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

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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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Contents

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

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-naive 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 ≥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 a1 and d, 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 to 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-β2 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 tuberinfundibular, 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-α2A 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-naive 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

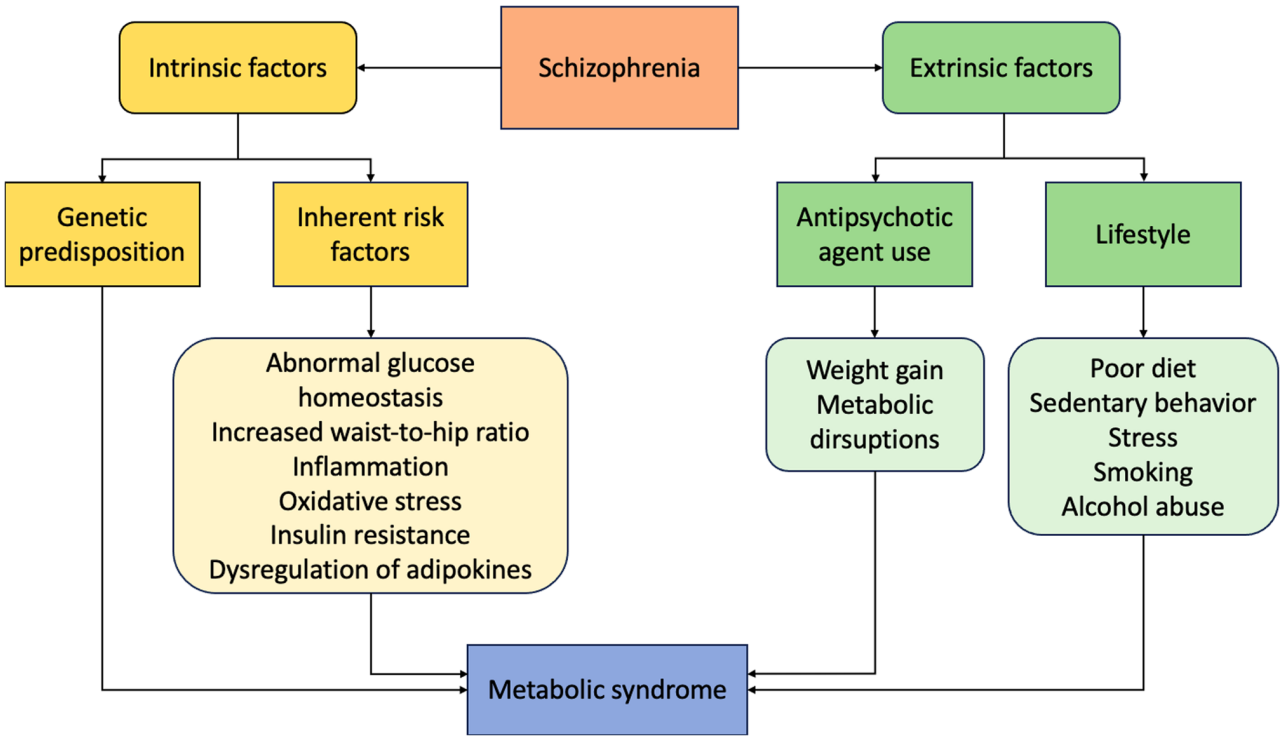

Figure 1. A summary of the underlying mechanisms linking schizophrenia and metabolic syndrome.

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/m^2 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).

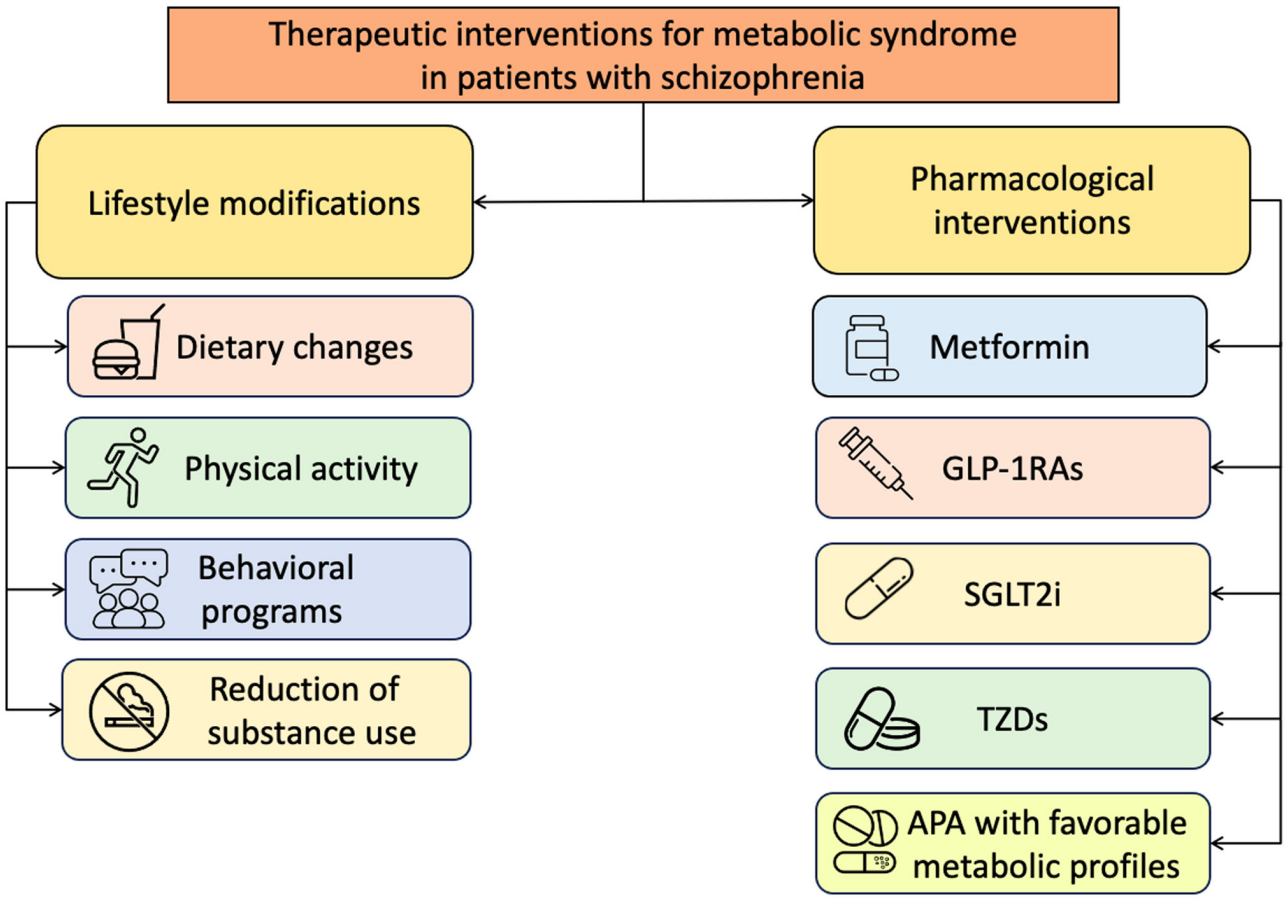

Figure 2. A summary of the main therapeutic interventions for MS in patients with schizophrenia and MS. MS, metabolic syndrome; GLP-1RAs, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose transport protein 2 inhibitor; TZDs, thiazolidinediones; APA, antipsychotic agents.

