Are Cardiometabolic and Endocrine Abnormalities Linked to Sleep Difficulties in Schizophrenia? A Hypothesis Driven Review

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Schizophrenia is a psychiatric disorder that includes symptoms such as hallucinations, disordered thoughts, disorganized or catatonic behaviour, cognitive dysfunction and sleep–wake disturbance. In addition to these symptoms, cardiometabolic dysfunction is common in patients with schizophrenia. While previously it has been thought that cardiometabolic symptoms in patients with schizophrenia were associated with medications used to manage this disorder, more recently it has been demonstrated that these symptoms are present in drug naive and unmedicated patients. Sleep–wake disturbance, resulting in chronic sleep loss has also been demonstrated to induce changes in cardiometabolic function. Chronic sleep loss has been associated with an increased risk for weight gain, obesity and cardiac and metabolic disorders, independent of other potentially contributing factors, such as smoking and body mass index. We hypothesise that the sleep–wake disturbance comorbid with schizophrenia may play a significant role in the high prevalence of cardiometabolic dysfunction observed in this patient population. Here we present a critical review of the evidence that supports this hypothesis.

KEY WORDS: Schizophrenia; Cardiometabolic risk; Causative links; Clock genes.

INTRODUCTION

Schizophrenia affects 0.5-1% of the population, a prevalence that is consistent across the world population.[1,2] This chronic psychiatric disorder causes mental perturbations that significantly alter social and occupational functioning with important consequences on the course and quality of life.

The main features of schizophrenia include delusions, hallucinations, disordered thoughts, disorganized or catatonic behaviour, blunted affect, alogia, avolition, cognitive dysfunctions and sleep difficulties.[3-5] In addition to these mental and affective symptoms, several physiological disturbances also increase the burden of schizophrenia. Changes in endocrine, metabolic and cardiovascular functions, with associated disorders affecting weight, glucose regulation, lipid metabolism and blood pressure are the source of major health problems commonly affecting people with schizophrenia. The mechanisms underlying these cardiometabolic changes are not yet fully understood.

In healthy individuals, alterations in the metabolic, cardiac and endocrine systems have been associated with chronically shortened sleep duration and circadian disruption.[3-6] To our knowledge, no study has directly addressed the possible relation between cardiometabolic dysfunctions and sleep/wake abnormalities in the schizophrenia population. Since circadian and sleep disturbances are often comorbid with schizophrenia, it could be hypothesised that sleep/circadian factors may play a role in the high rates of co-occurrence of cardiovascular and metabolism abnormalities in patients with schizophrenia.

This non-systematic review presents evidence supporting this hypothesis. The characteristics of sleep and circadian rhythms in schizophrenia will be briefly summarized before the cardiovascular, metabolic and endocrine profiles typical of this population will be exposed. Evidence on the implications of sleep in cardiometabolic, endocrine

and metabolic functions obtained from studies in the general population will then be discussed. This evidence will lay the rationale supporting the possible role of sleep as a modulating factor in the association between cardiometabolic abnormalities and schizophrenia. The implications of common genes linked with schizophrenia, sleep patterns and cardiometabolic functions will be discussed.

SLEEP AND CIRCADIAN DISTURBANCES IN SCHIZOPHRENIA

Up to 55% of medicated patients with schizophrenia report sleep problems.[7,8] While sleep-wake abnormalities may be exacerbated by antipsychotics, especially first generation antipsychotics, evidence suggests that sleep and circadian disruptions are linked to schizophrenia independent of pharmacological treatment.[5,7,9]

Sleep-wake cycle regulation operates through two interactive but distinct processes.[10] The circadian process represents the rhythmic variation of sleep and wake propensity over 24 hours that is regulated by the body clock. The homeostatic process represents the accumulation of sleep pressure (relating to the notion of sleep 'debt') with increasing time awake and its dissipation during sleep.[11] A precise interaction between the circadian and homeostatic processes defines the timing of sleep and wake periods. It also supports the maintenance of consolidated sleep episodes during the night and consolidated wake episodes during the day.[10,12] These two processes may come to play in the sleep disturbances experienced by people with schizophrenia.

