REVIEW

Exploring the Association between Schizophrenia and Cardiovascular Diseases: Insights into the Role of Sigma 1 Receptor

Julie RAFCIKOVA[1], Marie NOVAKOVA[1], Tibor STRACINA[1]

[1]Department of Physiology, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Received March 15, 2023
Accepted June 15, 2023

Summary

Contemporary society is characterized by rapid changes. Various epidemiological, political and economic crises represent a burden to mental health of nowadays population, which may at least partially explain the increasing incidence of mental disorders, including schizophrenia. Schizophrenia is associated with premature mortality by at least 13–15 years. The leading cause of premature mortality in schizophrenia patients is high incidence of cardiovascular diseases. The specific-cause mortality risk for cardiovascular diseases in schizophrenia patients is more than twice higher as compared to the general population. Several factors are discussed as the factor of cardiovascular diseases development. Intensive efforts to identify possible link between schizophrenia and cardiovascular diseases are made. It seems that sigma 1 receptor may represent such link. By modulation of the activity of several neurotransmitter systems, including dopamine, glutamate, and GABA, sigma 1 receptor might play a role in pathophysiology of schizophrenia. Moreover, significant roles of sigma 1 receptor in cardiovascular system have been repeatedly reported. The detailed role of sigma 1 receptor in both schizophrenia and cardiovascular disorders development however remains unclear. The article presents an overview of current knowledge about the association between schizophrenia and cardiovascular diseases and proposes possible explanations with special emphasis on the role of the sigma 1 receptor.

Key words

Schizophrenia • Cardiovascular diseases • Sigma 1 receptor

Corresponding author

Tibor Stracina, Department of Physiology, Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic. E-mail: stracina@med.muni.cz

Schizophrenia as a public health concern

Ageing of population in the developed countries together with migration of vast groups of population result in new epidemiological situations worldwide. Age-related diseases appear together with almost eradicated (and also new) infectious diseases [1]. Moreover, all sorts of economic and political events represent a burden to mental health of nowadays population. All abovementioned factors may at least partially explain the increasing incidence of mental disorders. Among them, schizophrenia represents one of the mental disorders with the highest mortality risk [2].

Schizophrenia is a severe mental illness falling under the category of psychotic disorders. It has a profound impact on how people think, feel, and behave. The global prevalence of schizophrenia is 0.28 %; however, the annual prevalence in the US has been reported to reach up to 4.01 % suggesting a rising prevalence compared to previous years in the same study [3,4]. Patients with schizophrenia often experience difficulties functioning in society and may require life-long treatment to manage their symptoms. Furthermore, schizophrenia is associated with several physical comorbidities, which increase the disease burden and therefore both represent a major health issue researched upon mainly in the last two decades.

Schizophrenia usually develops in late adolescence or early adulthood. Its symptoms are typically categorized as positive, negative, and cognitive symptoms (Table 1). These symptoms may vary in each patient, range in severity, and change over time. Although, cognitive impairments are not yet an official

Table 1. List of the most common symptoms of schizophrenia.

Positive symptoms	Negative symptoms	Cognitive impairments
hallucinations	flat affect	working memory
delusions	anhedonia	executive function
disorganized behaviour	asociality	attention
motor symptoms	alogia	processing speed
disorganized speech	avolition - apathy	long-term memory
thought disorder symptoms	diminished activities of daily living	social cognition

diagnostic criterion for schizophrenia according to Diagnostic and Statistical Manual for Mental Disorders, a current resource to clinical practice, they are often present in patients with schizophrenia [5,6]. These symptoms can make it difficult for the person with schizophrenia to maintain relationships, hold down a job and integrate into society in general. This can lead to social isolation and, eventually, drug abuse with consequent increased risk for other diseases.

While the exact pathophysiology of schizophrenia is not yet fully understood, research has suggested several possible explanations, such as genetic, physical, psychological, and environmental factors [7]. However, these can only partially explain the disease process, as the underlying pathological mechanisms are complex and require further research.

Several hypotheses have been proposed throughout the years. Among them, the dopaminergic hypothesis dominates since all currently used antipsychotic drugs on the market target type 2 dopamine receptors (D2). First- and second-generation antipsychotics as D2 antagonists have been linked to ameliorating positive symptoms [8]. The third-generation antipsychotics, such as aripiprazole, are debated to be partial agonists or functionally selective for D2 receptors [9,10]. Long-term antipsychotic treatment has been linked with various side effects.

Since the dopaminergic hypothesis attributes primarily to positive symptoms, it wasn't sufficient to explain the complex pathogenesis of schizophrenia entirely. Therefore, the pathological process likely affects other neurotransmitter systems, such as glutamatergic, serotonergic, cholinergic, and gamma-aminobutyric acid (GABA) [11]. Inflammation and oxidative stress may also play an important role [12,13].

Schizophrenia is associated with premature mortality by at least 13–15 years, higher for men than women [14]. Even with declining all-cause mortality rates in the last two decades for both patients with schizophrenia and the general population, the 3-times greater mortality in schizophrenia persisted during this period [15]. Several reasons for premature mortality have been identified, including higher risk of suicide and accidents. However, the leading cause of excessive mortality in schizophrenia patients is increased incidence of somatic illnesses. Among them, cardiovascular diseases (CVD) account for most of the excessive deaths [16]. Other causes include various respiratory, urogenital, and gastroenterological diseases and tumours, with different contribution rates [2,17,18].

The article presents an overview of current knowledge about the association between schizophrenia and CVD and describes possible mechanisms of such association with special emphasis on the role of sigma 1 receptor.

Schizophrenia is associated with increased risk of cardiovascular diseases

Compared to the general population, the incidence and mortality of CVD are higher in patients with schizophrenia. In recent meta-analysis, a 2.2-fold greater specific-cause mortality risk was identified for CVD among patients with schizophrenia compared to the general population [2]. Moreover, the relative mortality risk for CVD was substantially higher in the young and the first-episode patients (relative risk 3.47) *versus* older and chronic patients (relative risk 1.98), which probably reflects the lower overall frequency of these diseases in the younger general population and of their earlier onset in schizophrenia patients [2].

Among CVD, schizophrenia is frequently associated with cerebrovascular disease and coronary heart disease [19]. For instance, higher risk of stroke incidence and mortality was identified in schizophrenia patients [20]. Increased short-term post-stroke mortality was reported to be more prominent in a younger-age group (<65) and in men [21]. Due to their social isolation,

patients with schizophrenia were less likely to receive reperfusion treatment, other interventions, and secondary pharmacological prevention [22–24]. Such findings highlight the importance of providing equal opportunities for patients with schizophrenia to receive appropriate treatment options to limit long-term disabilities from a stroke.

The leading cause of cerebral infarction is atrial fibrillation, with a 4 times increased risk of mortality for patients compared to the general population [25]. The risk of atrial fibrillation-related stroke can be effectively reduced by oral anticoagulation therapy [26]. In schizophrenia patients, the oral anticoagulation therapy initiation was significantly lower compared to atrial fibrillation controls in several studies [27–29]. One of possible explanations might be a higher risk of bleeding which represents a risk in these patients with frequent hazardous behaviour. However, a recent study reported no association of schizophrenia with higher risk of bleeding in patients with atrial fibrillation [30]. Although the same findings were presented in atrial fibrillation patients with other mental health diseases in a previous study [31], a recent meta-analysis showed that in atrial fibrillation patients with mental disease both bleeding risk and ischemic stroke risk are increased compared to patients without any mental disease [32].