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 to 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 SGLT2i 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 SGLT2i 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 SGLT2i 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 serotoninergic 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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References

1. Orsolini L, Pompili S and Volpe U: Schizophrenia: A narrative review of etiopathogenetic, diagnostic and treatment aspects. J Clin Med 11: 5040, 2022.
2. McGrath J, Saha S, Chant D and Welham J: Schizophrenia: A concise overview of incidence, prevalence, and mortality. Epidemiol Rev 30: 67-76, 2008.
3. Brink M, Green A, Bojesen AB, Lamberti JS, Conwell Y and Andersen K: Excess medical comorbidity and mortality across the lifespan in schizophrenia. Schizophr Res 206: 347-354, 2019.
4. Penninx BWJH and Lange SMM: Metabolic syndrome in psychiatric patients: Overview, mechanisms, and implications. Dialogues Clin Neurosci 20: 63-73, 2018.
5. Nielsen RE, Banner J and Jensen SE: Cardiovascular disease in patients with severe mental illness. Nat Rev Cardiol 18: 136-145, 2021.
6. Correll CU, Solmi M, Croatto G, Schneider LK, Rohani-Montez SC, Fairley L, Smith N, Bitter I, Gorwood P, Taipale H and Tiihonen J: Mortality in people with schizophrenia: A systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry 21: 248-271, 2022.
7. Tzur Bitan D, Krieger I, Berkovitch A, Comaneshter D and Cohen A: Chronic kidney disease in adults with schizophrenia: A nationwide population-based study. Gen Hosp Psychiatry 58: 1-6, 2019.
8. Hsu YH, Cheng JS, Ouyang WC, Lin CL, Huang CT and Hsu CC: Lower incidence of end-stage renal disease but suboptimal pre-dialysis renal care in Schizophrenia: A 14-year nationwide cohort study. PLoS One 10: e0140510, 2015.
9. Kazlauskienė L, Butnorienė J and Norkus A: Metabolic syndrome related to cardiovascular events in a 10-year prospective study. Diabetol Metab Syndr 7: 102, 2015.
10. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC Jr, *et al*: Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 112: 2735-2752, 2005.
11. Saklayen MG: The global epidemic of the metabolic syndrome. Curr Hypertens Rep 20: 12, 2018.
12. Vancampfort D, Stubbs B, Mitchell AJ, De Hert M, Wampers M, Ward PB, Rosenbaum S and Correll CU: Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. World Psychiatry 14: 339-347, 2015.
13. Salari N, Maghami N, Ammari T, Mosafer H, Abdullahi R, Rasoulpoor S, Babajani F, Mahmodzadeh B and Mohammadi M: Global prevalence of metabolic syndrome in Schizophrenia patients: A systematic review and meta-analysis. J Prev (2022) 45: 973-986, 2024.
14. Vancampfort D, Wampers M, Mitchell AJ, Correll CU, De Herdt A, Probst M and De Hert M: A meta-analysis of cardio-metabolic abnormalities in drug naïve, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry 12: 240-250, 2013.
15. Sugai T, Suzuki Y, Yamazaki M, Shimoda K, Mori T, Ozeki Y, Matsuda H, Sugawara N, Yasui-Furukori N, Minami Y, *et al*: High prevalence of obesity, hypertension, hyperlipidemia, and diabetes mellitus in japanese outpatients with Schizophrenia: A nationwide survey. PLoS One 11: e0166429, 2016.
16. Carney R, Cotter J, Bradshaw T, Firth J and Yung AR: Cardiometabolic risk factors in young people at ultra-high risk for psychosis: A systematic review and meta-analysis. Schizophr Res 170: 290-300, 2016.
17. Emul M and Kalelioglu T: Etiology of cardiovascular disease in patients with schizophrenia: Current perspectives. Neuropsychiatr Dis Treat 11: 2493-2503, 2015.

18. Rouillon F and Sorbara F: Schizophrenia and diabetes: Epidemiological data. Eur Psychiatry 20 (Suppl 4): S345-S348, 2005.
19. Suvisaari J, Keinänen J, Eskelinen S and Mantere O: Diabetes and Schizophrenia. Curr Diab Rep 16: 16, 2016.
20. Peet M: Diet, diabetes and Schizophrenia: Review and hypothesis. Br J Psychiatry (Suppl 184): S102-S105, 2004.
21. Pillinger T, Beck K, Gobjila C, Donocik JG, Jauhar S and Howes OD: Impaired glucose homeostasis in first-episode Schizophrenia: A systematic review and meta-analysis. JAMA Psychiatry 74: 261-269, 2017.
22. Bora E, Akdede BB and Alptekin K: The relationship between cognitive impairment in Schizophrenia and metabolic syndrome: A systematic review and meta-analysis. Psychol Med 47: 1030-1040, 2017.
23. Grover S, R P, Sahoo S, Gopal S, Nehra R, Ganesh A, Raghavan V and Sankaranarayan A: Relationship of metabolic syndrome and neurocognitive deficits in patients with Schizophrenia. Psychiatry Res 278: 56-64, 2019.
24. Bosia M, Buonocore M, Bechi M, Santarelli L, Spangaro M, Cocchi F, Guglielmino C, Bianchi L, Bringheli S, Bosinelli F and Cavallaro R: Improving cognition to increase treatment efficacy in Schizophrenia: Effects of metabolic syndrome on cognitive remediation's outcome. Front Psychiatry 9: 647, 2018.
25. Lindenmayer JP, Khan A, Kaushik S, Thanju A, Praveen R, Hoffman L, Cherath L, Valdez G and Wance D: Relationship between metabolic syndrome and cognition in patients with schizophrenia. Schizophr Res 142: 171-176, 2012.
26. Mizuki Y, Sakamoto S, Okahisa Y, Yada Y, Hashimoto N, Takaki M and Yamada N: Mechanisms underlying the comorbidity of schizophrenia and type 2 diabetes mellitus. Int J Neuropsychopharmacol 24: 367-382, 2021.
27. Kalejahi P, Kheirouri S, Noorazar SG and Sanayei M: The relationship between brain-derived neurotrophic factor and metabolic syndrome in patients with chronic schizophrenia: A systematic review. Neuropeptides 87: 102135, 2021.
28. Rojo LE, Gaspar PA, Silva H, Risco L, Arena P, Cubillos-Robles K and Jara B: Metabolic syndrome and obesity among users of second generation antipsychotics: A global challenge for modern psychopharmacology. Pharmacol Res 101: 74-85, 2015.
29. Henderson DC, Vincenzi B, Andrea NV, Ulloa M and Copeland PM: Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. Lancet Psychiatry 2: 452-464, 2015.