Homeostatic Aspects of Sleep in Schizophrenia

Sleep studies in patients with schizophrenia highlight objective abnormalities in sleep quality and quantity that can lead to increased sleep pressure. A meta-analytic review of 20 studies with a total of 652 subjects with schizophrenia concluded that, compared to healthy controls, patients with schizophrenia take longer to fall asleep and have shorter sleep duration with lower sleep efficiency (i.e., proportion of the time in bed that is spent sleeping).[13] Additionally, there is decreased rapid eye movement (REM) sleep latency,[14] and reduced stage 4 of non-REM sleep.[15] Over time, these changes are likely to lead to a progressive accumulation of sleep debt, pressuring the homeostatic sleep system.

Because they tend to intensify before psychotic episodes, sleep disturbances are thought to be precursor symptoms of decompensation in patients with schizo-

phrenia.[16-21] Accordingly, the sleep literature provides examples depicting how sustained increases in homeostatic pressure caused by multiple sleepless days with psychostimulant intake can induce psychotic symptoms such as depersonalization, reduced connection with reality, visual hallucinations and persecutory ideation, even in non-clinical populations.[20,22-24] Such findings suggest that sleep disturbances may play a role in the pathogenesis of symptoms associated with schizophrenia.

Circadian Aspects of Sleep in Schizophrenia

Circadian rhythms refer to 24 hours endogenous biological variations originating from the body clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus and from peripheral oscillators located in various organs across the body that are synchronised by the SCN.[25] SCN dysfunction leads to alteration in the timing and duration of sleep, often misaligning sleep episodes with socially adequate timing (i.e., delaying or advancing the internal rhythms) and/or fragmenting the sleep-wake cycle with intrusions of numerous awakenings during the night and naps during the day.

Inferences about circadian rhythms are generally made by measuring 24-hour variations of behavioural/biological functions known to follow a robust circadian rhythm. These include activity levels, core body temperature and hormonal secretion. Melatonin and cortisol are often used as endocrine markers to read endogenous circadian rhythms. Melatonin is a soporific hormone secreted by the pineal gland during the night, which shows very low levels during the day. Cortisol, a glucocorticoid catabolic hormone regulated through the hypothalamic-pituitary-adrenal (HPA) axis, is associated with vigilance and stress and reaches its higher levels during the day with lower levels during the night.

Circadian studies in the schizophrenia population have reported abnormalities in the timing of these physiological rhythms in the form of phase advances and delays.[26-31] It is not yet clear what shifts circadian rhythms in one direction or the other in patients with schizophrenia. Many factors such as the phase of illness, the presence of other comorbidities, occupational status and schedules imposed by the living environment vary substantially within the schizophrenia population and are likely to influence circadian rhythms differently from one individual to another.

More consistent findings have shown that people with schizophrenia have lower melatonin levels.[32-35] and higher cortisol levels at night.[36] Consistent with these physio-

logical changes, schizophrenia is also associated with a global disorganisation of sleep-wake episodes, with more diurnal sleep and nocturnal wake periods.[27]

It has recently been proposed that the sleep-wake disturbances in schizophrenia may reflect SCN dysfunctions.[37,38] Importantly, the nitric oxide synthase immuno-reactive neurons in the SCN have been reported to be significantly less numerous in patients with schizophrenia.[37] This physiological characteristic of patients with schizophrenia could possibly come to play in the emergence of sleep-wake regulation as nitric oxide is thought to modulate sleep.[39,40]