Another CVD - myocardial infarction - in schizophrenia patients resulted in lower coronary revascularization rates compared to those without schizophrenia in several studies. This is an important factor contributing to higher-than-expected mortality risk in schizophrenic population [33,34]. The same was described in other severe mental illnesses [35]. The 36-years follow-up study of myocardial infarction in schizophrenia patients did not reveal statistical significance of the trend in increased long-term mortality. However, compared to myocardial infarction patients, in which the long-term mortality significantly declined due to improvement in diagnostics and treatment, such a trend emphasizes the need to pay special attention to post-infarction follow-up in schizophrenia patients [36]. More than doubled risk of major adverse cardiac events (all-cause mortality, reinfarction, stroke or heart failure) within 5 years after myocardial infarction was also reported in schizophrenia patients [37]. It has been reported that schizophrenia patients after myocardial infarction refused offers of both examination and treatment in an insignificant trend [38]. A more personalized approach and collaboration between cardiologists and psychiatrists might result in better treatment outcomes for these patients.

Hypertension, one of the most common CVD in the general population, represents a factor contributing to an increased risk of developing other CVD. The evidence of the association between schizophrenia and hypertension is ambiguous. A meta-analysis from 2018 claims that there is no such evidence and some other studies report similar findings [39–41]. While some studies found lower prevalence of hypertension in patients with schizophrenia [42,43], a recent study on drug-naive patients in their first episode of schizophrenia reported higher prevalence of hypertension [44]. Despite the lower prevalence compared to controls, hypertension was the most prevalent diagnosed comorbidity in schizophrenia patients [45].

On the other hand, hypertension - among other physical comorbidities - was significantly associated with development of schizophrenia [46] and with global cognitive impairment [47]. Hypertension also increases a risk of sudden cardiac death in schizophrenia patients and such risk even increases with age [48]. Moreover, several reports suggest that hypertension remains under-diagnosed and patients with schizophrenia receive low levels of overall and preventative care [39,49,50].

As mentioned previously, increased risk for heart failure within 5 years following MI was observed in schizophrenia patients [37]. In recent meta-analysis, increased incidence of HF in schizophrenia patients was also reported [51]. Furthermore, a higher mortality risk for HF compared to the general population [16,52] may partially explain the extending mortality gap between patients with and without schizophrenia.

Newly diagnosed HF patients with schizophrenia were less likely to receive high-quality HF care, defined as meeting more than 80 % of the guideline-based process-performance measures of care [52]. However, this study reported that these patients are not at higher risk of early 4-week readmission for nonpsychiatric diagnose.

In schizophrenia patients, congestive HF significantly contributed to an age-related elevated risk of sudden cardiac death. The overall risk of sudden cardiac arrest was reported to be significantly higher in all schizophrenia patients, regardless age and sex. The highest risk was reported in patients aged <35, specifically in the males [48]. For this study, a sudden cardiac death was defined as a death with a cardiac disease reported as the cause and occurring outside of

hospital (including the emergency room) or being classified as "death on arrival".

Despite the fact that CVD and CVD-related mortality are well known in schizophrenia patients, a Norwegian study reports that 66 % of schizophrenia patients were more likely to die due to undiagnosed CVD [53].

Cardiovascular risk factors in schizophrenia patients

Several factors contributing to the development of cardiovascular diseases are discussed in patients with schizophrenia (Fig. 1) [54,55]. Patients with schizophrenia exhibit a tendency towards an unhealthy lifestyle, which comes from the nature of their disease. Negative schizophrenia symptoms, including amotivation and anhedonia, lead to decreased physical activity [56]. Besides other factors (e.g., neurotransmitter and hormonal changes), physical inactivity contributes to development of obesity and metabolic syndrome in schizophrenia patients [57]. Alcoholism, nicotine abuse and other addictions – all of which are frequent among patients with schizophrenia - may even worsen the situation [58]. For example, the rate of hypertension in schizophrenia patients with substance abuse was significantly higher than in schizophrenia patients without such disorder [59]. Additionally, smoking has been associated with a higher prevalence of hypertension in patients with schizophrenia [60]. Moreover, physical disorders are frequently underdiagnosed and treated insufficiently due to social isolation and negative discrimination of the patients [61,62].

Some of the above-mentioned factors, such as weight gain and metabolic dysregulation, are frequently accelerated by adverse effects of antipsychotic treatment [63–65]. Obesity and accompanying metabolic effects are particularly frequent in second-generation antipsychotics [66,67]. Antipsychotic treatment is also associated with dyslipidaemia and impaired glucose metabolism. Dyslipidaemia is strongly related to weight gain and significantly increases risk of cardiovascular mortality [65].

Direct cardiovascular adverse effects of antipsychotics are sporadic and include arterial hypertension [68], QTc interval prolongation and sudden cardiac death [69]. In a recent study of a cohort treated with clozapine, hypertension was associated with increased hazard ratio for mortality [70].

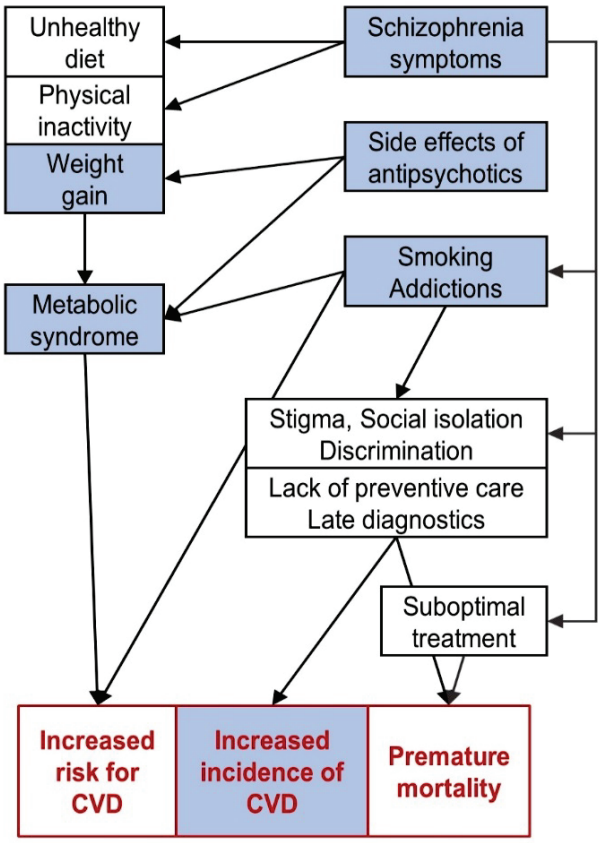

Fig. 1. Contributing factors to the development of cardiovascular diseases and subsequent premature mortality in patients with schizophrenia. Blue panels represent factors, in which sigma 1 receptor may play a role. CVD – cardiovascular diseases. Figure is adopted from [55].

