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Review Article

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Schizophrenia as a Complex Neuromedical Disease

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Abstract

Introduction: Schizophrenia (SZ) is a severe chronic psychiatric disease that significantly affects individuals' quality of life. The life expectancy of patients with SZ is 11 to 30 years less than that of the general population. An association between SZ and a range of comorbid chronic diseases and conditions, including cardiometabolic diseases, has been discovered, which in part explains the decrease in life expectancy and quality of life. This association has been linked to the use of antipsychotics. However, scientific evidence has also demonstrated that SZ patients are intrinsically susceptible to developing chronic diseases. Moreover, the link between cardiometabolic risk and the time course of SZ evolution has not been explored.

Method: The authors reviewed 147 papers to provide an update on chronic cardiometabolic diseases and sleep, bone, kidney, and cancer alterations associated with SZ to increase awareness of the specific and multidisciplinary care that these patients require.

Results: Patients with SZ have a high prevalence of risk behaviours, including tobacco use and poor diet. As a result, SZ patients have worse cardiometabolic profiles than the general population and a greater probability of developing metabolic syndrome, diabetes, and cardiovascular diseases. SZ has also been linked to other chronic diseases, including sleep disorders (particularly obstructive sleep apnoea), osteoporosis, chronic kidney disease, and certain types of cancer. The high prevalence of these comorbidities cannot be exclusively attributed to the use of antipsychotic medication. Researchers postulate that several inherent SZ mechanisms can also contribute to the development of chronic diseases.

Conclusion: SZ is a severe disease that worsens both life expectancy and quality of life. Newly available information forces us to move toward a multidisciplinary medical approach to study and manage schizophrenic patients.

Keywords: Schizophrenia • Antipsychotic • Cardiometabolic syndrome

Introduction

Schizophrenia (SZ) is a serious and chronic psychiatric disorder that significantly impacts the quality of life of individuals, the prevalence of which is approximately 0.38 to 0.58, and the lifetime prevalence is 0.7%. The disorder is characterized by positive symptoms (hallucinations, delirium, catatonic symptoms, and disorganized speech), negative symptoms (including emotional blunting and anhedonia), cognitive disorders (alterations in attention, memory, and executive functions), affective disorders and hostility [1]. In addition, SZ patients present with serious physiological disturbances that increase the severity of the disorder. These include endocrinological, sleep, cardiovascular, and metabolic alterations that affect weight, glycaemic regulation, lipid metabolism, and blood pressure. The mechanisms underlying these alterations are not fully understood [2].

The life expectancy of SZ patients is 11 to 30 years less than that of the general population, and SZ patients have more cardiovascular-related deaths than does the general population [3]. Antipsychotic treatment has been linked to cardiometabolic alterations. However, evidence shows that patients who have never received treatment also present with the same concomitant disorders [4] and are already present for some patients during their first psychotic episode. For this reason, it is believed that SZ per se is linked to high rates of metabolic comorbidity, including type 2 diabetes, and that individuals lose 15-20 years of life due to Cardio Vascular Diseases (CVD) [5-7]. Our work provides an update regarding the chronic comorbidities associated with SZ to help optimize the clinical management of these patients.

Methodology

Search strategy and selection criteria

A stepwise literature review was conducted by searching PubMed, MEDLINE, and Web of Science databases for published peer-reviewed papers and scientific websites using the following keywords: "SZ and comorbidities" and "medical co-morbidity risk factors" from January first, 1999, to December 2022. The keywords were screened in the titles and abstracts.

Eligibility criteria

Inclusion criteria: To be included in this review, the articles had to meet all following criteria: (a) include adolescents and adults, (b) be published in English and Spanish, (c) published research, meta- analysis and review papers. OG and CR applied the eligibility criteria and screened the records to select included studies. The total number of articles identified was 302 and the selection criteria applied were: review of titles and abstracts to determine the relevance of the studies. The full texts of studies that met the inclusion criteria were obtained and reviewed.

Exclusion criteria: The following exclusion criteria were used: (a) no reviews, comments or clinical cases, (b) methodological features: number of participants included ≤10, adults included only, lack of comparison group, participants whose diagnosis has been confirmed by a classification other than the DSM-III or the DSM-IV and V, test validation studies, (e) anatomical, biological or fMRI studies (isolated, contradictory and/or non-replicated results) are difficult to interpret and (g) qualitative studies.

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Relevant data from 147 selected studies, such as analyzed variables, main results, and conclusions, were then extracted in order to identify patterns and trends in the relationship between SZ and comorbidities. Finally, a synthesis of the findings was carried out in a narrative review.

Quality assessment

All included studies were observational, with a similar comparative framework. Quality assessments in such observational studies is controversial, with no clear agreement on rating methods. Therefore we performed a qualitative assessment of the quality of the studies, reviewing: the study design, considering whether it is appropriate to address the research question, the sample size in relation to the research question and the precision of the results, the sample selection methods; whether they were adequate and representative of the population of interest, the quality of the measurement of the variables of interest, the control of biases in the design and analysis of the study, the adequacy and precision of the statistical analysis used, whether the results are generalizable to the population of interest and whether the authors discuss the limitations and applicability of their findings. Finally, whether the results are consistent between different studies and whether there is evidence of heterogeneity or contradictions.