The many negative outcomes resulting from sleep and circadian difficulties may have more disturbing effects on the life of people with schizophrenia compared to the general population. Notably, it has been proposed that sleep abnormalities in schizophrenia may impair memory consolidation processes occurring during sleep and could therefore contribute to the altered cognitive profile associated with schizophrenia.[41] Sleep loss has also been associated with poorer quality of life and reduced coping resources in people with schizophrenia.[42-44] Globally, poor sleep is likely to further impair the already fragile social and occupational functioning of persons experiencing schizophrenia.[45] Social functioning may also be secondarily impaired due to the schizophrenia patient having reversed sleep/wake periods along with fragmented daytime sleep. Physiologically, these phenomena might manifest behaviourally as, or at least contribute to, negative symptoms such as anergia, and apathetic social engagement. Negative symptoms have been associated with lower counts of frontal delta waves, and loss of asymmetry in studies of all night sleeping, suggesting that there may be also physiological impairments at work too.[46]

CARDIOMETABOLIC AND ENDOCRINE ABNORMALITIES ASSOCIATED WITH SCHIZOPHRENIA

Sudden cardiac deaths are three times more frequent in patients with schizophrenia than in the general population.[47,48] Moreover, the prevalence of natural deaths related to cardiovascular diseases in the schizophrenia population is estimated to range between 40 to 45%.[49] However, it is *premature* death from cardiovascular disease that is alarming, with persons with schizophrenia having ≥20% shorter life spans with up to 25 years of life lost.[50,51] While patient care in schizophrenia often primarily addresses mental disturbances, these statistics high-

light the importance of monitoring and treating cardiovascular and metabolic functions in this population, especially when one considers that the gap in the differential rates of standardised mortality between the general population and those with schizophrenia is widening.[52] Understanding of the phenomenon of cardiometabolic disorders in the specific context of schizophrenia is necessary to develop adapted therapeutic interventions for these patients.

While antipsychotic medication is often linked to cardiovascular and metabolic perturbations, important cardiometabolic abnormalities have been reported in drug naïve or drug-withdrawn patients with schizophrenia.[53] Therefore, even though cardiometabolic changes are likely to be modulated to a variable degree by different antipsychotic medications, schizophrenia per se is thought to be associated with cardiovascular and metabolic abnormalities independently of the concomitant effect of pharmacological agents.[53]

Cardiovascular Function

Despite the wide promotion of good life habits and cardiovascular health, rates of cardiovascular abnormalities remain especially high in people with schizophrenia, who experience multiple barriers to receiving adequate physical health care.[53]

Notably, Bär et al.[54] found that mean systolic and diastolic blood pressure were significantly higher in adults with schizophrenia (135 mmHg/84 mmHg) compared to healthy control subjects (120 mmHg/74 mmHg). This difference raises the average blood pressure values close to the clinical threshold for hypertension, in the hazardous range of pre-hypertension (120-139 mmHg/80-89 mmHg; American Heart Association, 2010). Not surprisingly, comorbidity studies estimate that the prevalence of hypertension in the schizophrenia population ranges between 27% and 45%.[55-57] This high prevalence bears considerable clinical significance, since high blood pressure is a risk factor for the development of many life-threatening conditions such as cardiovascular diseases, strokes and renal failure. Aside from these physical health concerns, hypertension has also been linked with decreased cognitive skills,[58] therefore further altering a dimension of life already vulnerable in schizophrenia.

While comparing the baroreflex sensitivity of patients with schizophrenia with healthy controls, Bär et al.[54] found significant alterations in the coordination of blood pressure with heart rate. These authors suggested that the decreased parasympathetic activity in schizophrenia con-

stituted a lower counterweight to sympathetic stimulation. Moreover, compared to healthy controls, the heart rate of people with schizophrenia is more than 25% faster and shows lower variability, suggesting altered cardiac autonomic function.[54,59] Importantly, reduced baroreflex sensitivity and heart rate have been associated with increased risk of vascular events and mortality.[60,61]

Smoking and Lifestyle

A recent study revealed that the prevalence of smoking in the schizophrenia population is almost two times more frequent than in the general population. These smokers with schizophrenia have been reported to have unhealthy life habits (e.g., poor diet, high intake of alcohol and caffeine, sedentary lifestyle) and to be at increased long term risk of cerebrovascular events.[62] Hence, while the full aetiology of cardiovascular abnormalities in schizophrenia remains multi-factorial, modifiable life habits are likely to potentiate them.