In addition, antipsychotics can induce various non-cardiovascular adverse effects that can indirectly impact cardiovascular health. Particularly, extrapyramidal symptoms, including dystonia, akinesia, akathisia, Parkinsonism, and tremor, as well as tardive dyskinesia characterized by slow, repetitive, involuntary movements, can further stigmatize patients undergoing antipsychotic treatment. Consequently, these symptoms may contribute to social isolation and negative discrimination experienced by patients with schizophrenia. Furthermore, the manifestation of these adverse effects may decrease patient adherence to therapy.

Despite the side effects, the non-use of antipsychotics has been linked to more than twofold increased mortality risk in schizophrenia patients [71]. Antipsychotics alleviate psychotic symptoms, which may also increase the adherence of the patients to cardiovascular treatment and healthier lifestyle [72].

Sigma 1 receptor: a key player in association between schizophrenia and cardiovascular diseases?

Sigma receptor can hardly be considered unexplored: it was first reported already in 1976 and since then thousands of studies have been performed focusing on its structure, signalling, location, ligands, and function(s) both in health and disease [73–77]. However, certain questions remain so far unanswered. The main puzzle is the identification of the endogenous ligand for the sigma receptor, which is still undiscovered, although numerous substances have been proposed as hot candidates for this role: steroids – namely progesterone and DHEA, endogenous opioids, phencyclidine, etc. Initially, the very promising substance NN-dimethyl-tryptamine [78] was disqualified as endogenous ligand for the sigma receptor [79].

Soon after the discovery the sigma receptors were classified as sigma 1 and sigma 2 [80]. Based on the present knowledge that sigma 1 receptor is a resident protein of the endoplasmic reticulum, it is able to translocate within the cell, and that it functions as an intracellular chaperon [81–83], question arises as to whether an endogenous ligand for this binding site is indeed necessary (in other words whether it truly exists): sigma receptor binds various proteins in numerous cells and it leads to numerous consequent processes, which is in agreement with vast list of papers reporting plentiful functions attributed to sigma receptor.

The history of sigma receptor is full of suggestions which were later refused and/or corrected by intensive research. For example, sigma receptors were first reported in the central nervous system, but later they were found to be widely expressed in numerous peripheral tissues, both neural and non-neural. In the CNS, high density of sigma receptors was reported in olfactory bulb, several hypothalamic nuclei, septum, central grey, certain motor nuclei of the hindbrain, and dorsal horn of spinal cord [84]. Among peripheral non-neural tissues, immune, endocrine, reproductive, and digestive tissues are most prevalent [85], although sigma receptors are found at high density also in other tissues, such as all types of muscle cells [86,87] and cancer cells [88,89]. The widespread locations of sigma receptors reflect the long list of functions that have been proposed for them – from modulation of immune system to cardiac contractility [90]. High density of sigma receptors in immune, endocrine and nervous systems may represent a sort of functional link among them as suggested by some authors [91,92].

Due to the absence of an endogenous ligand, the sigma receptor is currently defined as a saturable, non-opioid, non-dopaminergic binding site exhibiting high affinity for several important classes of psychotropic drugs [93]. It is well documented that numerous chemical compounds binding with high affinity to sigma receptors are drugs targeting dopamine receptors, mostly substances used in the treatment of various mental disorders [94]. The impact of sigma ligands on modulation of various receptor systems and/or types of second messengers was studied soon after sigma receptor classification [95] and numerous studies were focused on dopamine receptors. For example, an increase in dopamine synthesis, its metabolism and modulation of its release by sigma receptors was reported by Weatherspoon *et al.* [96]. Nuwayhid and Werling [97] reported NMDA-stimulated dopamine release in rat striatal slices mediated by sigma receptor activation. Lencesova *et al.* [98] studied the role of dopamine receptors in upregulation of sigma 1 receptors in H9c2 cells, caused by prototypic sigma ligand haloperidol, antipsychotic agent acting likewise as dopamine type 2 receptor antagonist. Antagonising dopamine 2 receptors by haloperidol led to upregulation of sigma 1 receptors and dopamine 2 receptor and to decreased expression of type 1 dopamine receptor. Gursoy *et al.* [99] observed attenuation of hypoxia-induced dopamine release by sigma ligand haloperidol in rat striatum slices. An interesting study focused on sigma 1 receptor as a regulator of dopamine neurotransmission was performed by Sambo *et al.* [100]: it was suggested that sigma 1 receptor may represent a potential target in the methamphetamine addiction treatment due to its unique chaperon activity.

By modulation of the activity of several neurotransmitter systems, including dopamine, glutamate, and GABA, sigma 1 receptor may play a role in pathophysiology of schizophrenia. Sigma 1 receptors have been shown to modulate the release of dopamine and glutamate in the brain, which are two neurotransmitters that are strongly implicated in the development of schizophrenia. Mice with sigma-1 receptor knockout show alterations in expression of the dopamine transporter and in phosphorylation of the glutamate NMDA NR2B receptor [101]. In addition, some studies have suggested that sigma 1 receptor agonists may have potential as a new class of antipsychotic drugs for the treatment of schizophrenia

[102]. Recent study reports that allosteric modulation of sigma 1 receptor elicits antipsychotic-like effects [103]. Overall, while the exact role of sigma 1 receptors in schizophrenia is still being investigated, there is evidence to suggest that they may be a promising target for the development of new treatment strategies for the disorder.

Roles of sigma 1 receptor in cardiovascular system have been repeatedly reported [74]. Recently, sigma 1 receptor signalling was reviewed as new therapeutic target for CVD [104]. Although sigma 1 receptor may participate in the pathogenesis of both schizophrenia and cardiovascular diseases, it is unclear whether it may represent a link between these diseases. However, various studies suggest that sigma 1 receptor plays a significant role in enhancing specific cardiovascular risk factors.

Sigma 1 receptor and metabolic risk factors

Well-known cardiovascular metabolic risk factors include insulin resistance, impaired glucose metabolism, dyslipidaemia, and abdominal obesity. Each of these factors represents an increased risk for CVD development. Moreover, the coexistence of these factors further increases the cardiovascular risk. Therefore, the aforementioned factors together with hypertension are integrated into a clinical unit - metabolic syndrome. The prevalence of metabolic syndrome in schizophrenia patients is higher than in normal population and is rising with age [105].

On the cellular level, sigma 1 receptor mediates an interplay between endoplasmic reticulum and mitochondria. Such interplay is crucial for maintaining cellular energy metabolism and integrity. Sigma 1 receptor knockdown led to dysfunction and apoptosis induced by fatty acids in MIN6 cells, cellular model of pancreatic beta cells derived from a mouse insulinoma [106]. The function of the sigma 1 receptor in obesity-induced metabolic dysfunction was studied using mice models [107]. Sigma 1 receptor expression was significantly increased in the hearts of male mice on high fat diet as compared to controls (on standard diet). Sigma 1 receptor knockout mice on high fat diet showed deteriorated cardiac function and adverse cardiac remodelling [107]. Such findings suggest a potential protective role of sigma 1 receptor in myocardium.