30. Goldsmith DR, Rapaport MH and Miller BJ: A meta-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 21: 1696-1709, 2016.
31. Flatow J, Buckley P and Miller BJ: Meta-analysis of oxidative stress in Schizophrenia. Biol Psychiatry 74: 400-409, 2013.
32. Perry BI, Burgess S, Jones HJ, Zammit S, Upthegrove R, Mason AM, Day FR, Langenberg C, Wareham NJ, Jones PB and Khandaker GM: The potential shared role of inflammation in insulin resistance and schizophrenia: A bidirectional two-sample mendelian randomization study. PLoS Med 18: e1003455, 2021.
33. Dasgupta A, Singh OP, Rout JK, Saha T and Mandal S: Insulin resistance and metabolic profile in antipsychotic naïve schizophrenia patients. Prog Neuropsychopharmacol Biol Psychiatry 34: 1202-1207, 2010.
34. Chen S, Broqueres-You D, Yang G, Wang Z, Li Y, Wang N, Zhang X, Yang F and Tan Y: Relationship between insulin resistance, dyslipidaemia and positive symptom in Chinese antipsychotic-naive first-episode patients with schizophrenia. Psychiatry Res 210: 825-829, 2013.
35. Zhao Z, Ksiezak-Reding H, Riggio S, Haroutunian V and Pasinetti GM: Insulin receptor deficits in schizophrenia and in cellular and animal models of insulin receptor dysfunction. Schizophr Res 84: 1-14, 2006.
36. Saxena A, Patel D, Ayesha IE, Monson NR, Klair N, Patel U and Khan S: Metabolic syndrome causing cognitive impairment in patients with Schizophrenia: A systematic review. Cureus 15: e47587, 2023.
37. Baothman OA, Zamzami MA, Taher I, Abubaker J and Abu-Farha M: The role of Gut Microbiota in the development of obesity and Diabetes. Lipids Health Dis 15: 108, 2016.
38. Müller N: Inflammation in Schizophrenia: Pathogenetic aspects and therapeutic considerations. Schizophr Bull 44: 973-982, 2018.
39. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, Codagnone MG, Cussotto S, Fulling C, Golubeva AV, *et al*: The microbiota-gut-brain axis. Physiol Rev 99: 1877-2013, 2019.
40. He Y, Kosciolek T, Tang J, Zhou Y, Li Z, Ma X, Zhu Q, Yuan N, Yuan L, Li C, *et al*: Gut microbiome and magnetic resonance spectroscopy study of subjects at ultra-high risk for psychosis may support the membrane hypothesis. Eur Psychiatry 53: 37-45, 2018.
41. Misiak B, Łoniewski I, Marlicz W, Frydecka D, Szulc A, Rudzki L and Samochowiec J: The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota? Prog Neuropsychopharmacol Biol Psychiatry 102: 109951, 2020.
42. Ferentinos P, Rizos E, Douzenis A, Papadopoulou A, Christodoulou C, Peppa M and Lykouras L: Androgen insensitivity and liability to drug-induced extrapyramidal Symptoms. Gend Med 8: 156-160, 2011.
43. Tsigkaropoulou E, Peppa M, Zompola C, Rizos E, Xelioti I, Chatziioannou S, Filippopoulou A and Lykouras L: Hypogonadism due to hyperprolactinemia and subsequent first episode of psychosis. Gend Med 9: 56-60, 2012.
44. Bellivier F: Schizophrenia, antipsychotics and diabetes: Genetic aspects. Eur Psychiatry 20 (Suppl 4): S335-S339, 2005.
45. Ayalew M, Le-Niculescu H, Levey DF, Jain N, Changala B, Patel SD, Winiger E, Breier A, Shekhar A, Amdur R, *et al*: Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. Mol Psychiatry 17: 887-905, 2012.
46. Fujihara K: Beyond the γ-aminobutyric acid hypothesis of schizophrenia. Front Cell Neurosci 17: 1161608, 2023.
47. Molina JD, Avila S, Rubio G and López-Muñoz F: Metabolomic Connections between Schizophrenia, antipsychotic drugs and metabolic Syndrome: A variety of players. Curr Pharm Des 27: 4049-4061, 2021.
48. Castillo RI, Rojo LE, Henriquez-Henriquez M, Silva H, Maturana A, Villar MJ, Fuentes M and Gaspar PA: From molecules to the clinic: Linking Schizophrenia and metabolic syndrome through sphingolipids metabolism. Front Neurosci 10: 488, 2016.
49. Tsubomoto M, Kawabata R, Zhu X, Minabe Y, Chen K, Lewis DA and Hashimoto T: Expression of transcripts selective for GABA neuron subpopulations across the Cortical visuospatial working memory network in the healthy state and Schizophrenia. Cereb Cortex 29: 3540-3550, 2019.
50. Fish KN, Rocco BR, Wilson JD and Lewis DA: Laminar-Specific alterations in calbindin-positive boutons in the prefrontal cortex of subjects with Schizophrenia. Biol Psychiatry 94: 142-152, 2023.
51. Curley AA, Arion D, Volk DW, Asafu-Adjei JK, Sampson AR, Fish KN and Lewis DA: Cortical deficits of glutamic acid decarboxylase 67 expression in Schizophrenia: Clinical, protein, and cell type-specific features. Am J Psychiatry 168: 921-929, 2011.
52. Uematsu M, Hirai Y, Karube F, Ebihara S, Kato M, Abe K, Obata K, Yoshida S, Hirabayashi M, Yanagawa Y and Kawaguchi Y: Quantitative chemical composition of cortical GABAergic neurons revealed in transgenic venus-expressing rats. Cereb Cortex 18: 315-330, 2008.
53. Dienel SJ, Dowling KF, Barile Z, Bazmi HH, Liu A, Vespoli JC, Fish KN and Lewis DA: Diagnostic specificity and association with cognition of molecular alterations in prefrontal somatostatin neurons in Schizophrenia. JAMA Psychiatry 80: 1235-1245, 2023.
54. Scheper M, Sørensen FNF, Ruffolo G, Gaeta A, Lissner LJ, Anink JJ, Korshunova I, Jansen FE, Riney K, van Hecke W, *et al*: Impaired GABAergic regulation and developmental immaturity in interneurons derived from the medial ganglionic eminence in the tuberous sclerosis complex. Acta Neuropathol 147: 80, 2024.
55. Rasband MN and Macklin WB: Myelin Structure and Biochemistry. In: Basic Neurochemistry. Elsevier, pp180-199, 2012.
56. Valdés-Tovar M, Rodríguez-Ramírez AM, Rodríguez-Cárdenas L, Sotelo-Ramírez CE, Camarena B, Sanabrais-Jiménez MA, Solís-Chagoyán H, Argueta J and López-Riquelme GO: Insights into myelin dysfunction in schizophrenia and bipolar disorder. World J Psychiatry 12: 264-285, 2022.
57. Takahashi N, Sakurai T, Davis KL and Buxbaum JD: Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. Prog Neurobiol 93: 13-24, 2011.
58. Boiko AS, Mednova IA, Kornetova EG, Semke AV, Bokhan NA and Ivanova SA: Cell adhesion molecules in Schizophrenia patients with metabolic syndrome. Metabolites 13: 376, 2023.