Body Weight

Overweight and obesity are estimated to be 1.5 to 2 times more frequent in patients with schizophrenia than in the general population.[50,63-66] Accordingly, body mass index, waist-hip ratio and waist circumference have all been shown to be significantly higher in people with schizophrenia.[36,56,67] Importantly, the fat distribution characteristic of schizophrenia differs to that of the general population. While total body fat, as measured by computed tomography scan, and subcutaneous fat are similar in schizophrenia and controls, people with schizophrenia have three times as much intra-abdominal (or central) fat.[36,68] This specific fat distribution is highly associated with cardiovascular disturbances, hypertension, type 2 diabetes and dyslipidaemia.[69,70] Central adiposity is thought to contribute to the insulin resistance syndrome and in conjunction with its enhanced inflammatory status, in turn enhances cardiovascular risk.[71]

Aside from its damaging physiological consequences, decreased physical fitness resulting from weight gain may confer an aversive aspect to physical activity and further contribute to sedentary lifestyle in schizophrenia. Alteration of body image following weight gain is thought to be a potential factor for low self-esteem and further social marginalisation in people with mental illness.[72]

Chronic antipsychotic medication, especially atypical antipsychotics, has been shown to increase weight in up to 80% of patients with schizophrenia[73,74] and to have a prominent effect on abdominal fat.[75-77] For those on anti-

psychotics, central H1, alpha-1-adrenergic, and 5-HT2C antagonism is highly predictive of poor hypothalamic energy balance control with subsequent weight increase.[78]

Some authors have proposed that the consequences of weight gain can be distressing enough to threaten medication adherence.[72,79] Inactivity, apathy, lower socioeconomic status and bad diet have also been suggested to play a role in the aetiology of weight problems in schizophrenia.[80] Importantly, epidemiological studies have reported that patients with schizophrenia have significantly higher weight levels even when compared to lifestyle-matched controls.[68] This suggests that, while possibly intensified by external factors such as medication, socio-economic variables, eating habits, or exercise levels, and weight gain in schizophrenia operates through endogenous mechanisms. Notably, the higher caloric intake associated with schizophrenia is thought to result in part from increased appetite and decreased satiation,[81,82] which could in turn be explained by endocrine and metabolic changes.

Eating Habits and Endocrine Abnormalities

Schizophrenia has been associated with altered self-control and cognitive distortions regarding one's relation to food, such as rigid weight regulation and fear of weight gain.[80] This combination is likely to generate maladaptive eating behaviour. In fact, food intake in schizophrenia has been paralleled with several types of eating behaviour disturbances such as pica, gorging, anhedonia, and paranoia-induced starvation.[83] Moreover, the diet of patients with schizophrenia has been observed to includes increased levels of saturated fat and food with high glycaemic index. Conversely, their diet tends to be low in fibre, fruits and vegetables.[84-87] While socioeconomic and cognitive variables may contribute to this eating profile, important perturbations of hormones implicated in the regulation of appetite, weight and metabolism may also come to play as primary drivers of poor diet choices.

Ghrelin is a hunger stimulating hormone released mainly by the stomach that is associated with increased body fat[88] and is reduced by glucose and insulin.[89] Medicated patients with schizophrenia have higher ghrelin levels than healthy controls.[67,90] This endocrine imbalance is thought to contribute to the increased food-intake characteristic of schizophrenia.[67]

Leptin, a hormone derived from the cells composing adipose tissues, signals satiety by sending information about ongoing energy reserves to the hypothalamus. These signals lead to a decrease in appetite. Because leptin

levels are correlated with fat mass, some authors have proposed that obesity may be linked with a decreased reaction to leptin signals.[91] Some studies have found higher leptin levels in medicated schizophrenia patients compared to healthy controls.[90,92] However, when body mass index is controlled, patients with schizophrenia are no different from groups of healthy subjects, suggesting that the high leptin levels associated with schizophrenia may be mediated by overweight.[92-95]