Literature Review

Pathophysiologic mechanisms of metabolic syndrome

1. Definition: In recent years, there has been increased awareness of the high prevalence of metabolic syndrome and cardiovascular-related deaths in SZ patients. Metabolic Syndrome (MetS) comprises a group of conditions that include carbohydrate intolerance, High Blood Pressure (HBP) and dyslipidaemia and is associated with a greater risk of cardiovascular diseases such as acute myocardial infarction and stroke, in addition to having higher mortality rates from atherogenic cardiovascular causes [8]. From a physiopathological perspective, this disorder involves overlapping lipid metabolism alterations with proinflammatory and prothrombotic states and insulin resistance and is characterized by an increase in free fatty acids commonly related to overweight. Cardiometabolic risk factors include abdominal obesity, hypertriglyceridemia, low HDL-C levels, high blood pressure, and elevated blood sugar levels. Moreover, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial, which used the consensus from the National Cholesterol Education Program (NCEP) and the criteria from the American Heart Association, reported that the prevalence of MetS in SZ patients was between 40.9% and 42.7% [9]. The risk of metabolic alterations can increase after starting antipsychotic treatment [10]. However, whether SZ has an inherent risk of triggering metabolic alterations or whether these alterations are caused by antipsychotic medication is still controversial. Some individual studies could not detect metabolic alterations in patients who had suffered their first episode with no prior drug treatment, but these nonsignificant findings could be the result of a small sample size or the low severity and duration of the disease [11]. In fact, recent findings suggest that metabolic alterations are a characteristic of SZ in the absence of medication and chronic behavioural alterations [12]. Other studies have shown that glucose homeostasis and visceral fat suffer alterations from the onset of the disorder and in the absence of antipsychotic use [13]. Additional studies have shown carbohydrate metabolism alterations in at-risk individuals who do not have SZ, such as family members and individuals in high-risk psychosis groups [13,14]. However, whether the intensity of metabolic instability is associated with worse SZ outcomes is unclear [10]. In this view, the study of metabolic and insulin homeostasis markers in naive or initial SZ patients could help elucidate this clinical and pathophysiological dilemma.

2. The pathophysiologic role of metabolic inflammation in SZ: The role of metabolic inflammation in SZ is being studied. In fact, some systemic inflammatory events have been associated with greater disease severity and even with resistance to drug treatment [15]. From a pathophysiological perspective, visceral obesity, a common attribute in some MetS patients, tends to cause systemic inflammation events and functional and structural injury to the central nervous system [16]. Proinflammatory markers such as cytokines and other mediators are probable etiological factors in some psychiatric disorders, including SZ [17]. In addition to this proinflammatory profile, the uncontrolled activity of microglia may be a risk factor that can induce SZ, as can genetic vulnerability and glutamatergic neurotransmission in the CNS [18,19]. Microglia are responsible for immunological surveillance within the CNS, the release of inflammatory mediators and the triggering of an efficient immune response against different organs. This event is followed by the release of anti-inflammatory mediators, beginning with the resolution of the inflammatory response. However, proinflammatory/anti-inflammatory balance has not been well characterized in this pathophysiologic context [19]. These markers are like those found in chronic systemic inflammation, as observed in visceral obesity, insulin resistance and other cardiometabolic risk factors. The inflammatory effects of metabolic syndrome have been linked to neurodegenerative diseases. For example, local and systemic inflammation induced by obesity or type 2 diabetes mellitus can cause degradation of the blood–brain barrier, a decrease in waste elimination and an increase in the infiltration of immune cells. The result is an interruption of glial cells and neurons, which causes hormone deregulation, augmented immune sensitivity or cognitive impairment, depending on which area of the brain is affected [20]. Recent studies have shown that adipokines, including leptin, adiponectin, tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), may be associated with MetS in schizophrenic patients [21]. In a recent clinical trial, the serum levels of adiponectin, insulin, leptin, TNF-α, and IL-6 were measured in 46 patients with SZ and MetS and were compared to those in patients with only SZ. Multiple regression analysis revealed multiple associations with leptin but only for TNF-α and IL-6. These results could provide support for the role that some adipokine profiles could play in SZ and MetS patients [22]. Additionally, interleukin- 6 (IL-6) may be involved in leptin regulation [23], and a recent study revealed that blood IL- 6 and leptin levels were significantly positively correlated in patients with schizophrenia but not in controls [24]. Leptin levels, compared to those of controls, cannot be entirely attributable to antipsychotic medication or increased body mass index [25]. Moreover, adiponectin is related to cardiovascular risk in patients with severe mental illness independent of antipsychotic therapy [26]. Moreover, adiponectin was significantly associated with elevated total cholesterol and triglyceride levels in patients with severe mental illness after further adjustment for other cardiometabolic risk factors, such as hypertension and elevated insulin levels. Similarly, higher serum levels of IL-1 may predict a subsequently greater possibility of hypercholesterolemia and hyperleptinemia following antipsychotic treatment with olanzapine in schizophrenia patients [27]. Therefore, the presence of MetS in SZ patients may be both a predisposing factor and a progressor of inflammation in patients with SZ who develop cardiovascular and metabolic risk factors. MetS can lead to the development of diabetes, hypertension, and other cardiovascular risk factors, which occur at two to three times greater rates in SZ patients than in the general population, causing an increase in cardiovascular morbidity and mortality in this vulnerable population [28-30].