59. Varden Gjerde K, Bartz-Johannessen C, Steen VM, Andreassen OA, Steen NE, Ueland T, Lekva T, Rettenbacher M, Joa I, Reitan SK, *et al*: Cellular adhesion molecules in drug-naïve and previously medicated patients with schizophrenia-spectrum disorders. Schizophr Res 267: 223-229, 2024.
60. Sheikh MA, O'Connell KS, Lekva T, Szabo A, Akkouh IA, Osete JR, Agartz I, Engh JA, Andreou D, Boye B, *et al*: Systemic cell adhesion molecules in severe mental Illness: Potential role of intercellular CAM-1 in linking peripheral and neuroinflammation. Biol Psychiatry 93: 187-196, 2023.
61. Vidal PP and Sans A: Vestibular System. In: The Rat Nervous System. Elsevier, pp965-996, 2004.
62. Brisch R, Saniotis A, Wolf R, Bielau H, Bernstein HG, Steiner J, Bogerts B, Braun K, Jankowski Z, Kumaratilake J, Henneberg M and Gos T: The role of dopamine in Schizophrenia from a neurobiological and evolutionary perspective: Old fashioned, but still in vogue. Front Psychiatry 5: 47, 2014.
63. Blaess S, Stott SRW and Ang SL: The generation of midbrain dopaminergic neurons. In: Patterning and Cell Type Specification in the Developing CNS and PNS. Elsevier, pp369-398, 2020.
64. Gragnoli C, Reeves GM, Reazer J and Postolache TT: Dopamine-prolactin pathway potentially contributes to the schizophrenia and type 2 diabetes comorbidity. Transl Psychiatry 6: e785, 2016.
65. Goh KK, Chen CYA, Wu TH, Chen CH and Lu ML: Crosstalk between Schizophrenia and metabolic Syndrome: The role of oxytocinergic dysfunction. Int J Mol Sci 23: 7092, 2022.
66. Yu H, Yan H, Li J, Li Z, Zhang X, Ma Y, Mei L, Liu C, Cai L, Wang Q, *et al*: Common variants on 2p16.1, 6p22.1 and 10q24.32 are associated with schizophrenia in Han Chinese population. Mol Psychiatry 22: 954-960, 2017.
67. Zhang P, Bian Y, Liu N, Tang Y, Pan C, Hu Y and Tang Z: The SNP rs1625579 in miR-137 gene and risk of schizophrenia in Chinese population: A meta-analysis. Compr Psychiatry 67: 26-32, 2016.
68. Boiko AS, Pozhidaev IV, Paderina DZ, Mednova IA, Goncharova AA, Fedorenko OY, Kornetova EG, Semke AV, Bokhan NA, Loonen AJM and Ivanova SA: Gene polymorphisms of hormonal regulators of metabolism in patients with Schizophrenia with metabolic syndrome. Genes (Basel) 13: 844, 2022.
69. Brandl EJ, Frydrychowicz C, Tiwari AK, Lett TA, Kitzrow W, Büttner S, Ehrlich S, Meltzer HY, Lieberman JA, Kennedy JL, *et al*: Association study of polymorphisms in leptin and leptin receptor genes with antipsychotic-induced body weight gain. Prog Neuropsychopharmacol Biol Psychiatry 38: 134-141, 2012.
70. Mulder H, Franke B, van der-Beek van der AA, Arends J, Wilmink FW, Scheffer H and Egberts AC: The association between HTR2C gene polymorphisms and the metabolic syndrome in patients with Schizophrenia. J Clin Psychopharmacol 27: 338-343, 2007.
71. Chen J, Wu J, Mize T, Shui D and Chen X: Prediction of Schizophrenia diagnosis by integration of genetically correlated conditions and traits. J Neuroimmune Pharmacol 13: 532-540, 2018.
72. Chen Y, Wang Y, Fang X, Zhang Y, Song L and Zhang C: Association of the HTR2C-759C/T polymorphism and antipsychotic-induced weight gain: A meta-analysis. Gen Psychiatr 33: e100192, 2020.
73. Sicard MN, Zai CC, Tiwari AK, Souza RP, Meltzer HY, Lieberman JA, Kennedy JL and Müller DJ: Polymorphisms of the HTR2C gene and antipsychotic-induced weight gain: An update and meta-analysis. Pharmacogenomics 11: 1561-1571, 2010.
74. Brummett BH, Babyak MA, Singh A, Hauser ER, Jiang R, Huffman KM, Kraus WE, Shah SH, Siegler IC and Williams RB: Lack of association of a functional polymorphism in the serotonin receptor gene with body mass index and depressive symptoms in a large meta-analysis of population based studies. Front Genet 9: 423, 2018.
75. Sneller MH, de Boer N, Everaars S, Schuurmans M, Guloksuz S, Cahn W and Luykx JJ: Clinical, biochemical and genetic variables associated with metabolic syndrome in patients with Schizophrenia spectrum disorders using second-generation antipsychotics: A systematic review. Front Psychiatry 12: 625935, 2021.
76. Shams TA and Müller DJ: Antipsychotic induced weight gain: Genetics, epigenetics, and biomarkers reviewed. Curr Psychiatry Rep 16: 473, 2014.
77. Wallace TJ, Zai CC, Brandl EJ and Müller DJ: Role of 5-HT(2C) receptor gene variants in antipsychotic-induced weight gain. Pharmgenomics Pers Med 4: 83-93, 2011.
78. Bah J, Westberg L, Baghaei F, Henningsson S, Rosmond R, Melke J, Holm G and Eriksson E: Further exploration of the possible influence of polymorphisms in HTR2C and 5HTT on body weight. Metabolism 59: 1156-1163, 2010.
79. Klerk M, Verhoef P, Clarke R, Blom HJ, Kok FJ and Schouten EG; MTHFR Studies Collaboration Group: MTHFR 677C→T polymorphism and risk of coronary heart disease: A mata analysis. JAMA 288: 2023-2031, 2002.
80. Lu ML, Ku WC, Syifa N, Hu SC, Chou CT, Wu YH, Kuo PH, Chen CH, Chen WJ and Wu TH: Developing a sensitive platform to measure 5-methyltetrahydrofolate in subjects with MTHFR and PON1 gene polymorphisms. Nutrients 14: 3320, 2022.
81. van Winkel R, Rutten BP, Peerbooms O, Peuskens J, van Os J and De Hert M: MTHFR and risk of metabolic syndrome in patients with Schizophrenia. Schizophr Res 121: 193-198, 2010.
82. Roffeei SN, Reynolds GP, Zainal NZ, Said MA, Hatim A, Aida SA and Mohamed Z: Association of ADRA2A and MTHFR gene polymorphisms with weight loss following antipsychotic switching to aripiprazole or ziprasidone. Hum Psychopharmacol 29: 38-45, 2014.
83. Roffeei SN, Mohamed Z, Reynolds GP, Said MA, Hatim A, Mohamed EH, Aida SA and Zainal NZ: Association of FTO, LEPR and MTHFR gene polymorphisms with metabolic syndrome in Schizophrenia patients receiving antipsychotics. Pharmacogenomics 15: 477-485, 2014.
84. Bathina S and Das UN: Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci 6: 1164-1178, 2015.
85. Priya I, Sharma S, Sharma I, Mahajan R and Kapoor N: A review of potential candidate genes polymorphism responsible for schiz-ophrenia risk. Int J Sci Res Biol Sci 5: 186-195, 2019.
86. Ping J, Zhang J, Wan J, Huang C, Luo J, Du B and Jiang T: A polymorphism in the BDNF Gene (rs11030101) is associated with negative symptoms in Chinese Han patients with Schizophrenia. Front Genet 13: 849227, 2022.
87. Fu X, Wang J, Du J, Sun J, Baranova A and Zhang F: BDNF Gene's Role in Schizophrenia: From risk allele to methylation implications. Front Psychiatry 11: 564277, 2020.
88. Vajagathali M and Ramakrishnan V: Genetic predisposition of BDNF (rs6265) gene is susceptible to Schizophrenia: A prospective study and updated meta-analysis. Neurología (Engl Ed) 39: 361-371, 2024.
89. Ehrhart F, Silva A, Amelsvoort TV, von Scheibler E, Evelo C and Linden DEJ: Copy number variant risk loci for schizophrenia converge on the BDNF pathway. World J Biol Psychiatry 25: 222-232, 2024.
90. Bednarova A, Habalova V, Krivosova M, Marcatili M and Tkac I: Association study of BDNF, SLC6A4, and FTO genetic variants with Schizophrenia spectrum disorders. J Pers Med 13: 658, 2023.
91. Czerwensky F, Leucht S and Steimer W: Association of the common MC4R rs17782313 polymorphism with antipsychotic-related weight gain. J Clin Psychopharmacol 33: 74-79, 2013.
92. Heald A, Pendlebury J, Anderson S, Narayan V, Guy M, Gibson M, Haddad P and Livingston M: Lifestyle factors and the metabolic syndrome in Schizophrenia: A cross-sectional study. Ann Gen Psychiatry 16: 12, 2017.
93. Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P and Mondelli V: The dietary pattern of patients with schizophrenia: A systematic review. J Psychiatr Res 47: 197-207, 2013.
94. Amani R: Is dietary pattern of schizophrenia patients different from healthy subjects? BMC Psychiatry 7: 15, 2007.
95. Aucoin M, LaChance L, Cooley K and Kidd S: Diet and psychosis: A scoping review. Neuropsychobiology 79: 20-42, 2020.
96. Kelly C and McCreadie R: Cigarette smoking and schizophrenia. Adv Psychiatr Treat 6: 327-331, 2000.
97. Myles N, Newall HD, Curtis J, Nielssen O, Shiers D and Large M: Tobacco use before, at, and after first-episode psychosis: A systematic meta-analysis. J Clin Psychiatry 73: 468-475, 2012.
98. Breese CR, Lee MJ, Adams CE, Sullivan B, Logel J, Gillen KM, Marks MJ, Collins AC and Leonard S: Abnormal regulation of high affinity nicotinic receptors in subjects with Schizophrenia. Neuropsychopharmacology 23: 351-364, 2000.
99. Koskinen J, Löhönen J, Koponen H, Isohanni M and Miettunen J: Prevalence of alcohol use disorders in schizophrenia-a systematic review and meta-analysis. Acta Psychiatr Scand 120: 85-96, 2009.

