates that genetic factors may contribute to the co-occurrence of SCZ and MS (26). These involve neurochemical substrates, including histamine, serotonin, adrenergic receptors (44) and several specific genes, such as those encoding leptin (LEP), leptin receptor (LEPR), 5-hydroxytryptamine receptor 2C (HTR2C), α -ketoglutarate dependent dioxygenase (FTO), brain-derived neurotrophic factor (BDNF) and methylenetetrahydrofolate reductase 1 (MTHFR), which is considerably associated with MS in patients with SCZ (27).

Basic molecular mechanisms. Potential mechanisms underlying the pathogenesis of SCZ and its association with MS include biological pathways such as γ -aminobutyric acid (GABA) signaling, myelination pathways, cell adhesion molecules and dopaminergic signaling (45). Research has indicated that the expression of genes associated with the GABAergic nervous system is altered in SCZ (46), and that the GABA signaling pathway could also be associated with the development of MS (47,48). A number of studies have documented a

Table I. Diagnostic criteria for metabolic syndrome.

Criterion	Definition
Abdominal obesity	Waist circumference ≥ 102 cm for men and ≥ 88 cm for women
Hyperglycemia	Fasting plasma glucose ≥ 100 mg/dl or ongoing treatment
Low HDL-cholesterol	HDL < 40 mg/dl for men and < 50 mg/dl for women or ongoing treatment
Hypertriglyceridemia	Triglycerides ≥ 150 mg/dl or ongoing treatment
Hypertension	Blood pressure $\geq 130/85$ mmHg or ongoing treatment
HDL, high-density lipoprotein.	

reduction in the mRNA and protein levels of the enzyme glutamate decarboxylase 67 (GAD67) in the cortex of individuals with SCZ (49,50). A notable decrease in GAD67 expression is observed in the parvalbumin neuronal group (51), which are key GABAergic neurons in humans (52). Given the essential role of parvalbumin in synchronizing action potentials within neuronal networks during working memory tasks, this reduction in GAD67 is hypothesized to contribute to the cognitive impairment observed in SCZ. Additional findings in the GABA pathway include decreased expression of somatostatin, another marker of GABAergic neuron subtypes (53), as well as reductions in the expression of the GABA-A receptor subunits $\alpha 1$ and δ , the GABA transporter, neuropeptide Y, and cholecystokinin (54).

A study revealed that myelin dysfunction has been associated with the presence of MS in patients with psychotropic disorders, including patients diagnosed with SCZ (47). Myelination, the production of the myelin sheath surrounding axons in the central and peripheral nervous system, is a precisely calibrated process essential for maintaining optimal connectivity between brain structures (55). This, in turn, enables advanced integration processes such as perception, memory and cognition (56). Oligodendrocyte and myelin dysfunction can also result in alterations to synapse formation and function, potentially contributing to the cognitive dysfunction observed as a key symptom of SCZ (57). This evidence suggests that oligodendrocyte and myelin dysfunction may be a primary factor in SCZ, rather than a secondary consequence of the disease or treatment (57).

Cell adhesion molecules (CAMs) have been observed to have a key role in regulating leukocyte trafficking, potentially linking peripheral and neuroinflammatory processes in patients with SCZ, especially patients with MS (58). These molecules can activate inflammatory and immune-mediated responses and facilitate signal transmission across the blood-brain barrier, making them a promising area of inquiry (59). Researchers have reported the potential involvement of CAM-1 in this process. An analysis of plasma levels of diverse vascular CAMs, including vascular CAM-1, intracellular CAM-1 (ICAM-1) and P-selectin, as well as neural CAMs in a cohort of patients with SCZ revealed an increase in ICAM-1, integrin- $\beta 2$ mRNA and increased release of soluble ICAM-1 in neurons derived from patients with SCZ (60). A comparative study between naïve and medicated patients also found markedly increased expression of ICAM-1 and VCAM-1 in patients with SCZ, indicating activation of the endothelial

system, similar to what is observed in inflammation (59). MS may be associated with endothelial dysfunction in patients with SCZ, which may result in intracerebral neuroinflammatory alterations (58).

Humans have five dopaminergic pathways: Mesocortical, nigrostriatal, mesolimbic, thalamic and tuberoinfundibular, of which, the mesolimbic and mesocortical pathways appear to be the most important in the pathophysiology of SCZ (61). An increase or diminution in dopamine activity in the mesolimbic pathway has been associated with a range of symptoms associated with SCZ, including positive symptoms such as delusions and hallucinations, and negative such as anhedonia, respectively (62). An increase in dopaminergic transmission gives rise to a psychotic state that resembles the positive symptoms of SCZ (62). The mesocortical pathway connects the ventral tegmental area with the frontal cortex and is closely related to the mesolimbic pathway. This pathway has been considered to malfunction in patients with neuropsychiatric disorders, such as SCZ (63). Certain studies have identified the dopaminergic pathways as a potential contributing factor in the development of MS in SCZ, however, further investigation is required to substantiate this hypothesis (4,64,65).