3. Oxidative stress markers in SZ: Oxidative stress, defined as the loss of cellular equilibrium when faced with a prooxidative injury or a decrease/depletion of antioxidant defences, could also be an important etiological factor for the onset and progression of neural damage in SZ patients [31,32]. This could be determined by the association between inflammatory phenomena and the prooxidative damage mechanism in microglia [33]. Experiments have demonstrated an association between the induction of Reactive Oxygen Species (ROS), for example, some of the enzymatic and mitochondrial types, such as the enzyme NADPH oxidase, and SZ models [34,35]. Moreover, a pro-oxidative imbalance or a decrease in antioxidant defences is observed in SZ patients with elevated oxidative stress markers measured in serum samples and cerebrospinal fluid [36,37]. Other pro-oxidative effects are observed through the depletion of glutathione, a component of the antioxidant defence system [38,39]. Many studies have highlighted the changes in the group of cells involved in the

etiology of this disease, referred to as "Parvalbumin Interneurons (PVIs)", which regulate cortical excitability, synaptic plasticity, and cognitive functions [40,41]. PVIs are the final cells that appear during brain development and have been shown to be affected by pro-oxidative states [42]. However, their clinical contribution to SZ is unclear. Further cohort studies are necessary to determine the underlying mechanisms of treatment with antioxidants and anti-inflammatory agents.

SZ: associated cardiovascular and metabolic alterations

CVDs are the main cause of increased mortality in the SZ population. Moreover, SZ patients are at greater risk of dying from CVD than is the general population [3,43]. The prevalence of dyslipidaemia in SZ patients is between 25% and 69%. Additionally, patients tend to be subdiagnosed and, most likely, subtreated about their cardiovascular diseases [44,45]. Patients with coronary disease and SZ have been observed to have a lower probability of receiving cardiology care and revascularization therapy than non-SZ patients [46]. A 2017 follow-up study revealed that SZ patients die due to CVD 10 years earlier than does the general population, and SZ patients hospitalized for CVD have a higher mortality rate after discharge. Coronary and cerebrovascular diseases were the leading causes of death [45]. Regarding coronary diseases, SZ patients have a high risk of suffering an acute myocardial infarction. While the incidence of ischaemic cardiac diseases has decreased in the general population, it has remained constant or has risen in the population with mental disorders, which includes individuals with SZ [47].

Regarding cerebrovascular diseases, a recent meta-analysis of cohort studies showed a positive association between SZ and stroke incidence and mortality, which persisted after correcting for cardiovascular risk factors [48]. However, the pathophysiologic mechanism involved remains unclear. However, existing evidence has demonstrated alterations in cerebral blood flow in patients with SZ, including changes in baseline flows in different regions of the brain and deficient autoregulation. These findings could be explained in part by alterations related to nitric oxide, a vasodilating substance that affects cerebral blood flow autoregulation, whose production and metabolism are altered in SZ patients [49].

SZ patients also have a higher risk of sudden cardiac death [50,51], which is mainly attributed to the use of antipsychotics [52] and commonly due to the blocking effect of cardiac repolarization, represented by the increase in the QT segment in an electrocardiograph [53,54].

Currently, Mendelian genetic correlations have recently been applied to assess causality between SZ and CVD [55]. With a multivariable assay, whether causal effects were mediated by smoking, body mass index, low physical activity, lipid levels, or type 2 diabetes was investigated. These investigators found that susceptibility to schizophrenia causally increases heart failure risk. There was also evidence that susceptibility to schizophrenia increases the early repolarization pattern, largely mediated by higher body mass index (BMI) and lipids. Finally, there was evidence that liability to schizophrenia increases heart rate variability, a direction of effect contrasting clinical studies using biomarkers [56]. Schizophrenia-related increases in heart failure are consistent with the notion that schizophrenia involves systemic autonomic dysregulation of the body with detrimental effects on the heart [55]. Thus, genetic risk for schizophrenia is associated with cardiac structural changes that can worsen cardiac outcomes. However, further work is required to determine whether these associations are specific to schizophrenia or are also present in other psychiatric conditions [57].

Consequently, SZ patients are at risk of sudden cardiac death (which is further supported by a study by Mothi et al. that demonstrated that cardiovascular and metabolic dysfunction are increased in first-degree relatives of SZ patients [58].

However, a study demonstrated that SZ patients have the electrocardiographic pattern of Brugada syndrome (a hereditary disease characterized by abnormal electrocardiographs and an elevated risk of suffering sudden cardiac death) as well as longer QT values, which cannot be explained using arrhythmogenic drugs [59].

1. Diabetes

One of the main reasons for the higher mortality rate and lower life expectancy in SZ patients is metabolic disorders such as type 2 Diabetes Mellitus (DM2). At the onset of disease, patients with SZ exhibit alterations in fasting blood sugar levels, baseline insulin levels, and cortisol levels [60]. Epidemiological studies indicate that, regardless of the use of antipsychotics, SZ patients have a greater chance of developing some level of intolerance to carbohydrates, including type 2 diabetes (DM2) (Figure 1). Up to 15% of patients with SZ may have diabetes, and a similar percentage may have impaired glucose tolerance. Increased age is associated with increased risk [61].