Cortisol is implicated in glucose homeostasis, suppresses insulin and is thought to promote obesity. Patients with schizophrenia have been reported to have higher cortisol levels than healthy controls,[96-100] possibly because of alterations in the suppression mechanisms regulating this hormone.[101-103] Cortisol receptors are especially dense in visceral fat stores and potentiate the activity of lipoprotein lipase, an enzyme implicated in fat deposition that is also highly concentrated in intra-abdominal fat stores.[104] Hence, it has been proposed that hypercortisolaemia associated with schizophrenia may increase lipoprotein lipase's central fat deposition, which is in turn associated with several cardiovascular and metabolic abnormalities.[36,67]

Cortisol has an important modulatory influence on cardiovascular and metabolic activity, notably to restore physiological homeostasis after stress. Hence, abnormalities affecting HPA axis functions can interact with cardiovascular and metabolic disturbances. Notably, high levels of anxiety have been shown to be significantly correlated with elevated diastolic blood pressure and heart rate in patients with schizophrenia.[105] Furthermore, it has recently been suggested that higher levels of stress in people suffering from schizophrenia and the subsequent frequent activation of the HPA axis could trigger symptoms associated with the metabolic syndrome.[106,107]

Importantly, alterations in leptin, ghrelin and cortisol have all been associated with cardiovascular and metabolic disturbances.[108-110] Therefore, their disturbed dynamics could possibly be implicated in the high occurrence of weight gain and other cardiometabolic abnormalities in schizophrenia.

Metabolic Perturbations

The rate of metabolic disorders is markedly high in the schizophrenia population.[111-113] Notably, epidemiological studies estimate that type 2 diabetes is 2 to 3 times higher in people with schizophrenia compared to the general population.[114] Similarly, metabolic syndrome, characterised by multiple metabolic risk factors such as over-

weight, elevated triglycerides, lowered high-density lipoprotein cholesterol, impaired fasting glucose levels and hypertension, is almost 2 times more prevalent in patients with schizophrenia.[50]

Compared to healthy controls, patients with schizophrenia show higher glucose and insulin plasma fasting levels as well as a higher increases following glucose intake.[98,115] Schizophrenia has also been associated with hepatic insulin resistance, a condition often leading to type 2 diabetes[98,116,117] that is also thought to mediate the association between intra-abdominal fat and cardiovascular problems.[118] Since cortisol is known to lower insulin inhibition of hepatic glucose,[119] hypercortisolaemia has been proposed to be implicated in the pathogenesis of diabetes in schizophrenia.[106,107,120]

In summary, many endogenous physiological abnormalities observed in schizophrenia are likely to affect cardiovascular, endocrine and metabolic functions. Higher blood pressure, reduced baroreflex sensitivity and slower heart rate put patients with schizophrenia at higher risk of cardiovascular events. Higher levels of ghrelin and cortisol, two hormones that respectively promote food intake and central fat deposition, may contribute to endogenous weight gain mechanisms. Furthermore, interactions between these cardiovascular and weight problems are catalysed by high rates of diabetes related to insulin and glucose dysregulation. Because these factors are not easily modifiable by life habits changes, in the context of schizophrenia, they add to the obstacles complicating weight management.

CARDIOMETABOLIC SENSITIVITY TO VARIATIONS IN SLEEP AND THE CIRCADIAN SYSTEM

Ongoing research constantly deepens our understanding of the various functions of sleep, including its contribution to the maintenance of physical health. Multiple studies in healthy subjects have proposed that the homeostatic and circadian processes can impact on the regulation of many cardiovascular, endocrine and metabolic parameters that have been reported to be abnormal in schizophrenia.