Sigma 1 receptor and antipsychotic treatment

As mentioned above, most of the metabolic risk factors are accelerated by antipsychotic treatment. Weight gain is very frequent side effect of olanzapine, clozapine, and other second-generation antipsychotics. In animal models, blockade of dopamine D2/3 receptors, histamine H1 receptors, and serotonin 5-HT2 receptors has been identified as a possible mechanism for antipsychotic-induced weight gain [108]. Through the blockade of the receptors, reward pathways associated with food consumption and satiation signalling are disrupted, which may lead to changes in food intake and subsequently to weight gain in schizophrenia patients treated with antipsychotics [109]. Sigma 1 receptor protein-protein interactions with all the aforementioned receptor systems have been clearly demonstrated in animal and cellular models [110]. Whether the sigma 1 receptor can directly affect the disrupted pathways remains unclear.

A few antipsychotic drugs are able to bind directly on sigma 1 receptor. Among them, haloperidol has the highest affinity. Haloperidol is connected with QT interval prolongation, increased risk of severe ventricular arrhythmias and sudden cardiac death, which has been reported by clinical studies and meta-analyses [111,112]. QT prolongation and QT/RR coupling disruption after haloperidol administration have been repeatedly reported in various animal models [113,114]. Effects of haloperidol on cardiac electric activity may be partially explained by direct effect on cardiac calcium and potassium ion channels [115,116]. Moreover, haloperidol administration led to increase of sigma 1 receptor expression in the heart [113,117]. However, all the above-mentioned findings were observed in animals without any neurobehavioral deficits. The sigma 1 receptor expression in schizophrenia patient treated with haloperidol has not been studied yet.

Sigma 1 receptor and substance abuse

Addictive behaviour is very frequent in schizophrenia patients (as repeatedly reported by large number of clinical studies, for review see [58]). Various hypotheses have been proposed to explain high incidence of addictions in schizophrenia patients, including the social-environmental hypothesis, the possible shared biological vulnerability (e.g., genetic determinants), and the theory of self-medication.

Extensive research has documented the significant role of sigma 1 receptor in addiction to several substances – particularly to methamphetamine and cocaine – due to their strong affinities to the sigma 1 receptor [118,119]. Sigma 1 receptor has also been suggested as a potential mediator of alcohol reward and

reinforcement in alcohol use disorder [120]. Despite extensive evidence suggesting that sigma 1 receptor antagonists can mitigate the toxic cellular or behavioural effect of addictive substances and/or decrease their consumption and rewarding effects, further studies are needed to demonstrate therapeutic potential of sigma 1 receptor modulation.

Future directions

Schizophrenia represents one of the major public health concerns. The burden of schizophrenia is progressively increasing with substantial economic and social consequences and significant impact on health worldwide [3]. Despite known risk factors, the incidence and mortality of CVD in schizophrenia patients is more than twice as high compared to the general population. Besides further research, better co-operation of psychiatric and cardiovascular health care is required to prolong life expectancy of schizophrenia patients.

Significant association of schizophrenia with CVD may indicate certain molecular mechanisms or genetic determinants common for both diseases. Nevertheless, no clear link between these two diseases has been proven yet. Sigma 1 receptor, a pluripotent cell modulator, may play a role in such association. However, further studies are needed to shed more light on a role of sigma 1 receptor in schizophrenia and the association between schizophrenia and CVD.

In particular, future studies should focus on: (1) investigating the molecular mechanisms by which sigma 1 receptor might influence the development of schizophrenia, CVD, and their associated risk factors; (2) evaluating the potential of sigma 1 receptor modulation as a therapeutic strategy for schizophrenia, CVD, and the management of associated risk factors, such as metabolic syndrome and substance abuse; (3) investigating the potential genetic determinants and shared biological vulnerabilities between schizophrenia and CVD, and how these may be influenced by sigma 1 receptor activity; (4) utilizing neurodevelopmental animal models with induced specific neurobehavioral deficits to elucidate the complex interplay between sigma 1 receptor function, schizophrenia, and CVD.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

This article was funded by Masaryk University as a part of the project no. MUNI/A/1343/2022 with the support of the Specific University Research Grant, as provided by the Ministry of Education, Youth and Sports of the Czech Republic in the year 2023.

References

1. Baker RE, Mahmud AS, Miller IF, Rajeev M, Rasambainarivo F, Rice BL, Takahashi S, Tatem AJ, Wagner CE, Wang LF, Wesolowski A, Metcalf CJE. Infectious disease in an era of global change. Nat Rev Microbiol. 2022;20:193-205. https://doi.org/10.1038/s41579-021-00639-z
2. Correll CU, Solmi M, Croatto G, Schneider LK, Rohani-Montez SC, Fairley L, Smith N, Bitter I, Gorwood P, Taipale H, Tiihonen J. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry. 2022;21:248-271. https://doi.org/10.1002/wps.20994
3. Charlson FJ, Ferrari AJ, Santomauro DF, Diminic S, Stockings E, Scott JG, McGrath JJ, Whiteford HA. Global epidemiology and burden of schizophrenia: findings from the global burden of disease study 2016. Schizophr Bull. 2018;44:1195-1203. https://doi.org/10.1093/schbul/sby058
4. Pilon D, Patel C, Lafeuille MH, Zhdanava M, Lin D, Côté-Sergent A, Rossi C, Joshi K, Lefebvre P.Prevalence, incidence and economic burden of schizophrenia among Medicaid beneficiaries. Curr Med Res Opin. 2021;37:1811-1819. https://doi.org/10.1080/03007995.2021.1954894
5. American Psychiatric Association, American Psychiatric Association, eds. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed. American Psychiatric Association; 2013. https://doi.org/10.1176/appi.books.9780890425596
6. Bora E, Akdede BB, Alptekin K. Neurocognitive impairment in deficit and non-deficit schizophrenia: a meta-analysis. Psychol Med. 2017;47:2401-2413. https://doi.org/10.1017/S0033291717000952