The prevalence of DM2 in SZ patients could be high because of the use of certain antipsychotics, which can cause weight gain as a side effect. Moreover, some cohorts show associations between SZ, diets high in saturated fats, and low socioeconomic levels [62]. Alterations in hormonal regulators of appetite, expressed as low levels of leptin and high levels of insulin, often occur in early psychosis before antipsychotic treatment [63–65]. Therefore, having SZ could predispose patients to the development of DM2. In addition to traditional and SZ risk factors, recent studies have shown that SZ patients who have not received treatment or who have suffered their first episode and their close relatives are at higher risk of developing DM2 [13,66]. Moreover, accumulated evidence shows the existence of common susceptibility genes for SZ and DM2 that can regulate neuron development in the brain and insulin secretion in the pancreas through common pathways for intracellular signalling [67,68]. These genes could be divided into two functional categories: one category for genes associated with inflammation (apolipoprotein E, interleukin-10, and tumour necrosis factor-α) and a second category for genes involved in oxidative stress (glutathione transferase, superoxide dismutase-2, and uncoupling protein 1 [69]. Based on what has been previously described, it is possible to postulate that metabolic and molecular abnormalities are inherent features of SZ.

2. High blood pressure

Patients with SZ and High Blood Pressure (HBP) have been observed to have higher morbidity and mortality worldwide, in part because they are at higher risk of suffering cardiovascular complications or because they receive less thorough clinical care when presenting high blood pressure levels [70]. Many studies have shown the positive pharmacological effects of antidepressants and antipsychotics on systolic and diastolic blood pressure [71–73]. Consequently, the positive effects of these drugs on mental health could prompt patients to adopt healthier lifestyles, to have better access to health services and to decrease their risk of developing HBP. An additional factor that may be involved in the risk of developing HBP in SZ patients is the high level of sedentary lifestyle activity observed in these patients, which is linked to a higher-than-average salt intake [70,74]. A probable pathophysiologic explanation for these findings would be endothelial dysfunction in SZ patients with HBP, which would add to the intrinsic proinflammatory effect of HBP on blood vessels. Proinflammatory states have been observed before and after treatment for a first episode of SZ [75,76].

3. Atherogenesis and coronary cardiopathy

Mounting epidemiological data show that individuals with severe mental illnesses, including SZ, bipolar disorder, and major depressive disorder, are at greater risk of developing coronary cardiopathy than are individuals in control groups [77]. A recent study of patients with SZ showed that these patients died 10 years earlier from coronary cardiopathy than did the general population. However, survival after a coronary event that required hospitalization was like that of the general population when compared by age [45]. This could be because some symptoms, such as dyspnoea and chest pain, may not be clear when assessing these patients and may be interpreted as psychogenic symptoms [78].

Researchers propose that many biological mechanisms are involved in the association between mental disorders and coronary cardiopathy. Mental

disorders have been associated with dysfunctions of the autonomic nervous system (decreased heart rate variability, high blood pressure, increased QT interval variability, increased QT and P-wave dispersion), dysregulation of the Hypothalamic–Pituitary–Adrenal (HPA) axis, systemic inflammation, atherogenic dyslipidaemia, oxidative stress, and increased platelet reactivity [79,80]. All of these physiopathological processes are involved in the development and progression of coronary disease. In addition, the use of some antipsychotics and, to a lesser extent, antidepressants and mood stabilizers can increase the risk of developing coronary cardiopathy [71,81]. For instance, dysfunction in the autonomic nervous system triggered by SZ can be aggravated by antipsychotic treatment through the blockade of peripheral dopamine receptors, increased sympathetic activity and increased risk of cardiomyopathy due to tachycardia or decreased coronary diastolic perfusion pressure [71,82]. This could worsen ischaemic symptoms in high-risk cardiovascular patients or trigger acute coronary syndrome. In conclusion, certain neurotrophic or neuroinflammatory substances can eventually mediate myocardial and central nervous system injuries in high quantities in the plasma of SZ patients [83]. This could also provide support for basic clinical research aimed at demonstrating the existence of a "heart-brain" axis.

4. Visceral obesity

Weight gain and obesity are critical issues for SZ patients. Both can increase the risk of developing diabetes mellitus and cardiovascular diseases during adulthood, cause a lack of adherence to drug regimens, worsen quality of life, and increase relapses [84]. Moreover, obesity also leads to the development of CVD and CVD mortality independent of other Cardio Vascular (CV) risk factors. More recent data highlight abdominal obesity, as determined by waist circumference, as a cardiovascular disease risk marker that is independent of body mass index [85]. Visceral obesity (central) is a well-known risk factor for the development of certain noncommunicable chronic diseases, such as essential hypertension and coronary cardiopathy [86]. Some cohort studies have shown that SZ patients have increased intra-abdominal fat, which could provide an explanation for why SZ patients have cardiovascular risk factors and die prematurely from cardiovascular diseases [87,88]. SZ patients with central obesity and elevated plasma cortisol levels have a higher rate of cardiovascular events, including cerebral stroke and coronary disease [89,90]. Additionally, prior exposure to neuroleptics does not affect these findings, as patients with and without medication present equally high levels of visceral fat. Obesity is usually accompanied by inflammation of fat tissue, with a prominent effect on visceral fat. Proinflammatory signalling in adipocytes causes the resident immune system to release increased amounts of proinflammatory and other mediators, resulting in enhanced tissue- protective responses [91]. Regarding CV risks, prohypertensive and prothrombotic mediators are associated with an increase in visceral fat. Finally, proinflammatory states and accelerated atherogenic risk associated with higher levels of visceral fat determine a worse prognosis of cardiovascular events in these patients, mainly those with diabetes and high CV risk [92].