Genetic loci linking MS and SCZ. Data suggests that common genetic variants, including those at chromosomal regions 2p16.1, 6p22.1 and 10q24.32, single nucleotide variations (SNV), as well as haplotypes, which represent groups of genetic variations inherited together, have become increasingly acknowledged for their contribution to the genetic connection between MS and SCZ (66). Genome-wide association studies have also implicated the rs1625579 single nucleotide polymorphism within the miR-137 gene as a potential risk factor for this disorder (67).

LEP and LEPR. A correlation between MS and polymorphisms in the LEP and LEPR genes was revealed in a study investigating their role in energy metabolism in patients with SCZ (68). A total of 20 distinct polymorphisms were tested in multiple genes, including those encoding insulin-induced gene 2 (INSIG2), ghrelin, LEP and LEPR. The genotypes and alleles of the rs3828942 polymorphism in the LEP gene and the genotypes of the rs17047718 polymorphism in the INSIG2 gene were significantly associated with MS (68). Moreover, the LEP rs7799039 polymorphism was associated with APA-induced weight gain in patients with SCZ treated with various APAs (69).

HTR2C. The HTR2C gene encodes a seven-transmembrane G-protein-coupled receptor. The encoded protein is responsive to signaling through the neurotransmitter serotonin. Several HTR2C polymorphisms appear to be associated with both MS and SCZ (70-74).

Research has revealed an association between 5-HTR2C and its polymorphisms and APA-induced weight gain, particularly the rs1414334 allele (75,76). A significant overrepresentation of the C-G-Cys23 haplotype has been identified in patients with weight gain (OR: 1.93; 95% CI: 1.04-3.56; $P=0.0015$). Additionally, the -759C allele may be associated with APA-induced weight gain (73,77), along with three specific polymorphisms within this variant (-697C/G, -997G/A and -1165A/G) that were identified as potential predictors of this side effect (77). A study by Bah *et al* (78) reports that the Cys23Ser (rs6318) and -759C/T (rs3813929) polymorphisms are also involved in APA-induced weight gain. The Cys23Ser allele was more prevalent in subjects with a low BMI, whereas the T allele of the -759C/T polymorphism was less common in the overweight group, compared to the normal and underweight subjects. These findings are consistent with the hypothesis that these polymorphisms in HTR2C are associated with weight maintenance.

MTHFR. The MTHFR gene plays a significant role in MS and SCZ through various genetic variants, including the rs1801133 (C677T) and rs1801131 (A1298C) polymorphisms, which contribute to elevated homocysteine levels and associated cardiovascular risks (79). The A1298C polymorphism has been linked to an increased risk of MS (80). Haplotype analysis further corroborates these findings, with the 677C/1298C haplotype conferring a greater risk of metabolic syndrome compared to the 677C/1298A haplotype. Interestingly, these associations were not influenced by circulating folate levels but were more pronounced in patients treated with clozapine or olanzapine, where the C/C genotype was associated with a 3.87-fold higher risk compared to A/A (81). Furthermore, the MTHFR 677C polymorphism has been implicated to weight loss in individuals taking aripiprazole or ziprasidone (82). Lastly, studies have indicated that the rs1801131 polymorphism of the MTHFR gene and two rs1800544 polymorphisms of the adrenoceptor- $\alpha 2A$ gene have a protective role against MS (82,83).

BDNF. BDNF is key for neuronal survival and growth, acting as a neurotransmitter modulator involved in neuronal plasticity (84). Normally, BDNF binds to its high-affinity receptor, tropomyosin receptor kinase B, and activates transduction cascades (insulin receptor substrate 1/2, phosphatidylinositol-4,5-bisphosphate 3-kinase and protein kinase B) that encode proteins implicated in b-cell survival (84). According to existing data, there is a correlation between the rs10835210 polymorphism and both SCZ and MS (67,85). It has also been proposed that the rs11030101, rs2030324 and rs6265 polymorphisms are associated with an elevated risk for SCZ (86). However, the genotypes at the rs11030101 and rs6265 loci have been demonstrated to influence the negative symptoms observed in individuals diagnosed with SCZ (86). Specifically, the rs6265 polymorphism has been found to have a positive association and appears to be protective against

SCZ in a study of an Asian population, with an association with multiple methylation sites (87). This is further supported by a recent meta-analysis that included 8384 patients with SCZ and 8821 controls, which found no considerable association between the rs6265 polymorphism and SCZ across five different genetic models, including allelic, homozygote, heterozygote, dominant and recessive models (88). Additionally, a separate study indicated that BDNF signaling has a key role in the etiology of SCZ associated with rare copy number variations (CNVs) (89). Recently, these CNVs have been associated with the development of MS in patients with SCZ and similar disorders (90).

Additional polymorphisms. In patients receiving treatment with second-generation APA, weight gain seems to be associated with the rs17782313 polymorphism of the melanocortin 4 receptor gene (91). Further studies have demonstrated that, although the identified correlation between weight gain and APA could not be predicted, certain genes were found to be involved in the development of MS, including the polymorphism rs9939609 of the FTO gene, as well as the neuropeptide Y and cannabinoid receptor 1 genes (76,83).

Extrinsic factors

Lifestyle. Lifestyle factors often associated with SCZ, such as poor dietary habits, sedentary behavior and high levels of stress, contribute to the metabolic burden and poor quality of life experienced by patients (92). Individuals with SCZ typically follow dietary patterns characterized by high saturated fats and low fiber intake, which contribute to their metabolic and cardiovascular health issues (93,94). Nutritional deficiencies are also common, as these patients consume less essential fatty acids, vitamins and other nutrients (95).