7. Janoutová J, Janácková P, Serý O, Zeman T, Ambroz P, Kovalová M, Varechová K, Hosák L, Jiríк V, Janout V. Epidemiology and risk factors of schizophrenia. Neuro Endocrinol Lett. 2016;37:1-8.
8. Leucht S, Leucht C, Huhn M, Chaimani A, Mavridis D, Helfer B, Samara M, Rabaioli M, Bächer S, Cipriani A, Geddes JR, Salanti G, Davis JM.Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry. 2017;174:927-942. https://doi.org/10.1176/appi.ajp.2017.16121358
9. Mailman RB, Murthy V. Third generation antipsychotic drugs: partial agonism or receptor functional selectivity? Curr Pharm Des. 2010;16:488-501. https://doi.org/10.2174/138161210790361461
10. tuplin ew, holahan mr. aripiprazole. a drug that displays partial agonism and functional selectivity. Curr Neuropharmacol. 2017;15:1192-1207. https://doi.org/10.2174/1570159X15666170413115754
11. Yang AC, Tsai SJ. New targets for schizophrenia treatment beyond the dopamine hypothesis. Int J Mol Sci. 2017;18:E1689. https://doi.org/10.3390/ijms18081689
12. Mongan D, Ramesar M, Föcking M, Cannon M, Cotter D. Role of inflammation in the pathogenesis of schizophrenia: A review of the evidence, proposed mechanisms and implications for treatment. Early Interv Psychiatry. 2020;14:385-397. https://doi.org/10.1111/eip.12859
13. Murray AJ, Rogers JC, Katshu MZUH, Liddle PF, Upthegrove R. Oxidative stress and the pathophysiology and symptom profile of schizophrenia spectrum disorders. Front Psychiatry. 2021;12. https://www.frontiersin.org/articles/10.3389/fpsyt.2021.703452. https://doi.org/10.3389/fpsyt.2021.703452
14. Hjorthøj C, Stürup AE, McGrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry. 2017;4:295-301. https://doi.org/10.1016/S2215-0366(17)30078-0
15. Gatov E, Rosella L, Chiu M, Kurdyak PA. Trends in standardized mortality among individuals with schizophrenia, 1993-2012: a population-based, repeated cross-sectional study. CMAJ. 2017; 189(37):E1177-E1187. https://doi.org/10.1503/cmaj.161351
16. Westman J, Eriksson SV, Gissler M, Hällgren J, Prieto ML, Bobo WV, Frye MA, Erlinge D, Alfredsson L, Ösby U.Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. Epidemiol Psychiatr Sci. 2018;27:519-527. https://doi.org/10.1017/S2045796017000166
17. Yung NCL, Wong CSM, Chan JKN, Chen EYH, Chang WC. Excess mortality and life-years lost in people with schizophrenia and other non-affective psychoses: an 11-year population-based cohort study. Schizophr Bull. 2021;47(2):474-484. https://doi.org/10.1093/schbul/sbaa137
18. Girardi P, Schievano E, Fedeli U, Braggion M, Nuti M, Amaddeo F. Causes of mortality in a large population-based cohort of psychiatric patients in Southern Europe. J Psychiatr Res. 2021;136:167-172. https://doi.org/10.1016/j.jpsychires.2021.01.050
19. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, Thapa-Chhetri N, *et al.* Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry. 2017;16:163-180. https://doi.org/10.1002/wps.20420
20. Li M, Fan YL, Tang ZY, Cheng XS. Schizophrenia and risk of stroke: A meta-analysis of cohort studies. Int J Cardiol. 2014;173:588-590. https://doi.org/10.1016/j.ijcard.2014.03.101
21. Yung NCL, Wong CSM, Chan JKN, Or PCF, Chen EYH, Chang WC. Mortality in patients with schizophrenia admitted for incident ischemic stroke: A population-based cohort study. Eur Neuropsychopharmacol. 2020;31:152-157. https://doi.org/10.1016/j.euroneuro.2019.12.107
22. Bongiorno DM, Daumit GL, Gottesman RF, Faigle R. Patients with stroke and psychiatric comorbidities have lower carotid revascularization rates. Neurology. 2019;92:e2514-e2521. https://doi.org/10.1212/WNL.0000000000007565
23. Willers C, Sunnerhagen KS, Lekander I, von Euler M. The association of pre-stroke psychosis and post-stroke levels of health, resource utilization, and care process: a register-based study. Front Neurol. 2018;9:1042. https://doi.org/10.3389/fneur.2018.01042

24. Kapral MK, Kurdyak P, Casaubon LK, Fang J, Porter J, Sheehan KA. Stroke care and case fatality in people with and without schizophrenia: a retrospective cohort study. BMJ Open. 2021;11:e044766. https://doi.org/10.1136/bmjopen-2020-044766
25. Lee E, Choi EK, Han KD, Lee H, Choe WS, Lee SR, Cha MJ, Lim WH, Kim YJ, Oh S. Mortality and causes of death in patients with atrial fibrillation: A nationwide population-based study. Plos One. 2018;13:e0209687. https://doi.org/10.1371/journal.pone.0209687
26. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857. https://doi.org/10.7326/0003-4819-146-12-200706190-00007
27. Højen AA, Nielsen PB, Riahi S, Jensen M, Lip GYH, Larsen TB, Søgaard M. Disparities in oral anticoagulation initiation in patients with schizophrenia and atrial fibrillation: A nationwide cohort study. Br J Clin Pharmacol. 2022;88:3847-3855. https://doi.org/10.1111/bcp.15337
28. Jaakkola J, Teppo K, Biancari F, Halminen O, Putaala J, Mustonen P, Haukka J, Linna M, Kinnunen J, Tiili P, Aro AL, Hartikainen J, Airaksinen KEJ, Lehto M. The effect of mental health conditions on the use of oral anticoagulation therapy in patients with atrial fibrillation: the FinACAF study. Eur Heart J - Qual Care Clin Outcomes. 2022;8:269-276. https://doi.org/10.1093/ehjqcco/qcab077
29. Fenger-Grøn M, Vestergaard CH, Ribe AR, Johnsen SP, Frost L, Sandbæk A, Davydow DS. Association between bipolar disorder or schizophrenia and oral anticoagulation use in Danish adults with incident or prevalent atrial fibrillation. JAMA Netw Open. 2021;4(5):e2110096. https://doi.org/10.1001/jamanetworkopen.2021.10096
30. Teppo K, Jaakkola J, Biancari F, *et al.* Mental health conditions and bleeding events in patients with incident atrial fibrillation: A Finnish nationwide cohort study. Gen Hosp Psychiatry. 2022;78:117-122. https://doi.org/10.1016/j.genhosppsych.2022.08.003
31. Søgaard M, Skjøth F, Kjældgaard JN, Larsen TB, Hjortshøj SP, Riahi S. Atrial fibrillation in patients with severe mental disorders and the risk of stroke, fatal thromboembolic events and bleeding: a nationwide cohort study. BMJ Open. 2017;7:e018209. https://doi.org/10.1136/bmjopen-2017-018209
32. Teppo K, Jaakkola J, Lehto M, Biancari F, Airaksinen KEJ. The impact of mental health conditions on oral anticoagulation therapy and outcomes in patients with atrial fibrillation: A systematic review and meta-analysis. Am J Prev Cardiol. 2021;7:100221. https://doi.org/10.1016/j.ajpc.2021.100221
33. Shao M, Zhuo C, Gao X, Chen C, Xu Y, Tian H, Li G, Jiang D, Wang W. Reduced rate of revascularization in schizophrenic patients with acute myocardial infarction: A systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2020;99:109870. https://doi.org/10.1016/j.pnpbp.2020.109870
34. Shao M, Tian H, Wang L, Jiang D, Ji F, Zhuo C. Mortality risk following acute coronary syndrome among patients with schizophrenia: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2020;96:109737. https://doi.org/10.1016/j.pnpbp.2019.109737
35. Fleetwood K, Wild SH, Smith DJ, Mercer SW, Licence K, Sudlow CLM, Jackson CA. Severe mental illness and mortality and coronary revascularisation following a myocardial infarction: a retrospective cohort study. BMC Med. 2021;19:67. https://doi.org/10.1186/s12916-021-01937-2
36. Kugathasan P, Laursen TM, Grøntved S, Jensen SE, Aagaard J, Nielsen RE. Increased long-term mortality after myocardial infarction in patients with schizophrenia. Schizophr Res. 2018;199:103-108. https://doi.org/10.1016/j.schres.2018.03.015
37. Attar R, Wester A, Koul S, *et al.* Higher risk of major adverse cardiac events after acute myocardial infarction in patients with schizophrenia. Open Heart. 2020;7(2):e001286. https://doi.org/10.1136/openhrt-2020-001286
38. Attar R, Johansen MB, Valentin JB, Aagaard J, Jensen SE. Treatment following myocardial infarction in patients with schizophrenia. PLOS ONE. 2017;12(12):e0189289. https://doi.org/10.1371/journal.pone.0189289
39. Ayerbe L, Forgnone I, Addo J, Siguero A, Gelati S, Ayis S. Hypertension risk and clinical care in patients with bipolar disorder or schizophrenia; a systematic review and meta-analysis. J Affect Disord. 2018;225:665-670. https://doi.org/10.1016/j.jad.2017.09.002
40. Chiu M, Rahman F, Vigod S, Wilton AS, Kurdyak P. Temporal trends in cardiovascular disease risk factor profiles in a population-based schizophrenia sample: a repeat cross-sectional study. J Epidemiol Community Health. 2018;72(1):71-77. https://doi.org/10.1136/jech-2017-209565