Antiobesity effects: Overweight and obesity, which are partially caused by antipsychotic drugs, are important factors that contribute to the development of diabetes and cardiovascular diseases in SZ patients. Multiple clinical trials have been performed for individuals who experience weight gain induced by taking antipsychotic medication, but no consensus has been reached on what is appropriate in a habitual clinical setting [93,94]. In addition, protective cardiometabolic effects or effects associated with the normalization of an unstable metabolic state with anti- obesity therapy have not been well described [95]. Melatonin, liraglutide, and the combination of naltrexone/bupropion are examples of drugs with different action mechanisms that may have favourable effects on obesity or drug-induced weight gain. The use of melatonin is appropriate for any patient who starts to use a psychotropic drug that is possibly linked to weight gain or other adverse metabolic effects. Liraglutide must also be considered appropriate for use in psychiatric patients who are overweight or obese, especially those with drug-induced weight gain. The use of naltrexone/bupropion can be problematic in patients with bipolar disorder or SZ due to the possible adverse effects of bupropion [95,96]. All the previously mentioned drugs deserve detailed studies in SZ patients.

Habits

The prevalence of tobacco smoking is greater in SZ patients than in the general population [97,98]. Research suggests that tobacco could influence the mesolimbic dopaminergic system, increasing the release of dopamine to the prefrontal cortex and partially alleviating positive and negative symptoms, which would in part provide an explanation for the levels of tobacco smoking in SZ patients [99]. Similarly, 50% of SZ patients present with a substance use disorder that is defined previously. Several mechanistic studies have demonstrated the interaction effect on intrinsic cholinergic neural lower tone, which explains the high risk of smoking in patients with SZ and supports the self-medication hypothesis. Moreover, schizophrenia-related, and smoking-related brain alterations in functional dynamics differ in cannabinoid and glutamate neurotransmission [100]. For example, when nicotine is administered through tobacco smoking, these deficits may be partially attenuated. First, nicotine binds directly to nicotine cholinergic receptors in mesolimbic dopaminergic pathways, which increase the expression of nicotine and contribute to a reduction in negative affect in response to smoking-related cues. In addition, nicotine binds to the $\alpha 7$ and $\alpha 4\beta 2$ receptors on glutamatergic and GABAergic neurons in the prefrontal cortex, attenuating deficits found in SZ patients and enhancing cognition [101]. Regarding weight drop and gain (regain), SZ patients consume more calories than does the general population, preferring sugary and saturated fat food over fruits and vegetables [102]. Additionally, overweight is associated with cardiovascular morbidity in SZ patients [103]. Negative symptoms have been associated with most baseline and two-year outcomes; negatively associated with 7 cardiorespiratory fitness and dietary quality; with High-Density Lipoprotein cholesterol (HDL); and with increasing waist circumference, BMI and HbA1c [104]. In this clinical setting, antipsychotic-induced weight gain is an extremely common problem in people with schizophrenia and is associated with increased morbidity and mortality. Therefore, adjunctive pharmacological interventions may be necessary to help manage antipsychotic- induced weight gain in patients with higher CV risk [105]. Therefore, weight gain and obesity, as independent pathogenic factors, may contribute not only to the cognitive impairment of SZ patients but also to CV and primary pro-atherogenic phenomena. These are modifiable factors observed in SZ patients who contribute to cardiometabolic alterations and, therefore, must be screened and managed to control any associated diseases.

Circadian rhythm disruption

SZ patients normally have sleep onset and maintenance insomnia, regardless of whether they find themselves on or off antipsychotic treatment, and are unrelated to mood stability, level of control of the disease, and daily functioning [106]. Sleep alterations are related to the dopaminergic and GABAergic pathways; genetic alterations connected to the circadian cycle, such as CLOCK and ARNTL; and melatonin disorders caused by deficient melatonin production or receptor alterations [107]. Although the evidence is limited, Obstructive Sleep Apnea (OSA) has also been associated with SZ. OSA increases cardiometabolic and psychiatric morbidity associated with SZ. The diagnosis and treatment of OSA in SZ patients can improve the overall health, mental health, and quality of life of these at-risk patients [108,109].

Sleep deprivation and circadian rhythm dysregulation are directly linked to the development of HBP, DM2, and other cardiometabolic alterations in the general population. It is suspected that these conditions could be important causes of sleep disorders in SZ patients [2]. This highlights the importance of screening and treating these conditions in SZ patients. Melatonin (MLT), the main hormone of the Pineal Gland (PG), is assumed to support the onset and maintenance of sleep and a stable sleep-wake cycle, exerting antioxidative and neuroprotective effects [110]. Evidence demonstrates that sleep and circadian rhythm abnormalities are very common in SZ patients.