Patients with SCZ also exhibit markedly higher rates of smoking compared with the general population (96), with this pattern persisting even in the early stages of the condition (97). Smoking is identified as a key risk factor for CVD and T2DM, mirroring the risks seen in the general population. Moreover, there is evidence suggesting that nicotine has pronounced effects on certain cognitive functions in SCZ (98), while a substantial proportion of individuals with SCZ abuse alcohol, contributing to additional risks for CVD and T2DM (99). In addition to side effects, complexity of treatment, stigma and prejudices negatively affect adherence to treatment (100), leading to increased rates of relapses, hospitalizations and decreased overall functioning (101).

The role of antipsychotic agents. Antipsychotic medications, notably clozapine and olanzapine, have been implicated in weight gain, abdominal obesity and causing disruptions in lipid and glucose metabolism, leading to IR (28,29). The risk of T2DM is elevated among individuals receiving APA compared with the general population (14), especially in patients who have experienced multiple psychotic episodes (102). A meta-analysis involving 24,892 participants revealed that 35.3% of patients taking APA develop MS, increasing the risk of physical illnesses such as T2DM, CVD and cancer (102). Major cardiovascular events are also more likely to occur when second-generation APA are used over an extended period of time (103).

Table II. Risk of weight gain among antipsychotic agents.

Antipsychotic agent	Weight gain risk	Antipsychotic agent	Weight gain risk
Haloperidol	Low	Quetiapine	Moderate
Ziprasidone	Low	Sertindole	Moderate/high
Lurasidone	Low	Chlorpromazine	Moderate/high
Aripiprazole	Low	Iloperidone	High
Amisulpride	Low	Clozapine	High
Asenapine	Low	Zotepine	High
Paliperidone	Moderate	Olanzapine	High
Risperidone	Moderate	-	-

Adapted from Leucht *et al* (111) and Cooper *et al* (112).

APA-induced weight gain is observed within 6-8 weeks of treatment initiation (104). Especially for drug-naïve individuals with first-episode psychosis, the start of treatment is accompanied by rapid and considerable effects on body weight. Risperidone and olanzapine cause an average body weight increase of 7-8 and 13%, respectively, over 3 months (105,106), which is associated with changes in cardiovascular risk factors, including elevated total cholesterol and triglycerides (106). The weight gain not only has physical health implications but also adversely affects self-perception, potentially leading to poor treatment adherence (107-109). The metabolic disturbances associated with APA use are attributed to various factors, including poor diet, sedentary lifestyle and genetic factors (110). Table II presents the risk of weight gain among different APAs (111,112).

Although second generation APA-associated weight gain is associated with most metabolic alterations (113), research suggests that these may occur even without noticeable weight gain (114). Changes in glucose regulation and insulin sensitivity have been observed in non-obese individuals taking APA, particularly clozapine and olanzapine, with the latter showing greater elevations in glucose levels (29,115).

Antipsychotics may disrupt metabolic homeostasis by acting on both the central nervous system and peripheral organs (65,116). The proposed mechanism suggests that APAs disturb the brain signaling pathways associated with reward and food consumption by blocking specific receptors, leading to an overactivation of the sympathetic nervous system (117). The net result is the increased appetite, decreased satiety and altered food reward processes, resulting in impaired glucose and lipid metabolism. This action is mediated through the central effects of the hypothalamus but also the peripheral effects in various tissues, including the liver, pancreatic β -cells, adipose tissue and skeletal muscle (117). APAs increase the hepatic synthesis of glucagon and glucose, resulting in elevated blood glucose levels, IR and lipid imbalance, effects that are mediated through the production of certain proteins that regulate glucose and lipid metabolism (117). The role of multiple receptors are important, such as serotonin, dopamine and histamine, which lead to increased food intake, impaired glucose tolerance and IR (118). APA may directly impair insulin secretion from pancreatic β -cells by blocking the dopamine and serotonin receptors, while also disrupting

glucagon secretion from α -cells by blocking the muscarinic and serotonin receptors (119).

Additionally, APA treatment in patients with SCZ affects several hormones that regulate appetite, food consumption and glucose metabolism, leading to metabolic disturbances. As previously noted, insulin secretion increases, which may be a response to IR or a direct effect of APA (120). Cortisol levels, initially elevated in patients with SCZ, decrease following APA treatment (121,122). Glucagon and glucagon-like peptide 1 (GLP-1) secretion are stimulated, causing excessive liver glucose production (123) and increased insulin secretion and satiety, respectively (124,125). Cholecystokinin, which aids digestion and suppresses hunger, remains unchanged with APA use but might be counteracted by these medications (126,127). By contrast, adiponectin and ghrelin levels decrease, promoting IR and high blood pressure (128-131). Orexin and leptin levels, which influence food intake and energy expenditure, are inconsistently affected, while a leptin resistance might be present (132-136). Lastly, prolactin, which is involved in lipid metabolism and energy balance, increases with APA treatment (137). These hormonal changes contribute to the risk of MS in individuals treated with APA.