Increased Homeostatic Sleep Pressure

In healthy volunteers, it has been experimentally demonstrated that increased homeostatic pressure through sleep deprivation causes a raise in systolic and diastolic blood pressure.[56,121,122] Moreover, sleep deprivation has

been shown to reduce the decrease in systolic blood pressure after an orthostatic perturbation.[123] Hence, sleep loss not only increases basal blood pressure but also induces alterations in arterial regulation, putting individuals with sleep difficulties at higher risk for vascular events.

Studies in chronic short sleepers and experimental studies using several days of sleep restriction indicate that high homeostatic pressure also alters metabolic and endocrine functions. For instance, shortened sleep increases morning glucose levels following food intake and reduces the insulin response to glucose.[6,124,125] These changes heighten the susceptibility of short sleepers to develop type 2 diabetes. Sleep restriction has also been shown to reduce leptin while increasing ghrelin levels,[125] an imbalance likely to potentiate weight gain. Accordingly, several epidemiological studies have linked sleep disturbances with being overweight.[126]

Circadian Rhythms Disruptions

Aside from regulating the sleep-wake cycle, the circadian system also has a strong influence on many cardiovascular and endocrine functions.

Leptin is subjected to a clear circadian modulation, reaching its maximum level in the evening and its lowest point in the morning. Although, ghrelin fluctuations are more affected by food intake than by circadian modulation, this hormone has also been shown to increase in the evening.[127] The secretion of cortisol by the adrenal gland also follows precise variations across 24 hours. Evening cortisol levels have been shown to increase in conditions of sleep restriction in healthy humans and high corticosterone, the dominant glucocorticoid in rodents, is associated with sleep fragmentation and lower deep sleep time.[6,128] Consequently, people with sleep difficulties are more likely to have high level of cortisol, especially in the evening when it is more likely to affect sleep onset. Glucose levels also fluctuate across 24 hours, peaking during the night. Moreover, serum glucose has a higher sensitivity to glucose intake in the evening and early night than in the morning and early afternoon,[129] while the insulin increase following glucose intake shows the reverse pattern.[130-132]

The SCN synchronises the circadian rhythms of blood pressure (through the myocardium), white adipose tissues, liver, and pancreas. When measured throughout a 24-hour cycle, blood pressure reaches its higher levels during the day and its lower levels during the night.[133]

Disorganization of some of those rhythms have been shown to lead to cardiovascular and metabolic disorders.[134-136] Moreover, using a 10-day forced desynchrony protocol, Scheer *et al.*[137] recently found that shifting eating and sleep-wake rhythms of healthy adults 12 hours from their usual schedule causes an increase in postprandial glucose, insulin and blood pressure, as well as a reduction in leptin.

In summary, studies in the healthy population have revealed that chronic short sleep is associated with high blood pressure, altered arterial regulation, increased postprandial glucose, decreased postprandial insulin, increased ghrelin and cortisol and reduced leptin. Importantly, some experimental studies demonstrated that sleep loss and circadian disruptions can play a causal role in those cardiometabolic and endocrine disturbances. Hence, the various physiological responses to increased homeostatic sleep pressure and deregulation of the circadian clock could contribute to the development of weight gain, cardiovascular and metabolic disorders in schizophrenia.

SLEEP AND CIRCADIAN RHYTHMS AS MODULATORS OF CARDIOMETABOLIC ABNORMALITIES IN SCHIZOPHRENIA

Because of their impacts on cardiovascular, metabolic and endocrine functions, the high prevalence of sleep and circadian disruptions in schizophrenia may play a role in the pathogenesis of cardiometabolic abnormalities. Additionally circadian dysregulation may effect inflammation, fibrinolysis, fluid balance, and vascular reactivity.[138] Metabolic disturbance may also disturb circadian rhythms in animal models.

By increasing blood pressure, ghrelin and cortisol levels, sleep loss may trigger a cascade of cardiovascular and endocrine changes increasing the risk for cardiovascular events and weight gain. Additionally, circadian misalignment observed in patients with schizophrenia may alter the circadian regulation of appetite and weight-related hormones as well as glucose tolerance and insulin dynamics.