41. Lurie I, Shoval G, Hoshen M, Balicer R, Weiser M, Weizman A, Krivoy A. The association of medical resource utilization with physical morbidity and premature mortality among patients with schizophrenia: An historical prospective population cohort study. Schizophr Res. 2021;237:62-68. https://doi.org/10.1016/j.schres.2021.08.019
42. Gur S, Weizman S, Stubbs B, Matalon A, Meyerovitch J, Hermesh H, Krivoy A. Mortality, morbidity and medical resources utilization of patients with schizophrenia: A case-control community-based study. Psychiatry Res 2018;260:177-181. https://doi.org/10.1016/j.psychres.2017.11.042
43. Attar R, Valentin JB, Freeman P, Andell P, Aagaard J, Jensen SE. The effect of schizophrenia on major adverse cardiac events, length of hospital stay, and prevalence of somatic comorbidities following acute coronary syndrome. Eur Heart J - Qual Care Clin Outcomes 2019;5:121-126. https://doi.org/10.1093/ehjqcco/qcy055
44. Lang X, Liu Q, Fang H, Zhou Y, Forster MT, Li Z, Zhang X. The prevalence and clinical correlates of metabolic syndrome and cardiometabolic alterations in 430 drug-naive patients in their first episode of schizophrenia. Psychopharmacology (Berl). 2021;238:3643-3652. https://doi.org/10.1007/s00213-021-05983-9
45. Gabilondo A, Alonso-Moran E, Nuño-Solinis R, Orueta JF, Iruin A. Comorbidities with chronic physical conditions and gender profiles of illness in schizophrenia. Results from PREST, a new health dataset. J Psychosom Res. 2017;93:102-109. https://doi.org/10.1016/j.jpsychores.2016.12.011
46. Chen YL, Pan CH, Chang CK, Chen PH, Chang HM, Tai MH, Su SS, Tsai SY, Chen CC, Kuo CJ. Physical illnesses before diagnosed as schizophrenia: a nationwide case-control study. Schizophr Bull. 2020;46:785-794. https://doi.org/10.1093/schbul/sbaa009
47. Hagi K, Nosaka T, Dickinson D, Lindenmayer JP, Lee J, Friedman J, Boyer L, Han M, Abdul-Rashid NA, Correll CU. Association between cardiovascular risk factors and cognitive impairment in people with schizophrenia: a systematic review and meta-analysis. JAMA Psychiatry. 2021;78(5):510-518. https://doi.org/10.1001/jamapsychiatry.2021.0015
48. Chen PH, Tsai SY, Pan CH, Chang HM, Chen YL, Su SS, Chen CC, Kuo CJ. Age effect on incidence, physical, and psychiatric comorbidity for sudden cardiac death in schizophrenia. (in French). Can J Psychiatry. 2021;66:367-375. https://doi.org/10.1177/0706743720948429
49. Nasrallah HA, Meyer JM, Goff DC, McEvoy JP, Davis SM, Stroup TS, Lieberman JA. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: Data from the CATIE schizophrenia trial sample at baseline. Schizophr Res. 2006;86:15-22. https://doi.org/10.1016/j.schres.2006.06.026
50. Launders N, Kirsh L, Osborn DPJ, Hayes JF. The temporal relationship between severe mental illness diagnosis and chronic physical comorbidity: a UK primary care cohort study of disease burden over 10 years. Lancet Psychiatry. 2022;9:725-735. https://doi.org/10.1016/S2215-0366(22)00225-5
51. Lambert AM, Parretti HM, Pearce E, *et al.* Temporal trends in associations between severe mental illness and risk of cardiovascular disease: A systematic review and meta-analysis. PLOS Med 2022;19(4):e1003960. https://doi.org/10.1371/journal.pmed.1003960
52. Jørgensen M, Mainz J, Egstrup K, Johnsen SP. Quality of care and outcomes of heart failure among patients with schizophrenia in Denmark. Am J Cardiol. 2017;120:980-985. https://doi.org/10.1016/j.amjcard.2017.06.027
53. Heiberg IH, Jacobsen BK, Balteskard L, Bramness JG, Naess Ø, Ystrom E, Reichborn-Kjennerud T, Hultman CM, Nesvåg R, Høye A. Undiagnosed cardiovascular disease prior to cardiovascular death in individuals with severe mental illness. Acta Psychiatr Scand. 2019;139:558-571. https://doi.org/10.1111/acps.13017
54. Perez-Pinar M, Mathur R, Foguet Q, Ayis S, Robson J, Ayerbe L. Cardiovascular risk factors among patients with schizophrenia, bipolar, depressive, anxiety, and personality disorders. Eur Psychiatry. 2016;35:8-15. https://doi.org/10.1016/j.eurpsy.2016.02.004
55. Peritogiannis V, Ninou A, Samakouri M. Mortality in schizophrenia-spectrum disorders: recent advances in understanding and management. Healthc Basel Switz. 2022;10:2366. https://doi.org/10.3390/healthcare10122366
56. Milian MJ, Fone K, Steckler T, Horan WP. Negative symptoms of schizophrenia: Clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. Eur Neuropsychopharmacol. 2014;24:645-692. https://doi.org/10.1016/j.euroneuro.2014.03.008
57. Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU. Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. Acta Psychiatr Scand. 2015;132:97-108. https://doi.org/10.1111/acps.12445