Research suggests that genetic variants may also predispose patients with SCZ to APA-related metabolic complications, including weight gain and IR (138,139), as well as influence their drug responses. The metabolism of antipsychotics occurs in the liver through the cytochrome P450 system, and genetic polymorphisms in CYP enzymes, such as CYP2D6, lead to differences in metabolizer phenotypes. Slow metabolizers have decreased enzyme activity, increasing the risk of adverse effects and toxicity, while extensive metabolizers have normal activity and may require higher doses. Conversely, ultra-rapid metabolizers have increased enzyme activity, raising the risk of therapeutic ineffectiveness (140,141). Individuals with certain CYP2D6 polymorphisms, particularly poor metabolizers and ultrarapid metabolizers, experience more substantial APA-induced weight gain compared to normal metabolizers (142,143). This is attributed to altered drug metabolism and increased drug exposure. The impact of CYP2D6 polymorphisms on IR is less clear; however, metabolic changes due to altered drug metabolism could be a contributing factor (144). Of note, CYP1A2 polymorphisms have been more directly associated with insulin and lipid

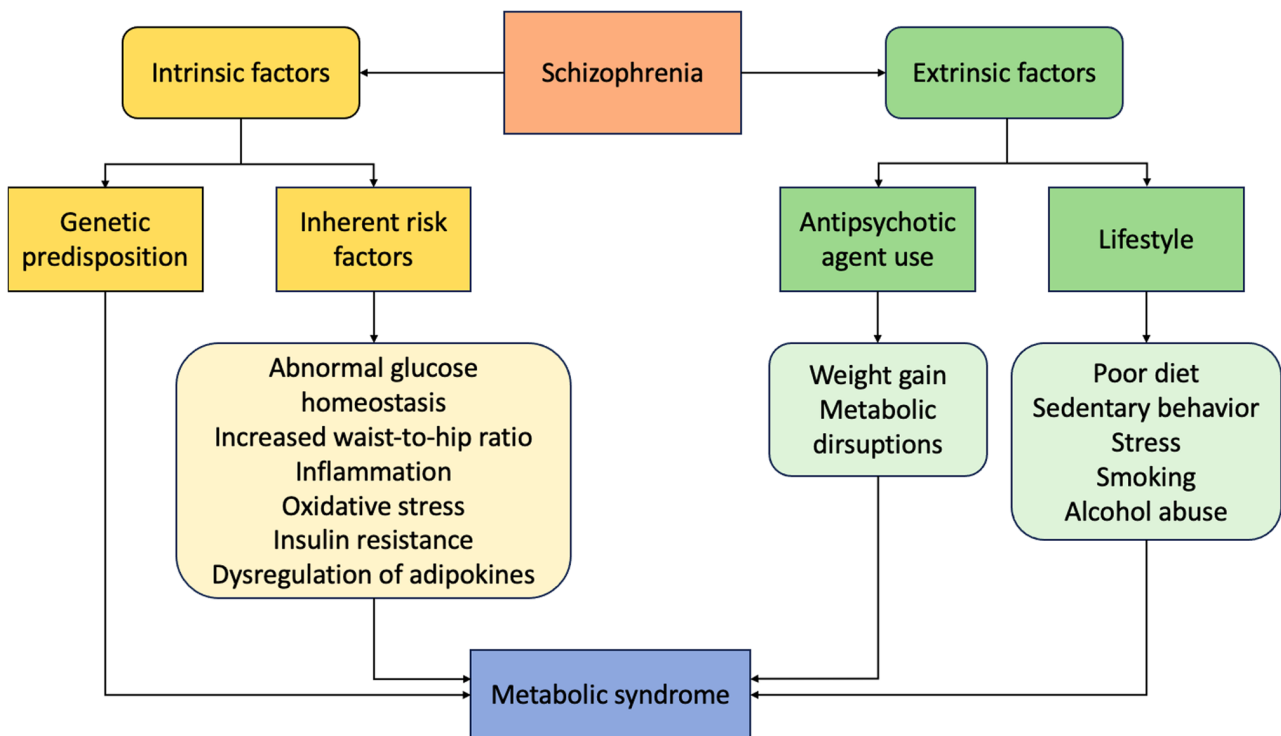


Figure 1. A summary of the underlying mechanisms linking schizophrenia and metabolic syndrome.

elevations in clozapine-treated patients, suggesting a complex interaction between different cytochrome P450 enzymes and metabolic side effects (145).

A summary of the underlying mechanisms linking SCZ and MS is presented in Fig. 1.

3. Therapeutic interventions

Therapeutic interventions are key for improving both the physical and mental health outcomes of patients with SCZ, particularly for patients with MS or its components. Treatment approaches consist of both lifestyle modifications and pharmacological modalities, aiming to address not only hyperglycemia and weight gain, but also overall cardiovascular and renal risk. A summary of the main therapeutic interventions for MS that can be used in patients with SCZ is presented in Fig. 2.

Lifestyle modifications. Lifestyle modifications, involving the implementation of specific dietary patterns and increased physical activity, are recommended as the primary approach for managing MS and its components in patients with SCZ, either induced by the disease itself or APA use (146). Lifestyle interventions should focus on promoting healthy eating habits, reducing energy intake, increasing physical activity levels and enhancing overall diet quality (146).