100. Fatma F, Baati I, Omri S, Sallemi R and Masmoudi J: Medication adherence in schizophrenia. Eur Psychiatry 33: S586-S586, 2016.
101. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW and Haddad PM: Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res 176: 109-113, 2010.
102. Mitchell AJ, Vancampfort D, De Herdt A, Yu W and De Hert M: Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early Schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. Schizophr Bull 39: 295-305, 2013.
103. Szmulewicz AG, Angriman F, Pedroso FE, Vazquez C and Martino DJ: Long-Term antipsychotic use and major cardiovascular events: A Retrospective Cohort Study. J Clin Psychiatry 78: e905-e912, 2017.
104. Foley DL and Morley KI: Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch Gen Psychiatry 68: 609-616, 2011.
105. Templeman LA, Reynolds GP, Arranz B and San L: Polymorphisms of the 5-HT2C receptor and leptin genes are associated with antipsychotic drug-induced weight gain in Caucasian subjects with a first-episode psychosis. Pharmacogenet Genomics 15: 195-200, 2005.
106. Zhang ZJ, Yao ZJ, Liu W, Fang Q and Reynolds GP: Effects of antipsychotics on fat deposition and changes in leptin and insulin levels. Br J Psychiatry 184: 58-62, 2004.
107. Faulkner G, Cohn T, Remington G and Irving H: Body mass index, waist circumference and quality of life in individuals with schizophrenia☆. Schizophr Res 90: 174-178, 2007.
108. Lester H, Marshall M, Jones P, Fowler D, Amos T, Khan N and Birchwood M: Views of young people in early intervention services for first-episode psychosis in England. Psychiatr Serv 62: 882-887, 2011.
109. Weiden PJ, Mackell JA and McDonnell DD: Obesity as a risk factor for antipsychotic noncompliance. Schizophr Res 66: 51-57, 2004.
110. Chang SC, Goh KK and Lu ML: Metabolic disturbances associated with antipsychotic drug treatment in patients with schizophrenia: State-of-the-art and future perspectives. World J Psychiatry 11: 696-710, 2021.
111. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, *et al*: Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: A multiple-treatments meta-analysis. Lancet 382: 951-962, 2013.
112. Cooper SJ, Reynolds GP; With expert co-authors (in alphabetical order):;Barnes T, England E, Haddad PM, Heald A, Holt R, Lingford-Hughes A, Osborn D, *et al*: BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. J Psychopharmacol 30: 717-748, 2016.
113. Fonseka TM, Müller DJ and Kennedy SH: Inflammatory cytokines and antipsychotic-induced weight gain: Review and clinical implications. Mol Neuropsychiatry 2: 1-14, 2016.
114. Newcomer JW: Antipsychotic medications: Metabolic and cardiovascular risk. J Clin Psychiatry 68 (Suppl 4): 8-13, 2007.
115. Newcomer JW: Second-generation (atypical) antipsychotics and metabolic effects: A comprehensive literature review. CNS Drugs 19 (Suppl 1): S1-S93, 2005.
116. Ballon JS, Pajvani U, Freyberg Z, Leibel RL and Lieberman JA: Molecular pathophysiology of metabolic effects of antipsychotic medications. Trends Endocrinol Metab 25: 593-600, 2014.
117. Carli M, Kolachalam S, Longoni B, Pintaudi A, Baldini M, Aringhieri S, Fasciani I, Annibale P, Maggio R and Scarselli M: Atypical antipsychotics and metabolic syndrome: From molecular mechanisms to clinical differences. Pharmaceuticals (Basel) 14: 238, 2021.
118. Siafis S, Tzachanis D, Samara M and Papazisis G: Antipsychotic drugs: From receptor-binding profiles to metabolic side effects. Curr Neuropharmacol 16: 1210-1223, 2018.
119. Grajales D, Ferreira V and Valverde ÁM: Second-Generation antipsychotics and dysregulation of glucose metabolism: Beyond weight gain. Cells 8: 1336, 2019.
120. Lis M, Stańczykiewicz B, Liśkiewicz P and Misiak B: Impaired hormonal regulation of appetite in schizophrenia: A narrative review dissecting intrinsic mechanisms and the effects of antipsychotics. Psychoneuroendocrinology 119: 104744, 2020.
121. Popovic V, Doknic M, Maric N, Pekic S, Damjanovic A, Miljic D, Popovic S, Miljic N, Djurovic M, Jasovic-Gasic M, *et al*: Changes in neuroendocrine and metabolic hormones induced by atypical antipsychotics in normal-weight patients with Schizophrenia. Neuroendocrinology 85: 249-256, 2007.
122. Venkatasubramanian G, Chittiprol S, Neelakantachar N, Shetty T and Gangadhar BN: Effect of antipsychotic treatment on Insulin-like Growth Factor-1 and cortisol in schizophrenia: A longitudinal study. Schizophr Res 119: 131-137, 2010.
123. Smith GC, Zhang ZY, Mulvey T, Petersen N, Lach S, Xiu P, Phillips A, Han W, Wang MW and Shepherd PR: Clozapine directly increases insulin and glucagon secretion from islets: Implications for impairment of glucose tolerance. Schizophr Res 157: 128-133, 2014.
124. Ebdrup BH, Knop FK, Madsen A, Mortensen HB, Søgaard B, Holst JJ, Szecsi PB and Lublin H: Glucometabolic hormones and cardiovascular risk markers in antipsychotic-treated patients. J Clin Psychiatry 75: e899-e905, 2014.
125. Klemettilä JP, Solismaa A, Seppälä N, Hämäläinen M, Moilanen E, Leinonen E and Kampman O: Glucagon-like peptide-1 serum levels are associated with weight gain in patients treated with clozapine. Psychiatry Res 306: 114227, 2021.
126. Basoglu C, Oner O, Ates AM, Algul A, Semiz UB, Ebrinc S, Cetin M, Ozcan O and Ipcioglu OM: Association between symptom improvement and change of body mass index, lipid profile, and leptin, ghrelin, and cholecystokinin levels during 6-week olanzapine treatment in patients with first-episode psychosis. J Clin Psychopharmacol 30: 636-638, 2010.
127. van der Zwaal EM, Merkestein M, Lam YK, Brans MA, Luijendijk MC, Bok LI, Verheij ER, la Fleur SE and Adan RA: The acute effects of olanzapine on ghrelin secretion, CCK sensitivity, meal size, locomotor activity and body temperature. Int J Obes (Lond) 36: 254-261, 2012.
128. Wu TH, Chiu CC, Goh KK, Chen PY, Huang MC, Chen CH and Lu ML: Relationship between metabolic syndrome and acylated/desacylated ghrelin ratio in patients with schizophrenia under olanzapine medication. J Psychopharmacol 34: 86-92, 2020.
129. Zhang Q, Deng C and Huang XF: The role of ghrelin signalling in second-generation antipsychotic-induced weight gain. Psychoneuroendocrinology 38: 2423-2438, 2013.
130. Goetz RL and Miller BJ: Meta-analysis of ghrelin alterations in schizophrenia: Effects of olanzapine. Schizophr Res 206: 21-26, 2019.
131. Bartoli F, Lax A, Crocamo C, Clerici M and Carrà G: Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: A meta-analysis. Psychoneuroendocrinology 56: 179-189, 2015.
132. Kelesidis T, Kelesidis I, Sharon C and Mantzoros SC: Narrative review: The role of leptin in human physiology: Emerging clinical applications. Ann Intern Med 152: 93-100, 2010.
133. Petrikis P, Karampas A, Leondaritis G, Markozannes G, Archimandriti DT, Spyrou P, Georgiou G, Skapinakis P and Voulgari PV: Adiponectin, leptin and resistin levels in first-episode, drug-naïve patients with psychosis before and after short-term antipsychotic treatment. J Psychosom Res 157: 110789, 2022.
134. Obradovic M, Sudar-Milovanovic E, Soskic S, Essack M, Arya S, Stewart AJ, Gojobori T and Isenovic ER: Leptin and obesity: Role and clinical implication. Front Endocrinol (Lausanne) 12: 585887, 2021.
135. Chen PY, Chang CK, Chen CH, Fang SC, Mondelli V, Chiu CC, Lu ML, Hwang LL and Huang MC: Orexin-a elevation in antipsychotic-treated compared to drug-free patients with schizophrenia: A medication effect independent of metabolic syndrome. J Formos Med Assoc 121: 2172-2181, 2022.
136. Basoglu C, Oner O, Gunes C, Semiz UB, Ates AM, Algul A, Ebrinc S, Cetin M, Ozcan O and Ipcioglu O: Plasma orexin A, ghrelin, cholecystokinin, visfatin, leptin and agouti-related protein levels during 6-week olanzapine treatment in first-episode male patients with psychosis. Int Clin Psychopharmacol 25: 165-171, 2010.
137. Zhu Y, Zhang C, Siafis S, Zhuo K, Zhu D, Wu H, Liu D, Jiang K, Wang J, Leucht S and Li C: Prolactin levels influenced by antipsychotic drugs in schizophrenia: A systematic review and network meta-analysis. Schizophr Res 237: 20-25, 2021.
138. Srisawat U, Reynolds GP, Zhang ZJ, Zhang XR, Arranz B, San L and Dalton CF: Methylenetetrahydrofolate reductase (MTHFR) 677C/T polymorphism is associated with antipsychotic-induced weight gain in first-episode schizophrenia. Int J Neuropsychopharmacol 17: 485-490, 2014.