58. Batel P. Addiction and schizophrenia. Eur Psychiatry J Assoc Eur Psychiatr. 2000;15:115-122. https://doi.org/10.1016/S0924-9338(00)00203-0
59. Onyeka IN, Collier Høegh M, Nåheim Eien EM, Nwaru BI, Melle I. Comorbidity of physical disorders among patients with severe mental illness with and without substance use disorders: a systematic review and meta-analysis. J Dual Diagn. 2019;15:192-206. https://doi.org/10.1080/15504263.2019.1619007
60. Li Z, Wang S, Chen Y, Wu X, Gu Y, Lang X, Wu F, Zhang XY. Smoking affects the patterns of metabolic disorders and metabolic syndrome in patients with first-episode drug-naive schizophrenia: a large sample study based on the chinese han population. Int J Neuropsychopharmacol. 2021;24:798-807. https://doi.org/10.1093/ijnp/pyab038
61. Bradford DW, Kim MM, Braxton LE, Marx CE, Butterfield M, Elbogen EB. Access to medical care among persons with psychotic and major affective disorders. Psychiatr Serv. 2008;59:847-852. https://doi.org/10.1176/ps.2008.59.8.847
62. Roberts L, Roalfe A, Wilson S, Lester H. Physical health care of patients with schizophrenia in primary care: a comparative study. Fam Pract. 2007;24:34-40. https://doi.org/10.1093/fampra/cml054
63. Tek C, Kucukgoncu S, Guloksuz S, Woods SW, Srihari VH, Annamalai A. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. Early Interv Psychiatry. 2016;10:193-202. https://doi.org/10.1111/eip.12251
64. Castillo-Sánchez M, Fàbregas-Escurriola M, Bergè-Baquero D, Foguet-Boreu Q, Fernández-San Martín MI, Goday-Arno A. Schizophrenia, antipsychotic drugs and cardiovascular risk: Descriptive study in primary care. Eur Psychiatry J Assoc Eur Psychiatr. 2015;30:535-541. https://doi.org/10.1016/j.eurpsy.2014.12.010
65. Abosi O, Lopes S, Schmitz S, Fiedorowicz JG. Cardiometabolic effects of psychotropic medications. Horm Mol Biol Clin Investig. 2018;36:/j/hmbci.2018.36.issue-1/hmbci-2017-0065/hmbci-2017-0065.xml. https://doi.org/10.1515/hmbci-2017-0065
66. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. The Lancet. 2009;373:31-41. https://doi.org/10.1016/S0140-6736(08)61764-X
67. Hirsch L, Yang J, Bresee L, Jette N, Patten S, Pringsheim T. Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies. Drug Saf. 2017;40:771-781. https://doi.org/10.1007/s40264-017-0543-0
68. Hammoudeh S, Al Lawati H, Ghuloum S, Iram H, Yehya A, Becetti I, Al-Fakhri N, Ghabrash H, Shehata M, Ajmal N, Amro I, Safdar H, Eltorki Y, Al-Amin H. Risk factors of metabolic syndrome among patients receiving antipsychotics: a retrospective study. Community Ment Health J. 2020;56:760-770. https://doi.org/10.1007/s10597-019-00537-y
69. Straus SMJM, Bleumink GS, Dieleman JP, *et al.* Antipsychotics and the risk of sudden cardiac death. Arch Intern Med. 2004;164(12):1293-1297. https://doi.org/10.1001/archinte.164.12.1293
70. Taub S, Hoshen M, Balicer R, Kamhi-Nesher S, Weizman A, Krivoy A. Metabolic predictors for mortality among patients treated with long-term clozapine - A longitudinal study. Eur Neuropsychopharmacol. 2020;41:63-69. https://doi.org/10.1016/j.euroneuro.2020.09.002
71. Strømme MF, Mellesdal LS, Bartz-Johannesen C, Kroken RA, Krogenes M, Mehlum L, Johnsen E. Mortality and non-use of antipsychotic drugs after acute admission in schizophrenia: A prospective total-cohort study. Schizophr Res. 2021;235:29-35. https://doi.org/10.1016/j.schres.2021.07.009
72. Laursen TM, Nordentoft M, Mortensen PB. Excess Early Mortality in Schizophrenia. Annu Rev Clin Psychol. 2014;10:425-448. https://doi.org/10.1146/annurev-clinpsy-032813-153657
73. Smith SB, Su TP, eds. Sigma Receptors: Their Role in Disease and as Therapeutic Targets. Vol 964. Springer International Publishing; 2017. https://doi.org/10.1007/978-3-319-50174-1_1
74. Stracina T, Novakova M. Cardiac Sigma Receptors - An Update. Physiol Res. Published online December 28, 2018:S561-S576. https://doi.org/10.33549/physiolres.934052
75. Aydar E, Cobos EJ, Maurice T, Murell-Lagnado RD, Safrany ST. Editorial: Sigma Receptors. Front Pharmacol. 2020;11. https://www.frontiersin.org/articles/10.3389/fphar.2020.590519, https://doi.org/10.3389/fphar.2020.590519

76. Aishwarya R, Abdullah CS, Morshed M, Remex NS, Bhuiyan MdS. Sigmar1's Molecular, Cellular, and Biological Functions in Regulating Cellular Pathophysiology. Front Physiol. 2021;12. Accessed January 14, 2023. https://www.frontiersin.org/articles/10.3389/fphys.2021.705575, https://doi.org/10.3389/fphys.2021.705575
77. Sałaciak K, Pytka K. Revisiting the sigma-1 receptor as a biological target to treat affective and cognitive disorders. Neurosci Biobehav Rev. 2022;132:1114-1136. https://doi.org/10.1016/j.neubiorev.2021.10.037
78. Fontanilla D, Johannessen M, Hajipour AR, Cozzi NV, Jackson MB, Ruoho AE. The hallucinogen N,N-Dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. Science. 2009;323(5916):934-937. https://doi.org/10.1126/science.1166127
79. Nichols DE. N,N-dimethyltryptamine and the pineal gland: Separating fact from myth. J Psychopharmacol (Oxf). 2018;32:30-36. https://doi.org/10.1177/0269881117736919
80. Quirion R, Bowen WD, Itzhak Y, Junien JL, Musacchio JM, Rothman RB, Su TP, Tam SW, Taylor DP. A proposal for the classification of sigma binding sites. Trends Pharmacol Sci. 1992;13:85-86 https://doi.org/10.1016/0165-6147(92)90030-A
81. Hayashi T, Su TP. Regulating ankyrin dynamics: Roles of sigma-1 receptors. Proc Natl Acad Sci. 2001;98(2):491-496. https://doi.org/10.1073/pnas.98.2.491
82. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER- mitochondrion interface regulate Ca2+ signaling and cell survival. Cell. 2007;131:596-610. https://doi.org/10.1016/j.cell.2007.08.036
83. Mori T, Hayashi T, Hayashi E, Su TP. Sigma-1 Receptor Chaperone at the ER-Mitochondrion Interface Mediates the Mitochondrion-ER-Nucleus Signaling for Cellular Survival. PLOS ONE. 2013;8(10):e76941. https://doi.org/10.1371/journal.pone.0076941
84. Alonso G, Phan V, Guillemain I, Saunier M, Legrand A, Anoal M, Maurice T. Immunocytochemical localization of the sigma1 receptor in the adult rat central nervous system. Neuroscience. 2000;97:155-170. https://doi.org/10.1016/S0306-4522(00)00014-2
85. Hellewell SB, Bruce A, Feinstein G, Orringer J, Williams W, Bowen WD. Rat liver and kidney contain high densities of σ1 and σ2 receptors: characterization by ligand binding and photoaffinity labeling. Eur J Pharmacol Mol Pharmacol. 1994;268:9-18. https://doi.org/10.1016/0922-4106(94)90115-5
86. Ela C, Barg J, Vogel Z, Hasin Y, Eilam Y. Sigma receptor ligands modulate contractility, Ca++ influx and beating rate in cultured cardiac myocytes. J Pharmacol Exp Ther. 1994;269(3):1300-1309.
87. Novakova M, Ela C, Barg J, Vogel Z, Hasin Y, Eilam Y. Inotropic action of σ receptor ligands in isolated cardiac myocytes from adult rats. Eur J Pharmacol. 1995;286:19-30. https://doi.org/10.1016/0014-2999(95)00424-J
88. Crawford KW, Bowen WD. Sigma-2 Receptor Agonists Activate a Novel Apoptotic Pathway and Potentiate Antineoplastic Drugs in Breast Tumor Cell Lines1. Cancer Res. 2002;62:313-322.
89. Megalizzi V, Le Mercier M, Decaestecker C. Sigma receptors and their ligands in cancer biology: overview and new perspectives for cancer therapy. Med Res Rev. 2012;32:410-427. https://doi.org/10.1002/med.20218
90. Novakova M. Sigma receptors: With special reference to cardiac muscle. Exp Clin Cardiol. 1998;3(3):113-120.
91. Su TP. σ receptors. Eur J Biochem. 1991;200:633-642. https://doi.org/10.1111/j.1432-1033.1991.tb16226.x
92. Wolfe SA, De Souza EB. Sigma and phencyclidine receptors in the brain-endocrine-immune axis. NIDA Res Monogr. 1993;133:95-123. https://doi.org/10.1037/e495962006-007
93. Brune S, Pricl S, Wünsch B. Structure of the σ 1 Receptor and its ligand binding site: miniperspective. J Med Chem. 2013;56:9809-9819. https://doi.org/10.1021/jm400660u
94. Hayashi T, Su TP, Kagaya A, Nishida A, Shimizu M, Yamawaki S. Neuroleptics with differential affinities at dopamine D2 receptors and sigma receptors affect differently the N-methyl-D-aspartate-induced increase in intracellular calcium concentration: Involvement of protein kinase. Synapse. 1999;31(1):20-28. https://doi.org/10.1002/(SICI)1098-2396(199901)31:1<20::AID-SYN4>3.0.CO;2-2
95. Bowen WD. Interaction of sigma receptors with signal transduction pathways and effects on second messengers. London: Academic Press; 1994:139-165.
96. Weatherspoon JK, Gonzalez-Alvear GM, Frank AR, Werling LL. Regulation of [3H]dopamine release from mesolimbic and mesocortical areas of guinea pig brain by sigma receptors. Schizophr Res. 1996;21:51-62. https://doi.org/10.1016/0920-9964(96)00030-8