Numerous studies have demonstrated the effectiveness of lifestyle interventions, commonly referred to as ‘behavioral lifestyle programs’, for individuals receiving APA (147-149). The programs typically involve a combination of group and individual sessions and may incorporate cognitive techniques or counseling. However, study designs vary, and there is a notable scarcity of research with long-term follow-up (146).

In contrast to standard therapy, behavioral lifestyle programs that enhance diet and physical exercise may decrease the effects of APA induced weight gain, leading to a 3 kg and 1 kg/m² weight and BMI reduction, respectively (148,150,151). Structured physical activity interventions have also demonstrated efficacy in enhancing quality of life and reducing sedentary behavior among adults with SCZ (152). Although data is limited regarding the long-term effectiveness and the ideal duration, ‘early behavioral intervention’ programs for individuals experiencing a first episode of psychosis appear to minimize weight gain compared with standard treatment (153,154). Although the benefits may be maintained to some extent, the general trend indicates a gradual decline, indicating the necessity for long-term availability of these sessions, similar to the general population (146).

Regarding dietary strategies, well-balanced meals high in plant-based foods and quality protein may help avert or delay psychotic episodes (155), whereas the Mediterranean diet has been shown to significantly improve cognitive function in individuals with SCZ and MS (156). Investigations into the ketogenic diet have shown encouraging results in addressing the abnormally low levels of GABA in the brain (157). Additionally, vitamin D, omega-3 fatty acids and certain amino acid supplements may improve cognitive symptoms and quality of life in patients with SCZ (158). Due to the detrimental repercussions mentioned above, smoking, alcohol overconsumption or any other hazardous substance use, abuse or dependence should be assessed, and patients should be referred to appropriate services as indicated. Overall, integrating diet, exercise and psychoeducational components can promote holistic well-being for individuals with SCZ and MS (159).

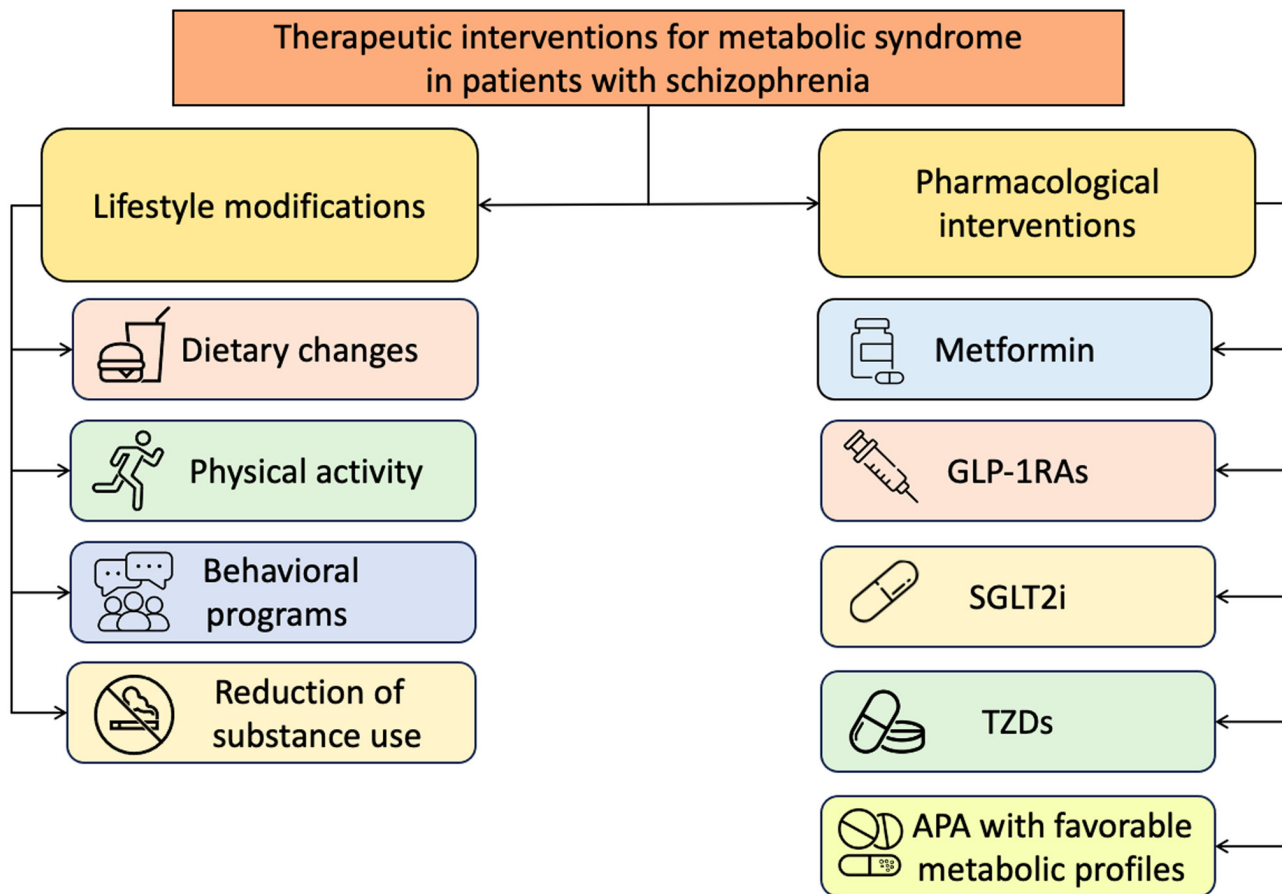


Figure 2. A summary of the main therapeutic interventions for MS in patients with schizophrenia and MS. MS, metabolic syndrome; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose transport protein 2 inhibitor; TZDs, thiazolidinediones; APA, antipsychotic agents.