139. Ellingrod VL, Miller DD, Taylor SF, Moline J, Holman T and Kerr J: Metabolic syndrome and insulin resistance in schizophrenia patients receiving antipsychotics genotyped for the methylenetetrahydrofolate reductase (MTHFR) 677C/T and 1298A/C variants. Schizophr Res 98: 47-54, 2008.
140. Cojocaru A, Braha A, Jeleriu R, Andreescu NI, Puiu M, Ageu L, Folescu R, Zamfir CL and Nussbaum LA: The implications of cytochrome P450 2D6/CYP2D6 polymorphism in the therapeutic response of atypical antipsychotics in adolescents with psychosis-A prospective study. Biomedicines 12: 494, 2024.
141. Bertilsson L, Dahl M, Dalén P and Al-Shurbaji A: Molecular genetics of CYP2D6: Clinical relevance with focus on psychotropic drugs. Br J Clin Pharmacol 53: 111-122, 2002.
142. Wannasuphoprasit Y, Andersen SE, Arranz MJ, Catalan R, Jurgens G, Kloosterboer SM, Rasmussen HB, Bhat A, Irizar H, Koller D, *et al*: CYP2D6 genetic variation and antipsychotic-induced weight gain: A systematic review and meta-analysis. Front Psychol 12: 768748, 2022.
143. Jürgens G, Kaas-Hansen BS, Nordentoft M, Werge T and Andersen SE: Is the CYP2D6 genotype associated with antipsychotic-induced weight gain? J Pers Med 12: 1728, 2022.
144. Austin-Zimmerman I, Wronska M, Wang B, Irizar H, Thygesen JH, Bhat A, Denaxas S, Fatemifar G, Finan C, Harju-Seppänen J, *et al*: The Influence of CYP2D6 and CYP2C19 genetic variation on diabetes mellitus risk in people taking antidepressants and antipsychotics. Genes (Basel) 12: 1758, 2021.
145. Melkersson KI, Scordo MG, Gunes A and Dahl ML: Impact of CYP1A2 and CYP2D6 Polymorphisms on drug metabolism and on insulin and lipid elevations and insulin resistance in clozapine-treated patients. J Clin Psychiatry 68: 697-704, 2007.
146. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Thibaut F and Möller HJ; WFSBP Task force on Treatment Guidelines for Schizophrenia: World federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of Schizophrenia, Part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry 14: 2-44, 2013.
147. Dombrowski SU, Avenell A and Sniehott FF: Behavioural interventions for obese adults with additional risk factors for morbidity: Systematic review of effects on behaviour, weight and disease risk factors. Obes Facts 3: 377-396, 2010.
148. Bruins J, Jörg F, Bruggeman R, Slooff C, Corpeleijn E and Pijnenborg M: The effects of lifestyle interventions on (Long-Term) weight management, cardiometabolic risk and depressive symptoms in people with psychotic disorders: A meta-analysis. PLoS One 9: e112276, 2014.
149. Caemmerer J, Correll CU and Maayan L: Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: A meta-analytic comparison of randomized controlled trials. Schizophr Res 140: 159-168, 2012.
150. Bartels SJ, Pratt SI, Aschbrenner KA, Barre LK, Naslund JA, Wolfe R, Xie H, McHugo GJ, Jimenez DE, Jue K, *et al*: Pragmatic replication trial of health promotion coaching for obesity in serious mental illness and maintenance of outcomes. Am J Psychiatry 172: 344-352, 2015.
151. Daumit GL, Goldberg RW, Anthony C, Dickerson F, Brown CH, Kreyenbuhl J, Wohlheiter K and Dixon LB: Physical activity patterns in adults with severe mental illness. J Nerv Ment Dis 193: 641-646, 2005.
152. Cristiano VB, Szortyka MF and Belmonte-de-Abreu P: A controlled open clinical trial of the positive effect of a physical intervention on quality of life in schizophrenia. Front Psychiatry 14: 1066541, 2023.
153. Álvarez-Jiménez M, González-Blanch C, Vázquez-Barquero JL, Pérez-Iglesias R, Martínez-García O, Pérez-Pardal T, Ramírez-Bonilla ML and Crespo-Facorro B: Attenuation of antipsychotic-induced weight gain with early behavioral intervention in drug-naive first-episode psychosis patients: A randomized controlled trial. J Clin Psychiatry 67: 1253-1260, 2006.
154. Curtis J, Watkins A, Rosenbaum S, Teasdale S, Kalucy M, Samaras K and Ward PB: Evaluating an individualized lifestyle and life skills intervention to prevent antipsychotic-induced weight gain in first-episode psychosis. Early Interv Psychiatry 10: 267-276, 2016.
155. Tang M, Zhao T, Liu T, Dang R, Cai H and Wang Y: Nutrition and schizophrenia: Associations worthy of continued revaluation. Nutr Neurosci 27: 528-546, 2024.
156. Adamowicz K, Mazur A, Mak M, Samochowiec J and Kucharska-Mazur J: Metabolic syndrome and cognitive functions in schizophrenia-implementation of dietary intervention. Front Psychiatry 11: 359, 2020.
157. Włodarczyk A, Wiglusz MS and Cubała WJ: Ketogenic diet for schizophrenia: Nutritional approach to antipsychotic treatment. Med Hypotheses 118: 74-77, 2018.
158. Hassan N, Dumlao N, Tran K and Zamiri A: Improving quality of life with nutritional supplementation in Schizophrenia: A literature review. Eur Psychiatry 65 (Suppl 1): S595, 2022.
159. Fernández-Abascal B, Suarez-Pinilla M, Cobo-Corrales C, Crespo-Facorro B and Suárez-Pinilla P: Lifestyle intervention on psychotherapy and exercise and their effect on physical and psychological health in outpatients with schizophrenia spectrum disorders. A pragmatic clinical trial. Eur Psychiatry 65 (Suppl 1): S130-S131, 2022.
160. Agarwal SM, Panda R, Costa-Dookhan KA, MacKenzie NE, Treen QC, Caravaggio F, Hashim E, Leung G, Kirpalani A, Matheson K, *et al*: Metformin for early comorbid glucose dysregulation and schizophrenia spectrum disorders: A pilot double-blind randomized clinical trial. Transl Psychiatry 11: 219, 2021.
161. Jarskog LF, Hamer RM, Catellier DJ, Stewart DD, Lavange L, Ray N, Golden LH, Lieberman JA and Stroup TS; METS Investigators: Metformin for weight loss and metabolic control in overweight outpatients with schizophrenia and schizoaffective disorder. Am J Psychiatry 170: 1032-1040, 2013.
162. de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N and Hanwella R: Metformin in prevention and treatment of antipsychotic induced weight gain: A systematic review and meta-analysis. BMC Psychiatry 16: 341, 2016.
163. Wu RR, Zhang FY, Gao KM, Ou JJ, Shao P, Jin H, Guo WB, Chan PK and Zhao JP: Metformin treatment of antipsychotic-induced dyslipidemia: An analysis of two randomized, placebo-controlled trials. Mol Psychiatry 21: 1537-1544, 2016.
164. Battini V, Cirnigliaro G, Leuzzi R, Rissotto E, Mosini G, Benatti B, Pozzi M, Nobile M, Radice S, Carnovale C, *et al*: The potential effect of metformin on cognitive and other symptom dimensions in patients with schizophrenia and antipsychotic-induced weight gain: A systematic review, meta-analysis, and meta-regression. Front Psychiatry 14: 1215807, 2023.
165. Rena G, Hardie DG and Pearson ER: The mechanisms of action of metformin. Diabetologia 60: 1577-1585, 2017.
166. Bu Y, Peng M, Tang X, Xu X, Wu Y, Chen AF and Yang X: Protective effects of metformin in various cardiovascular diseases: Clinical evidence and AMPK-dependent mechanisms. J Cell Mol Med 26: 4886-4903, 2022.
167. Shah M and Vella A: Effects of GLP-1 on appetite and weight. Rev Endocr Metab Disord 15: 181-187, 2014.
168. Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, Fritsche A, Gribble F, Grill HJ, Habener JF, *et al*: Glucagon-like peptide 1 (GLP-1). Mol Metab 30: 72-130, 2019.
169. Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, Lam CSP, Lopes RD, McMurray JJV, Pratley RE, *et al*: Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: A systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 9: 653-662, 2021.
170. Medak KD, Shamshoum H, Peppler WT and Wright DC: GLP1 receptor agonism protects against acute olanzapine-induced hyperglycemia. Am J Physiol Endocrinol Metab 319: E1101-E1111, 2020.
171. Larsen JR, Vedtofte L, Jakobsen MSL, Jespersen HR, Jakobsen MI, Svensson CK, Koyuncu K, Schjerning O, Oturai PS, Kjaer A, *et al*: Effect of liraglutide treatment on prediabetes and overweight or obesity in clozapine- or olanzapine-treated patients with schizophrenia spectrum disorder. JAMA Psychiatry 74: 719-728, 2017.
172. Siskind DJ, Russell AW, Gamble C, Winckel K, Mayfield K, Hollingworth S, Hickman I, Siskind V and Kisely S: Treatment of clozapine-associated obesity and diabetes with exenatide in adults with schizophrenia: A randomized controlled trial (CODEX). Diabetes Obes Metab 20: 1050-1055, 2018.
173. Babic I, Gorak A, Engel M, Sellers D, Else P, Osborne AL, Pai N, Huang XF, Nealon J and Weston-Green K: Liraglutide prevents metabolic side-effects and improves recognition and working memory during antipsychotic treatment in rats. J Psychopharmacol 32: 578-590, 2018.