Some imaging studies suggest structural abnormalities of the PG in these patients as well. Meta-analytical evaluation of the data was possible only for MLT secretion, as midnight plasma levels were significantly lower in individuals with SZ than in healthy controls. Imaging studies demonstrated a greater prevalence of enlarged calcifications (>1 cm) in the PG and a smaller PG volume in patients than in healthy controls. Anatomic and functional abnormalities of the PG were not associated with duration of illness or with treatment factors, possibly suggesting that these abnormalities are primary characteristics of the disease and are genetically based [111]. Preliminary studies have shown the pathophysiologic role of MLT in SZ as an important therapeutic area, but additional studies are needed to confirm its usefulness [112]. Recently, a systematic review of 15 studies was performed on the following primary outcomes regarding the use of melatonin: sleep (n=6), metabolic profile (n=3), tardive dyskinesia (n=3), cognitive function (n=2) and benzodiazepine discontinuation (n=1). Melatonin therapy has some positive effects on sleep quality, metabolic profiles and tardive dyskinesia in patients with schizophrenia. No beneficial effects of melatonin were observed on the outcomes of cognition or benzodiazepine discontinuation. Future studies utilizing larger samples and investigations specifically comparing the effect of melatonin as adjunctive therapy with different antipsychotics are needed [113].

SZ and cognitive alterations associated with cardiometabolic risk

SZ has detrimental effects on quality of life, mainly because cognitive symptoms start at an early age, and recovery is partially achieved through current therapies. SZ is characterized by multiple cognitive deficits, including attention, memory, and executive function. Most psychosocial issues, for instance, difficulties completing education and/or maintaining job stability (which determine poverty and social exclusion), are associated with this cognitive deficiency [114].

The role of the HBP in cognitive impairment in SZ patients has been studied. Some studies that associate blood pressure control with cognitive impairment progression, mainly in patients older than sixty years, have shown greater progression of cognitive impairment in more severely hypertensive patients [115]. A cohort study was able to demonstrate that HBP can predict general cognitive deficits in SZ patients but not in control patients without HBP when matched by age [116]. Blood sugar and abdominal obesity did not significantly predict cognitive performance in any group. Other studies have associated metabolic instability with HBP levels and greater incidence of kidney failure in SZ patients with uncontrolled HBP [117]. More findings can provide support for the role that metabolic abnormalities play in general and/or specific cognitive deficits and whether HBP treatment could be a new supplementary treatment objective to remedy these deficits in SZ patients.

Obesity and underweight have also been linked to deficits in cognitive performance, which increases the risk of developing dementia. Hyperlipidaemia has contradictory results. However, some evidence points to the existence of a relationship between total cholesterol levels and deficient cognitive performance, suggesting that high cholesterol is an important risk factor for developing cognitive impairment and dementia [118]. Although still preliminary, what has been described could aggravate the existing cognitive deficits of patients with SZ, many of which are clinically modifiable factors. Individuals with SZ are at greater risk for MetS, which is associated with cognitive deficits in the general population [119]. MetS might be an important contributing factor to cognitive impairment in patients with SZ. In the Bora review and meta-analysis, the findings of 18 studies investigating the association between MetS (and its components) and cognitive impairment in SZ patients were reviewed. Comorbidities of MetS (d=0.28) and diabetes mellitus (d=0.28) were both associated with more severe cognitive deficits in SZ patients. There was also evidence for a significant relationship between cognitive impairment in SZ patients and each of the components of MetS, including hypertension, dyslipidemia, abdominal obesity, and diabetes. MetS is significantly associated with cognitive impairment in SZ patients and can potentially contribute to the functional decline observed in some patients with SZ throughout the course of disease [120].

SZ and other medical conditions

1. Osteoporosis: Osteoporosis is a systemic disease of the skeleton characterized by a decrease in bone mass and degradation of the bone tissue microstructure, increasing the brittleness and susceptibility to fracture [121]. Osteoporosis is a pressing global health issue [122].

Compared with the general population, patients with SZ have a greater incidence of osteoporosis, bone fractures, and reduced bone density [122,123]. Osteoporosis risk factors identified in SZ patients can be grouped into two categories: modifiable and nonmodifiable risk factors. The nonmodifiable risk factors included advanced age, Caucasian or Asian race, and family history of osteoporosis. Regarding sex, the results are controversial for patients who suffer from SZ [123].

Modifiable risk factors include BMI, tobacco use, physical inactivity, a low-calcium diet, vitamin D deficiency, certain antipsychotic medications, coffee, and alcohol [123,124]. Behaviours associated with negative symptoms could have an influence on low physical activity and a lesser tendency to go out, which would influence vitamin D production [125]. An important consideration is that low bone density and osteoporosis are observed particularly in SZ patients treated with antipsychotic medication [126]. The mechanisms underlying the induction of osteoporosis by antipsychotic medication are complex, but the most important mechanism is likely hyperprolactinemia caused by some antipsychotics, mainly Risperidone, paliperidone, and amisulpride. The mechanism for hyperprolactinemia involves blocking the dopaminergic receptor D2 in lactotrophs, which impairs prolactin secretion via dopamine [123]. Hyperprolactinemia induced by antipsychotics can affect bone metabolism in two ways: it can directly affect bone turnover by stimulating bone reabsorption, and prolonged hyperprolactinemia can cause hypogonadotropic hypogonadism, which decreases sex hormone secretion and consequently impact bone metabolism (hypoestrogenism increases the risk of osteoporosis, and low testosterone levels are associated with osteopenia and osteoporosis) [122].