Pharmacological Interventions

Metformin. Metformin has been extensively investigated in the management of MS in individuals with SCZ, particularly patients undergoing treatment with APA (160-164). The primary mechanisms of metformin involve enhancing insulin sensitivity, reducing hepatic glucose production and improving glucose uptake by peripheral tissues (165). Given that second generation APAs often induce IR and contribute to MS development, metformin becomes key in patients with SCZ under treatment to improve IR (160). In parallel, metformin may be able to reverse weight gain in these patients, leading to a weight loss of ~3 kg (161,162). In patients with a first episode of SCZ, metformin has also demonstrated favorable effects on APA-induced dyslipidemia, manifesting as reductions in total cholesterol, LDL-cholesterol and triglyceride levels (163). Furthermore, metformin offers cardiovascular benefits, demonstrating value for individuals susceptible to cardiovascular complications (166). Currently, metformin is one of the first-line choices as an adjunctive medication in patients receiving APA and at high risk of MS, after lifestyle modifications have been attempted (146).

Notably, a recent meta-analysis suggests that, beyond its metabolic impacts, metformin improves psychiatric and cognitive symptoms in patients with SCZ treated with APA (164). As a frequently employed adjunctive therapy alongside APA, the role of metformin in preventing and managing metabolic disturbances underscores its significance in the comprehensive

treatment approach for individuals managing both SCZ and MS.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs). GLP-1 is an incretin hormone secreted by the intestine and has a considerable role in maintaining glucose homeostasis by decreasing gastric emptying and glucagon production, while increasing insulin secretion (167). GLP-1 affects responses of the central nervous system to meals, which is essential for the central control of hunger and satiety (167).

GLP-1RAs mimic the effects of GLP-1 and contribute considerably to enhancing glucose metabolism and weight control (168). They also provide considerable cardiovascular and renal benefits, reducing the risk of major cardiovascular events and all-cause mortality and delaying the progression of CKD (169). These features have made GLP-1RAs a valuable tool in the therapeutic approach of treating T2DM, as they complement both organ-centric and glucose-centric approaches.

In individuals with SCZ, particularly patients on second generation APAs, GLP-1RAs offer a targeted approach to controlling glucose homeostasis. Notably, fasting glucose and insulin levels, as well as glycated hemoglobin (HbA1c) and glucagon levels, show improvement with the use of GLP-1RAs (112,170-178). A recent meta-analysis confirms the safety and efficacy of GLP-1RA treatment for APA-treated patients, positively impacting various cardio-metabolic

parameters, such as body weight, waist circumference and blood pressure (179).

Several clinical studies have also demonstrated positive effects in APA-induced weight gain (171-173,175-177,180,181). Especially for obesity associated with clozapine, GLP-1RAs could potentially serve as an effective intervention (182). GLP-1RAs exhibit positive effects on lipid metabolism, as evidenced by improvements in lipid blood levels and visceral adiposity across reviewed studies (112,171,173,178). Given the heightened cardiorenal risk associated with MS in patients with SCZ, the benefits of these agonists, including enhancements in endothelial function, blood pressure and renal protection, are particularly apparent (183,184).

In addition to the well-known metabolic effects of GLP-1RAs, recent research has focused on their potential to improve cognitive function in patients with T2DM, though further research is required (185-187). The proposed neuroprotective effects seem to be mediated through influencing neurogenesis, synaptic plasticity, neuroinflammation, neurotransmission, insulin signaling transduction, neuroapoptosis and oxidative damage reduction (185,187). Current clinical research indicates partial evidence of GLP-1 receptor agonism improving cognitive performance in patients with SCZ, but further research is needed to validate the mechanism by which GLP-1RAs improve cognition (188). Although some favorable effects following treatment with GLP-1RAs in SCZ were not consistently maintained in long-term follow-up studies (178,189), a case report demonstrates continuous effects over a 2-year period (181).

Currently, ongoing clinical trials are further exploring the role of the GLP-1RA semaglutide in APA-treated patients with SCZ (190-192).

Sodium-glucose transport protein 2 inhibitors (SGLT2is). SGLT2is constitute an important treatment modality, acting by impeding glucose reabsorption in the kidneys, leading to glycosuria, glucose control and weight reduction (193). In addition, this class of antidiabetic medications has shown a favorable effect on cardiorenal syndrome, presenting as medications aimed not only at glucose control, but also at organ protection. These effects are so substantial that SGLT2is are used even in the absence of T2DM (194).

For individuals with SCZ, SGLT2is presents a targeted approach for controlling glucose homeostasis (195). Notably, the weight-reducing effects of SGLT2is prove valuable in managing obesity-related components of MS, effectively counteracting the weight gain often associated with specific APA (196).