174. Lykkegaard K, Larsen PJ, Vrang N, Bock C, Bock T and Knudsen LB: The once-daily human GLP-1 analog, liraglutide, reduces olanzapine-induced weight gain and glucose intolerance. Schizophr Res 103: 94-103, 2008.
175. Whicher CA, Price HC, Phiri P, Rathod S, Barnard-Kelly K, Ngianga K, Thorne K, Asher C, Peveler RC, McCarthy J and Holt RIG: The use of liraglutide 3.0 mg daily in the management of overweight and obesity in people with schizophrenia, schizoaffective disorder and first episode psychosis: Results of a pilot randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab 23: 1262-1271, 2021.
176. Perlis LT, Lamberti JS and Miedlich SU: Glucagon-like peptide analogs are superior for diabetes and weight control in patients on antipsychotic medications. Prim Care Companion CNS Disord 22: 19m02504, 2020.
177. Lee SE, Lee NY, Kim SH, Kim KA and Kim YS: Effect of liraglutide 3.0mg treatment on weight reduction in obese antipsychotic-treated patients. Psychiatry Res 299: 113830, 2021.
178. Siskind D, Russell A, Gamble C, Baker A, Cosgrove P, Burton L and Kisely S: Metabolic measures 12 months after a randomised controlled trial of treatment of clozapine associated obesity and diabetes with exenatide (CODEX). J Psychiatr Res 124: 9-12, 2020.
179. Khaity A, Mostafa Al-dardery N, Albakri K, Abdelwahab OA, Hefnawy MT, Yousef YAS, Taha RE, Swed S, Hafez W, Hurlemann R and Elsayed MEG: Glucagon-like peptide-1 receptor-agonists treatment for cardio-metabolic parameters in schizophrenia patients: A systematic review and meta-analysis. Front Psychiatry 14: 1153648, 2023.
180. Ishøy PL, Knop FK, Vilsbøll T, Glenthøj BY and Ebdrup BH: Sustained weight loss after treatment with a glucagon-like peptide-1 receptor agonist in an obese patient with schizophrenia and type 2 diabetes. Am J Psychiatry 170: 681-682, 2013.
181. Siskind D, Wysoczanski D, Russell A and Ashford M: Weight loss associated with exenatide in an obese man with diabetes commenced on clozapine. Aust N Z J Psychiatry 50: 702-703, 2016.
182. Mayfield K, Siskind D, Winckel K, Russell AW, Kisely S, Smith G and Hollingworth S: Glucagon-like peptide-1 agonists combating clozapine-associated obesity and diabetes. J Psychopharmacol 30: 227-236, 2016.
183. del Olmo-Garcia MI and Merino-Torres JF: GLP-1 receptor agonists and cardiovascular disease in patients with type 2 diabetes. J Diabetes Res 2018: 4020492, 2018.
184. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M and Drucker DJ: Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation 136: 849-870, 2017.
185. Pelle MC, Zaffina I, Giofrè F, Pujia R and Arturi F: Potential role of glucagon-like peptide-1 receptor agonists in the treatment of cognitive decline and dementia in diabetes mellitus. Int J Mol Sci 24: 11301, 2023.
186. Lewitt MS and Boyd GW: Role of the insulin-like growth factor system in neurodegenerative disease. Int J Mol Sci 25: 4512, 2024.
187. Yaribeygi H, Rashidy-Pour A, Atkin SL, Jamialahmadi T and Sahebkar A: GLP-1 mimetics and cognition. Life Sci 264: 118645, 2021.
188. Flintoff J, Kesby JP, Siskind D and Burne TH: Treating cognitive impairment in schizophrenia with GLP-1RAs: An overview of their therapeutic potential. Expert Opin Investig Drugs 30: 877-891, 2021.
189. Svensson CK, Larsen JR, Vedtofte L, Jakobsen MSL, Jespersen HR, Jakobsen MI, Koyuncu K, Schjerning O, Nielsen J, Ekstrøm CT, *et al*: One-year follow-up on liraglutide treatment for prediabetes and overweight/obesity in clozapine- or olanzapine-treated patients. Acta Psychiatr Scand 139: 26-36, 2019.
190. Ganeshalingam AA, Uhrenholt NG, Arnfred S, Gæde PH, Bilenberg N and Frystyk J: home-based intervention with semaglutide treatment of neuroleptic-related prediabetes (HISTORI): Protocol describing a prospective, randomised, placebo controlled and double-blinded multicentre trial. BMJ Open 14: e077173, 2024.
191. Siskind D, Baker A, Russell A, Warren N, Robinson G, Parker S, Medland S, Kisely S, Hager T and Arnautovska U: Effects of semaglutide on body weight in clozapine-treated people with schizophrenia and obesity: Study protocol for a placebo-controlled, randomised multicentre trial (COaST). BJPsych Open 9: e136, 2023.
192. Sass MR, Danielsen AA, Köhler-Forsberg O, Storgaard H, Knop FK, Nielsen MØ, Sjödin AM, Mors O, Correll CU, Ekstrøm C, *et al*: Effect of the GLP-1 receptor agonist semaglutide on metabolic disturbances in clozapine-treated or olanzapine-treated patients with a schizophrenia spectrum disorder: Study protocol of a placebo-controlled, randomised clinical trial (SemaPsychiatry). BMJ Open 13: e068652, 2023.
193. Chao EC: SGLT-2 inhibitors: A new mechanism for glycemic control. Clin Diabetes 32: 4-11, 2014.
194. Salvatore T, Galiero R, Caturano A, Rinaldi L, Di Martino A, Albanese G, Di Salvo J, Epifani R, Marfella R, Docimo G, *et al*: An overview of the cardiorenal protective mechanisms of SGLT2 inhibitors. Int J Mol Sci 23: 3651, 2022.
195. Vasiliu O: Impact of SGLT2 inhibitors on metabolic status in patients with psychiatric disorders undergoing treatment with second-generation antipsychotics (Review). Exp Ther Med 25: 125, 2023.
196. Ashraf GM, Alghamdi BS, Alshehri FS, Alam MZ, Tayeb HO and Tarazi FI: Empagliflozin effectively attenuates olanzapine-induced body weight gain in female wistar rats. Front Pharmacol 12: 578716, 2021.
197. Cernea S, Dima L, Correll CU and Manu P: Pharmacological management of glucose dysregulation in patients treated with second-generation antipsychotics. Drugs 80: 1763-1781, 2020.
198. Lally J, O' Loughlin A, Stubbs B, Guerandel A, O'Shea D and Gaughran F: Pharmacological management of diabetes in severe mental illness: A comprehensive clinical review of efficacy, safety and tolerability. Expert Rev Clin Pharmacol 11: 411-424, 2018.
199. Barbosa M and Fernandes V: Rapid-onset clozapine-induced hyperglycaemia: pathways of glycaemic dysregulation. BMJ Case Rep 14: e243938, 2021.
200. National Library of Medicine: Empagliflozin Addition in Modulating Metabolic Disturbances Associated With Olanzapine in Schizophrenia Patients. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT05669742. Accessed October 5, 2024.
201. Cochrane Central Register of Controlled Trials: Effect of Sodium Glucose Co-transporter 2 (SGLT2) inhibitor on reducing atypical antipsychotics-induced weight gain in schizophrenia spectrum disorder - A Randomized Controlled Trial. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02750108/full?highlightAbstract=inhibitors%7Cschizophreni%7Cschizophrenia%7Cinhibitor%7C*sglt2. Accessed October 5, 2024.
202. Quinn CE, Hamilton PK, Lockhart CJ and McVeigh GE: Thiazolidinediones: Effects on insulin resistance and the cardiovascular system. Br J Pharmacol 153: 636-645, 2008.
203. Smith RC, Jin H, Li C, Bark N, Shekhar A, Dwivedi S, Mortiere C, Lohr J, Hu Q and Davis JM: Effects of pioglitazone on metabolic abnormalities, psychopathology, and cognitive function in schizophrenic patients treated with antipsychotic medication: A randomized double-blind study. Schizophr Res 143: 18-24, 2013.
204. Edlinger M, Ebenbichler C, Rettenbacher M and Fleischhacker WW: Treatment of antipsychotic-associated hyperglycemia with pioglitazone. J Clin Psychopharmacol 27: 403-404, 2007.
205. Iranpour N, Zandifar A, Farokhnia M, Goguol A, Yekehtaz H, Khodaie-Ardakani MR, Salehi B, Esalatmanesh S, Zeionoddini A, Mohammadinejad P, *et al*: The effects of pioglitazone adjuvant therapy on negative symptoms of patients with chronic schizophrenia: A double-blind and placebo-controlled trial. Hum Psychopharmacol 31: 103-112, 2016.
206. Yi Z, Fan X, Wang J, Liu D, Freudenreich O, Goff D and Henderson DC: Rosiglitazone and cognitive function in clozapine-treated patients with schizophrenia: A pilot study. Psychiatry Res 200: 79-82, 2012.
207. Henderson DC, Fan X, Sharma B, Copeland PM, Borba CP, Boxill R, Freudenreich O, Cather C, Eden Evins A and Goff DC: A double-blind, placebo-controlled trial of rosiglitazone for clozapine-induced glucose metabolism impairment in patients with Schizophrenia. Acta Psychiatr Scand 119: 457-465, 2009.
208. Baptista T, Rangel N, El Fakih Y, Uzcátegui E, Galeazzi T, Beaulieu S and Araujo de Baptista E: Rosiglitazone in the assistance of metabolic control during olanzapine administration in Schizophrenia: A pilot double-blind, placebo-controlled, 12-week trial. Pharmacopsychiatry 42: 14-19, 2009.
209. Wallach JD, Wang K, Zhang AD, Cheng D, Grossetta Nardini HK, Lin H, Bracken MB, Desai M, Krumholz HM and Ross JS: Updating insights into rosiglitazone and cardiovascular risk through shared data: Individual patient and summary level meta-analyses. BMJ 368: l7078, 2020.