2. Chronic kidney disease: SZ patients have been observed to have a 25% greater chance of developing Chronic Kidney Disease (CKD) than does the general population, regardless of the use of antipsychotics or other clinical comorbidities (DM, HBP, CVD); moreover, SZ patients are believed to be directly related to SZ, although the causes of these associations are still unknown. Researchers believe that the same endothelial dysfunction observed in DM2 and the HBP is the cause of CKD. However, additional studies are necessary in this area. The recommendation is to actively screen for CKD in SZ patients and to control comorbidities to prevent a decrease in renal function [127,128].

Moreover, Moreno-DeLuca et al. described that the contiguous gene syndrome related to the 17q12 deletion (a rare genetic disorder whose phenotypic characteristics include macrocephaly, renal cysts, diabetes, and cognitive impairment) confers a very high risk of developing SZ and autism spectrum disorders, as well as a high risk of CKD [129]. This case could illustrate a certain genetic association between SZ and CKD but requires additional investigation to provide further clarity.

3. Cancer: The incidence of cancer in SZ patients compared to that in the general population has been controversial; initial papers have shown a lower incidence of cancer, while others have shown a higher incidence than in the general population. Recently, Li et al. published a meta- analysis in 2017 that included 16 cohort studies and showed a decrease in the general risk of cancer in SZ patients. An analysis of specific cancer sites revealed a decrease in the risk of colorectal cancer and prostate cancer. However, the incidence of lung cancer has increased in women [130]. Regarding the association between SZ and cancer mortality, the results from previous studies have presented positive, null, or inverse associations. Zhuo et al. performed a meta-analysis that included 19 studies, 15 of which reported Standardized Mortality Ratios (SMRs) for patients with SZ compared to the general population; the pooled SMR was 1.40 (95% CI 1.29-1.52, P < 0.001). The other four studies reported Hazard Ratios (HRs) comparing individuals with SZ with those without SZ; the pooled Hazard Ratio (HR) was 1.51 (95% CI 1.13-2.03, P=0.006) [131].

Patients diagnosed with SZ have an approximately 50% increased risk of death from cancer compared to age- and sex-matched people in the general population. Studies have confirmed increased mortality from breast, lung, and colon cancer in patients with SZ. Analyses of the incidence of cancer revealed contradicting results, with some studies showing no increase in incidence and others showing a modest increase in overall incidence of cancer. Studies of the incidence of specific types of cancer have shown a modestly increased risk of pancreatic, esophageal, and breast cancer and contradicting results regarding lung cancer. One study revealed that, compared to those in the general population, patients with SZ were at an increased risk of not being diagnosed or treated for cancer before death from cancer. In addition, patients with SZ had a lower chance of receiving optimal treatment for colon cancer after diagnosis. This review revealed that patients with SZ are at increased risk of dying of cancer and of several specific types of cancer. This increased mortality can be reduced if the price of tobacco is increased, if smoking cessation programs are offered systematically, if screening programs are better implemented in this highly vulnerable group, or if procedures to facilitate access to early diagnosis and effective treatment are implemented [132].

Antipsychotics and cardiometabolic risk

Weight gain during SZ treatment, either acute or maintenance treatment, is well known and is a demonstrated side effect of antipsychotic drugs [133]. The main mechanism underlying these side effects seems to be appetite stimulation caused by the interaction of these drugs with different brain receptors.

There is a marked difference in the risk of weight gain between patients taking different antipsychotics. However, no agent should be considered neutral because the proportion of individuals experiencing greater than 7% weight gain is greater with any atypical antipsychotic than with a placebo [134].

Demographic and clinical factors must also be taken into consideration, as they can cause a greater predisposition toward weight gain associated with the use of antipsychotics. Evidence suggests that children and adolescents taking antipsychotic medication are at greater risk of weight gain and metabolic effects than adults using the same drugs are [133,135]. Prospective studies show that the use of antipsychotics is associated with an increase in LDL cholesterol and a decrease in HDL cholesterol. There is also an effect of these drugs on triglycerides, with clear differences between drugs in this case: drugs that were associated with a greater increase in weight, such as olanzapine and clozapine, were also associated with a greater increase in plasma triglycerides [134].

Second-Generation Antipsychotic (SGA) use is associated with metabolic abnormalities and may exacerbate this condition by causing weight gain and glucose and lipid metabolism dysregulation. Antipsychotics can influence metabolic parameters within 2 weeks of treatment [136]. However, the existing body of research suggests that the degree of metabolic dysregulation varies considerably among different SGAs. Evidence for weight gain was found for clozapine, zotepine, olanzapine, sertindole, iloperidone, quetiapine, risperidone, paliperidone, and brexpiprazole. SGA are also associated with glucose abnormalities; for example, they may inhibit glucose reuptake in skeletal and liver cells through inhibition of the glucose transporter and thereby determine insulin resistance development in patients with DM2. Pillinger et al. performed a large meta-analysis to compare and rank antipsychotics based on their metabolic side effects and to identify predictors of antipsychotic-induced metabolic dysregulation. Increased baseline weight, male sex, and non-white ethnicity were found to be predictors of susceptibility to antipsychotic-induced metabolic changes [13]. Dyslipidaemia, mainly characterized by low levels of high-density lipoprotein cholesterol, was associated with a greater risk of CVD and was especially evident in patients treated with olanzapine, zotepine, or clozapine [137]. Furthermore, several studies have demonstrated lipid disturbances following SGA-use. Moreover, prediabetes is highly prevalent in adults treated with antipsychotic drugs and is correlated with increased intraabdominal adiposity, enhanced lipolysis, and insulin resistance [84]. For example, clozapine promotes gluconeogenesis and represses glycogenesis in some animal models, along with an increase in fasting blood glucose and HbA1c levels and a decrease in insulin and hepatic glycogen levels [138]. Finally, research indicates that patients using SGAs have increased cholesterol levels, especially patients using quetiapine, olanzapine, or clozapine. Clozapine is the most effective treatment for improving symptom severity and reducing the risk of recurrent suicidal behavior in patients with SZ or schizoaffective disorder. Moreover, together with olanzapine, it is also associated with the highest increases in weight, BMI and total cholesterol, suggesting that the greatest metabolic disturbances are caused by the most efficacious antipsychotics [136].