Current guidelines and clinical studies encourage exploring SGLT2is as an adjunct to metformin for treating T2DM in the setting of antipsychotic therapy (112,197-199). Although the recommendation is based on limited preclinical and clinical evidence, particularly for patients receiving olanzapine or clozapine (196,199), their considerable advantages, including low hypoglycemia risk, weight-loss potential and cardiovascular and renal benefits, constitute them as a promising second-line therapy in patients with severe mental illnesses (195). Ongoing randomized clinical trials examining the effect of empagliflozin on APA-associated weight gain are expected to further elucidate

the potential of SGLT2is as a viable therapeutic strategy in this population (200,201).

Thiazolidinediones (TZDs). TZDs are a class of antidiabetic medications that enhance insulin sensitivity through stimulation of the peroxisome proliferator-activated receptor- γ in adipose tissue (202). Findings on the use of TZDs in patients with SCZ are conflicted. Pioglitazone has been reported as beneficial and safe for addressing metabolic abnormalities, such as fasting glucose and insulin levels, IR and lipid levels in patients with SCZ treated with APA (203,204). Pioglitazone may also potentially benefit depressive symptoms (203) and, when used in conjunction with risperidone, it has been found effective in reducing negative symptoms (205).

By contrast, the cognitive benefits of rosiglitazone remain inconclusive (206) and, despite some positive results on IR and lipid abnormalities associated with clozapine (207), its impact on metabolic control appears limited in specific APA contexts (208). Notably, rosiglitazone was withdrawn in several European countries in 2010 over concerns of an elevated risk of CVD. Although pioglitazone is still accessible, its use in severe mental diseases is limited (209).

Antipsychotics with favorable metabolic profile

Antipsychotic switching. Given that weight gain aggravates T2DM and poses a considerable challenge in management of TDM, specific attention should be given to the weight gain profiles of APAs. Based on the findings of several meta-analyses, APAs may be categorized into three groups based on the likelihood of causing weight gain (Table II) (111,112).

For individuals with SCZ and associated MS, a reasonable approach would be to switch to a metabolically less harmful APA regimen (210,211). The World Federation of Societies of Biological Psychiatry and Cochrane recommendations, which summarize available research, indicate that transitioning from olanzapine to aripiprazole may be advantageous (146,212). Limited evidence supports switches between the rest of the APA (112).

The ability of a patient to control symptoms and prevent relapses may be compromised when switching APAs, therefore this must be carefully considered before making a decision. Engaging the patient in conversations on the advantages, disadvantages and potential side effects of the alternative medication is key (112).

Adjunctive aripiprazole. Aripiprazole is considered one of the metabolically safest APAs, with a minimal effect on weight compared with the alternatives (111). Due to this characteristic, aripiprazole has been investigated as an adjunctive treatment to other medications that have caused weight increase, notably olanzapine or clozapine, when switching APAs may not be a viable option (213-216).

This approach has shown potential in achieving a mean weight loss of ~2 kg when compared with placebo (213-216). While studies on the effects of aripiprazole on cholesterol, triglyceride and glucose levels are inconclusive, there is a tendency toward improvement (214,215,217). Aripiprazole is unlikely to exacerbate psychotic symptoms. As a result, supplementary therapy with aripiprazole could be a safe and possibly useful technique for reducing weight gain without markedly

impacting symptoms. There is little evidence supporting the use of aripiprazole to supplement other APAs, emphasizing the significance of evaluating the possible drawbacks of polypharmacy against the potential benefits (112).

Other interventions. A number of medications have been investigated in clinical trials for their potential involvement in resolving MS in patients with SCZ, particularly APA-induced weight gain. Based on the available data, these therapies are not indicated for routine clinical application (112).

The combination of bupropion and naltrexone has been investigated for its potential to address negative symptoms and comorbid conditions such as obesity and smoking in individuals with SCZ. The effects of bupropion on dopamine and the action of naltrexone as an opioid receptor antagonist may influence brain pathways involved in SCZ, potentially improving negative symptoms (218). However, research has revealed no significant impact of these agents on weight loss, BMI, lipid levels or smoking cessation in SCZ (219). The use of this combination is limited due to the increased risk of psychosis associated with higher doses of bupropion, particularly in individuals with preexisting psychotic symptoms, substance abuse history or concurrent use of dopaminergic medications (220,221). Immediate-release formulations and overdose cases are most frequently associated with psychosis, though sustained-release versions also pose a risk (222,223). Psychosis has even been reported in patients without prior psychiatric issues. The use of antipsychotics may reduce this risk, which is likely associated with dopaminergic hyperactivity (222). Additional research is required to improve understanding of these mechanisms.

Amantadine, an antiviral medication known for mitigating extrapyramidal adverse effects, has been investigated for its impact on weight gain through the modulation of dopaminergic and serotonergic neurotransmission. Clinical trials have demonstrated small but considerable weight loss in the amantadine group compared with placebo, particularly for those with bipolar disorder and SCZ (224,225). However, the weak dopamine agonist properties of amantadine and the potential to induce psychotic symptoms raise concerns (226).