Chronic sleep loss increases evening cortisol and high levels of cortisol are likely to reduce the ability to initiate and/or maintain consolidated sleep. Hence, bidirectional interactions between higher cortisol levels and sleep disruptions may contribute to the perpetuation of sleep and cardiometabolic disturbances in schizophrenia.

Importantly, in the general population, reversal of sleep loss and circadian disruption minimises/ameliorates negative metabolic and cardiovascular effects. Therefore, if cardiometabolic problems in schizophrenia are linked to

sleep/wake difficulties, sleep could be an efficient intervention target.

GENETIC EVIDENCE

The pathogenesis of schizophrenia is thought to result from the interaction between genetic and environmental factors.[139] For instance, the risk associated with genetic predisposition thought to be is further increased by exposure to prenatal infection,[140] depression of the mother during pregnancy,[141] birth in an urbanised milieu[142] and cannabis use, among others.[143]

While studies assessing the contribution of specific genes and genome-wide studies have not yet reach a consensus about the genetic profile of schizophrenia, recent research has highlighted associations with genes implicated in circadian rhythms and sleep homeostasis. Notably, these studies suggested that the schizophrenia phenotype was linked with some of the core molecular clock components, such as CLOCK, ARNTL, TIMELESS, NPAS2, PER1, PER2, PER3 and ROR β [144-146] (See Fig. 1 in Maury et al.[138]).

Importantly, some of those circadian genes have also been associated with cardiovascular dysfunction[147] and the metabolic syndrome.[138] Notably, CLOCK has been linked with lipid and glucose metabolism, platelet rhythmic activity and response of cardiomyocytes to fatty acids.[148-150] PER2 has been associated with variations in cholesterol and with the aortic endothelial function, while PER3 is linked with sympathovagal balance.[151,152] Moreover, an animal study has shown that mutation of the CLOCK gene leads to hyperphagia, obesity and metabolic syndrome characterised by hyperleptinemia, hyperlipidaemia, hepatic steatosis, hyperglycaemia, and hypoinsulinaemia.[153]

These overlaps between the clock genes associated with schizophrenia and cardiovascular/metabolic factors support the hypothesis that common mechanisms may be implicated in the pathogenesis of sleep/circadian disorders and cardiometabolic disturbances in schizophrenia.

CONCLUSION

Cardiometabolic disorders, such as hypertension, type 2 diabetes, obesity and the metabolic syndrome pose a serious threat to the physical health of people with schizophrenia. Many cardiometabolic and endocrine functions are modulated by sleep and circadian factors in the general population. This hypothesis driven review proposed that the high prevalence of sleep and circadian disturbances in people with schizophrenia might impact on their cardiovascular and metabolic health.

Management of cardiometabolic disturbances in schizophrenia should include support for a healthier lifestyle and diet, appropriate psychosocial interventions, close medical monitoring with proper pharmacological treatment and careful selection of antipsychotic medication in relation to each patient's cardiometabolic risk factors. Because treatment of sleep and circadian disorders has been shown to have positive outcomes on cardiometabolic functions in the general population, future empirical studies should assess the association between sleep and cardiometabolic disturbances in patients with schizophrenia. If such an association is confirmed, it would be important to integrate the management of sleep and circadian difficulties as an additional intervention target for cardiovascular and metabolic disorders in schizophrenia.

Simple non-pharmacological interventions have proven useful to address sleep and circadian disturbances in the general population. Notably, restoration of healthy sleep habits can be achieved through behavioural and cognitive interventions, and luminotherapy can be used to realign circadian rhythms.[154-159] The efficiency of these interventions in the schizophrenia population and the subsequent effects on cardiometabolic factors should be examined to assess their possible contribution to holistic physical health intervention programs in schizophrenia. It is feasible to suggest that the measurement of basic sleep and circadian parameters should be part of any new outcomes trial for the treatment of schizophrenia, perhaps revealing an independent axis of intervention for later studies.

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