210. Agarwal SM and Stogios N: Cardiovascular health in severe mental illness: Potential role for metformin. J Clin Psychiatry 83: 22ac14419, 2022.
211. Liao X, Ye H and Si T: A review of switching strategies for patients with schizophrenia comorbid with metabolic syndrome or metabolic abnormalities. Neuropsychiatr Dis Treat 17: 453-469, 2021.
212. Mukundan A, Faulkner G, Cohn T and Remington G: Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. Cochrane Database Syst Rev 2010: CD006629, 2010.
213. Henderson DC, Kunkel L, Nguyen DD, Borba CP, Daley TB, Louie PM, Freudenreich O, Cather C, Evins AE and Goff DC: An exploratory open-label trial of aripiprazole as an adjuvant to clozapine therapy in chronic schizophrenia. Acta Psychiatr Scand 113: 142-147, 2006.
214. Fleischhacker WW, Heikkinen ME, Olié JP, Landsberg W, Dewaele P, McQuade RD, Loze JY, Hennicken D and Kerselaers W: Effects of adjunctive treatment with aripiprazole on body weight and clinical efficacy in schizophrenia patients treated with clozapine: A randomized, double-blind, placebo-controlled trial. Int J Neuropsychopharmacol 13: 1115-1125, 2010.
215. Henderson DC, Fan X, Copeland PM, Sharma B, Borba CP, Boxill R, Freudenreich O, Cather C, Evins AE and Goff DC: Aripiprazole added to overweight and obese olanzapine-treated schizophrenia patients. J Clin Psychopharmacol 29: 165-169, 2009.
216. Mizuno Y, Suzuki T, Nakagawa A, Yoshida K, Mimura M, Fleischhacker WW and Uchida H: Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: A systematic review and meta-analysis. Schizophr Bull 40: 1385-1403, 2014.
217. Fan X, Borba CP, Copeland P, Hayden D, Freudenreich O, Goff DC and Henderson DC: Metabolic effects of adjunctive aripiprazole in clozapine-treated patients with schizophrenia. Acta Psychiatr Scand 127: 217-226, 2013.
218. El Hayek SA, Shatila MA, Adnan JA, Geagea LE, Kobeissy F and Talih FR: Is there a therapeutic potential in combining bupropion and naltrexone in schizophrenia? Expert Rev Neurother 22: 737-749, 2022.
219. Lyu X, Du J, Zhan G, Wu Y, Su H, Zhu Y, Jarskog F, Zhao M and Fan X: Naltrexone and bupropion combination treatment for smoking cessation and weight loss in patients with schizophrenia. Front Pharmacol 9: 181, 2018.
220. Naguy A and Badr BHM: Bupropion-myth-busting! CNS Spectr 27: 545-546, 2022.
221. Kumar S, Kodela S, Detweiler JG, Kim KY and Detweiler MB: Bupropion-induced psychosis: Folklore or a fact? A systematic review of the literature. Gen Hosp Psychiatry 33: 612-617, 2011.
222. Grover S and Das PP: Can bupropion unmask psychosis. Indian J Psychiatry 51: 53-54, 2009.
223. Wang TS, Shiah IS, Yeh CB and Chang CC: Acute psychosis following sustained release bupropion overdose. Prog Neuropsychopharmacol Biol Psychiatry 29: 149-151, 2005.
224. Deberdt W, Winokur A, Cavazzoni PA, rzaskoma QN, Carlson CD, Bymaster FP, Wiener K, Floris M and Breier A: Amantadine for weight gain associated with olanzapine treatment. Eur Neuropsychopharmacol 15: 13-21, 2005.
225. Graham KA, Gu H, Lieberman JA, Harp JB and Perkins DO: Double-Blind, placebo-controlled investigation of amantadine for weight loss in subjects who gained weight with olanzapine. Am J Psychiatry 162: 1744-1746, 2005.
226. Xu WJ, Wei N, Xu Y and Hu SH: Does amantadine induce acute psychosis? A case report and literature review. Neuropsychiatr Dis Treat 12: 781-783, 2016.
227. Raskind MA, Burke BL, Crites NJ, Tapp AM and Rasmussen DD: Olanzapine-induced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. Neuropsychopharmacology 32: 284-288, 2007.
228. Romo-Nava F, Alvarez-Icaza González D, Fresán-Orellana A, Saracco Alvarez R, Becerra-Palars C, Moreno J, Ontiveros Uribe MP, Berlanga C, Heinze G and Buijs RM: Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord 16: 410-421, 2014.
229. Modabbernia A, Heidari P, Soleimani R, Sobhani A, Roshan ZA, Taslimi S, Ashrafi M and Modabbernia MJ: Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: Randomized double-blind placebo-controlled study. J Psychiatr Res 53: 133-140, 2014.
230. Padwal R, Kezouh A, Levine M and Etminan M: Long-term persistence with orlistat and sibutramine in a population-based cohort. Int J Obes (Lond) 31: 1567-1570, 2007.
231. Tchoukhine E, Takala P, Hakko H, Raidma M, Putkonen H, Räsänen P, Terevnikov V, Stenberg JH, Eronen M and Joffe G: Orlistat in clozapine- or olanzapine-treated patients with overweight or obesity: A 16-week open-label extension phase and both phases of a randomized controlled trial. J Clin Psychiatry 72: 326-330, 2011.
232. Kramer CK, Leitão CB, Pinto LC, Canani LH, Azevedo MJ and Gross JL: Efficacy and safety of topiramate on weight loss: A meta-analysis of randomized controlled trials. Obes Rev 12: e338-47, 2011.
233. Thompson PJ, Baxendale SA, Duncan JS and Sander JW: Effects of topiramate on cognitive function. J Neurol Neurosurg Psychiatry 69: 636-641, 2000.
234. Loring DW, Williamson DJ, Meador KJ, Wiegand F and Hulihan J: Topiramate dose effects on cognition: A randomized double-blind study. Neurology 76: 131-137, 2011.
235. Poyurovsky M, Isaacs I, Fuchs C, Schneidman M, Faragian S, Weizman R and Weizman A: Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: A double-blind, placebo-controlled study. Am J Psychiatry 160: 297-302, 2003.
236. Poyurovsky M, Fuchs C, Pashinian A, Levi A, Faragian S, Maayan R and Gil-Ad I: Attenuating effect of reboxetine on appetite and weight gain in olanzapine-treated schizophrenia patients: A double-blind placebo-controlled study. Psychopharmacology (Berl) 192: 441-448, 2007.
237. Ghanizadeh A, Nikseresht MS and Sahraian A: The effect of zonisamide on antipsychotic-associated weight gain in patients with schizophrenia: A randomized, double-blind, placebo-controlled clinical trial. Schizophr Res 147: 110-115, 2013.
238. Hamoui N, Kingsbury S, Anthone GJ and Crookes PF: Surgical treatment of morbid obesity in schizophrenic patients. Obes Surg 14: 349-352, 2004.
239. Fuchs HF, Laughter V, Harnsberger CR, Broderick RC, Berducci M, DuCoin C, Langert J, Sandler BJ, Jacobsen GR, Perry W and Horgan S: Patients with psychiatric comorbidity can safely undergo bariatric surgery with equivalent success. Surg Endosc 30: 251-258, 2016.
240. Shelby SR, Labott S and Stout RA: Bariatric surgery: A viable treatment option for patients with severe mental illness. Surg Obes Relat Dis 11: 1342-1348, 2015.
241. Ahmed AT, Warton EM, Schaefer CA, Shen L and McIntyre RS: The effect of bariatric surgery on psychiatric course among patients with bipolar disorder. Bipolar Disord 15: 753-763, 2013.
242. D'Arcey J, Torous J, Asuncion TR, Tackaberry-Giddens L, Zahid A, Ishak M, Foussias G and Kidd S: Leveraging personal technologies in the treatment of schizophrenia spectrum disorders: Scoping review. JMIR Ment Health 11: e57150, 2024.