Melatonin, a hormone involved in circadian rhythm regulation, seems a promising agent in blocking olanzapine-induced weight gain in animal studies (227). Two double-blind randomized controlled trials have indicated that melatonin, when compared with placebo, attenuated weight gain in individuals with SCZ or bipolar disorder receiving olanzapine (228,229).

Orlistat, an inhibitor of gastric and pancreatic lipase that prevents fat absorption, has demonstrated weight loss in the general population; however, its adverse effects limit its long-term adherence (230). In studies involving individuals with SCZ, orlistat exhibited weight loss effects primarily in male participants (231).

Topiramate, a third-generation anticonvulsant, has been investigated for its potential to reduce obesity. Several double-blind, placebo-controlled randomized clinical trials, ranging from 8-12 weeks, revealed a considerable benefit in weight reduction when topiramate was added to treatment with APA (232). The potential cognitive side effects (233) and the need for cautious dose titration are highlighted (234).

Reboxetine, a selective noradrenaline reuptake inhibitor, demonstrated considerable attenuation of olanzapine-related weight gain in patients with SCZ (235,236). A meta-analysis has also indicated a weighted mean difference in favor of reboxetine compared with placebo (216).

Zonisamide, a sulfonamide anticonvulsant, seems promising in causing weight loss in various populations, including in patients with SCZ. A 10-week double-blind, placebo-controlled randomized clinical trial demonstrated a decrease in BMI and weight with zonisamide compared with placebo in individuals with SCZ. Adverse effects were reported as similar between groups, supporting its potential as an intervention for weight management (237).

Last, while bariatric surgery has not undergone formal clinical trials in individuals with SCZ, some small case series have been collected from bariatric surgical cohorts (238-240). The consensus from these studies suggests that individuals with severe SCZ experience similar post-surgical weight reduction compared with individuals without psychiatric diagnoses. Excess weight loss, measured as the percentage above the ideal weight, has also been reported, with no considerable differences compared with control groups (238). Despite the observed weight loss benefits, concerns arise from reports of post-surgery mental state deteriorations in some cases, although other studies show minimal change. Notably, a two-year follow-up study on individuals with bipolar disorder revealed no differences in hospital admissions or outpatient service utilization between patients who underwent surgery and patients who did not (241). Overall, bariatric surgery in accordance with international obesity treatment recommendations may be suitable, but individual cases must be evaluated for post-surgical compliance, including prospective dietary modifications and the unknown influence on APA absorption (112).

4. Monitoring of metabolic risk factors

The recommendations for monitoring health risk factors in patients with SCZ involve assessing various parameters before or shortly after initiating APA treatment, as well as at regular time points thereafter. Weight changes should be monitored with regular measurements during the initial treatment phase, preferably weekly for the first 4-6 weeks and then every 2-4 weeks for the next 12 weeks. Subsequent assessments should be scheduled at 6 months and at least annually thereafter unless more frequent evaluations are necessary. Blood glucose control should be monitored using fasting or random plasma glucose measurements initially and HbA1c in the long term. Glucose control assessments should occur at 12 weeks, 6 months and annually. Lipid profile, including the total cholesterol/HDL cholesterol ratio, should be evaluated at 12 weeks, 6 months and annually. Blood pressure should also be monitored every 12 weeks, 6 months and once a year. Any modification in APA warrants a revisit of the outlined monitoring steps when appropriate. Additionally, regular inquiries regarding smoking and alcohol use are essential (112). These assessments establish a baseline and trajectory against which the impact of future therapeutic changes may be evaluated.

Digital health technologies hold promise in facilitating the monitoring of metabolic risk factors for patients with SCZ.

These technologies demonstrate potential in supporting individuals across the illness trajectory, from early identification to ongoing symptom management and vocational rehabilitation. Smartphone apps, digital phenotyping and human-supported digital tools can enhance accessibility to care and medication adherence. However, their long-term effectiveness and ethical considerations, such as data privacy and equitable access, warrant rigorous investigation to ensure responsible integration into comprehensive, person-centered care (242).

5. Conclusion

Individuals with SCZ face a considerably increased risk of MS, mediated through both shared pathophysiological mechanisms and extrinsic factors, notably the use of APA. Lifestyle interventions, focusing on optimal diet and physical activity, while also addressing smoking and alcohol overconsumption, are proposed as primary strategies. Pharmacological treatments, including metformin, GLP-1RAs, SGLT2i and TZDs have a role in regulating metabolic dysfunctions and mitigating APA-induced weight gain. Antipsychotics with a favorable metabolic profile could also be used, while aripiprazole has shown beneficial results as an adjunct treatment. Monitoring metabolic risk variables is key for guiding treatment decisions. Overall, the complexities of SCZ and MS interactions necessitate a tailored therapy strategy that addresses both psychological and metabolic components in patients with SCZ. Further research is needed to evaluate the long-term sustainability of these interventions and explore personalized approaches, particularly in pharmacogenomics, to optimize treatment in this population.

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MP conceptualized the study. AM, AG and AR wrote and prepared the original draft of the manuscript. AM, AG, VZ, DAS, ER and MP were responsible for reviewing and editing. Supervision was provided by DAS, ER and MP. Data authentication is not applicable. All authors read and approved the final manuscript.

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Not applicable.

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