Qualitative research shows that patients have concerns about the negative long-term effects of antipsychotics on their physical appearance and physical health. Multiple studies have shown that patients taking antipsychotic medication exhibit weight gain, possibly leading to overweight and obesity; this is one of the most common adverse events and is therefore one of the major reasons for nonadherence to therapy. Considering this, elucidating the factors that contribute to the occurrence of Metabolic Syndrome (MetS) in patients taking specific antipsychotics is useful for clinical practice [136].

Despite all the possible adverse cardiovascular effects of antipsychotics, the association between prolonged exposure to antipsychotics and Myocardial Infarction (MI) has been controversial due to the methodological heterogeneity of the studies [139]. However, a 2017 meta-analysis based on 10 observational studies concluded that SZ patients using typical or atypical antipsychotic medication have a greater risk of suffering an MI than SZ patients who are not using medication [140]. About early exposure to antipsychotics, a recent study from Wu et al. showed that early usage of antipsychotics is associated with a greater risk of MI [3]. However, it is important to consider that the use of antipsychotics has been shown to reduce mortality in patients with severe mental illness, so the benefits of the use of antipsychotics most likely outweigh the risk of an MI [3].

Finally, the clinical and methodological heterogeneity between the studies that followed up SZ patients receiving antipsychotic therapy and those reporting prothrombotic risk led to an inconclusive answer to the question of whether the use of antipsychotics is associated with the incidence of MI in adults.

Summary

SZ is a systemic disease per se, regardless of what is traditionally described. Newly available information mandates a change in the approach used in the study and management of patients with SZ, stressing the need for cardiometabolic prevention and screening of the previously mentioned diseases in all patients diagnosed with SZ, with a multidisciplinary team including psychiatrists, cardiologists, diabetologists, and dietitians.

Long-term follow-up studies of SZ patients who analyse how their cardiovascular profiles, lipid profiles, and other parameters vary over time and how the use of antipsychotics impacts them have not been published to date. However, studies observing the impact of intervention strategies for modifiable risk factors in this population are still in an initial stage.

An example of the latter is Bobes et al. [97], who analysed the high prevalence of tobacco use in SZ patients and the benefits for those who quit smoking. Another example is the work of Bartels and Desilets et al. 2012, which concluded that lifestyle interventions (exercise and diet) seem to be effective in patients with serious mental illnesses and overweight to achieve clinically significant weight loss [102]. Other studies have shown that unhealthy diets, heavy saturated fats, and lack of exercise are common in these patients, demonstrating that lifestyle interventions have small effects [141,142]. These patients are at higher risk of suffering myocardial infarction and cerebrovascular accidents but are at lower risk of having to undergo an invasive procedure than the general population is. The data show that nonmental health physicians have a negative attitude toward patients with serious mental illnesses.

A recent paper investigated the clinical records of patients with SZ or schizoaffective disorder, analysed their cardiometabolic status with weight loss and reported a decrease in cardiovascular mortality, including heart attack and cerebrovascular accident, associated with the magnitude of weight loss [143].

Regarding dietary interventions, limitations exist related to the design of clinical studies and the capacity to extrapolate the results of studies that use dietary supplements in SZ patients [144]. An example of this is the effect of plasmatic levels of vitamin D and long-chain omega- 3 fatty acids, such as docosahexaenoic (DHA) derivatives, both of which are neuroprotective and associated with a decreased risk of developing SZ [145]. These clinical effects could be explained by the antioxidant and anti-inflammatory properties of these compounds [146]. It is important that physicians actively search for different diagnoses and refer patients to them. SZ patients normally do not present clear symptoms, and a timely response can be effective at preventing morbidities and mortality.

Conclusion

In conclusion, current knowledge allows us to better understand SZ, although it presents many lines of investigation that need to be followed. First, what is the extent of systemic involvement in SZ? Second, and even more relevant: What are the origins of the diseases associated with SZ, and how are systemic diseases connected to mental disorders? Finally, what is the impact of early treatment for MetS on the clinical and cognitive progression of SZ? There is an absence of studies or pathophysiological approaches that include the global metabolic evaluation of SZ patients and alterations in the levels of markers that can predict CV risk or incipient endothelial dysfunction. Answering these questions will enable a better quality of life for this highly vulnerable population.

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