97. Nuwayhid SJ, Werling LL. ς 1 Receptor agonist-mediated regulation of N-Methyl-d-aspartate-stimulated [3H] dopamine release is dependent upon protein kinase C. J Pharmacol Exp Ther. 2003;304:364-369. https://doi.org/10.1124/jpet.102.043398
98. Lencesova L, Szadvari I, Babula P, Kubickova J, Chovancova B, Lopusna K, Rezuchova I, Novakova Z, Krizanova O, Novakova M. Disruption of dopamine D1/D2 receptor complex is involved in the function of haloperidol in cardiac H9c2 cells. Life Sci. 2017;191:186-194. https://doi.org/10.1016/j.lfs.2017.10.026
99. Gursoy M, Gul Z, Buyukuysal RL. Sigma receptor ligands haloperidol and ifenprodil attenuate hypoxia induced dopamine release in rat striatum. Neurol Res. 2022;44:927-936. https://doi.org/10.1080/01616412.2022.2072100
100. Sambo DO, Lebowitz JJ, Khoshbouei H. The sigma-1 receptor as a regulator of dopamine neurotransmission: A potential therapeutic target for methamphetamine addiction. Pharmacol Ther. 2018;186:152-167. https://doi.org/10.1016/j.pharmthera.2018.01.009
101. Hong J, Sha S, Zhou L, Wang C, Yin J, Chen L. Sigma-1 receptor deficiency reduces MPTP-induced parkinsonism and death of dopaminergic neurons. Cell Death Dis. 2015;6:e1832. https://doi.org/10.1038/cddis.2015.194
102. Hayashi T, Su TP. An update on the development of drugs for neuropsychiatric disorders: focusing on the σ1 receptor ligand. Expert Opin Ther Targets. 2008;12:45-58. https://doi.org/10.1517/14728222.12.1.45
103. Chen J, Li G, Qin P, *et al.* Allosteric Modulation of the Sigma-1 Receptor Elicits Antipsychotic-like Effects. Schizophr Bull. 2022;48:474-484. https://doi.org/10.1093/schbul/sby054, https://doi.org/10.1093/schbul/sbab137
104. Munguia-Galaviz FJ, Miranda-Diaz AG, Cardenas-Sosa MA, Echavarria R. Sigma-1 receptor signaling: in search of new therapeutic alternatives for cardiovascular and renal diseases. Int J Mol Sci. 2023;24:1997. https://doi.org/10.3390/ijms24031997
105. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders - a systematic review and meta-analysis. Schizophr Bull. 2013;39:306-318. https://doi.org/10.1093/schbul/sbs082, https://doi.org/10.1093/schbul/sbr148
106. Ke M, He G, Wang H, Cheng S, Xu Y. Sigma receptor knockdown augments dysfunction and apoptosis of beta cells induced by palmitate. Exp Biol Med Maywood NJ. 2021;246:1491-1499. https://doi.org/10.1177/1535370221997780
107. Abdullah CS, Alam S, Aishwarya R, *et al.* Molecular function of Sigma-1 receptor in obesity-induced metabolic dysfunction. J Mol Cell Cardiol. 2017;112:149. https://doi.org/10.1016/j.yjmcc.2017.07.058
108. Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. Neuropharmacology. 2020;172:107704. https://doi.org/10.1016/j.neuropharm.2019.107704
109. Grimm O, Kaiser S, Plichta MM, Tobler PN. Altered reward anticipation: Potential explanation for weight gain in schizophrenia? Neurosci Biobehav Rev. 2017;75:91-103. https://doi.org/10.1016/j.neubiorev.2017.01.029
110. Su TP, Su TC, Nakamura Y, Tsai SY. The sigma-1 receptor as a pluripotent modulator in living systems. Trends Pharmacol Sci. 2016;37:262-278. https://doi.org/10.1016/j.tips.2016.01.003
111. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet Lond Engl. 2013;382:951-962. https://doi.org/10.1016/S0140-6736(13)60733-3
112. Wu C, Tsai Y, Tsai H. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation‐wide case‐crossover study. J Am Heart Assoc. 4:e001568.
113. Stracina T, Slaninova I, Polanska H, Axmanova M, Olejnickova V, Konecny P, Masarik M, Krizanova O, Novakova M. Long-term haloperidol treatment prolongs qt interval and increases expression of sigma 1 and IP3 receptors in guinea pig hearts. Tohoku J Exp Med. 2015;236:199-207. https://doi.org/10.1620/tjem.236.199
114. Vesely P, Stracina T, Hlavacova M, Halamek J, Kolarova J, Olejnickova V, Mrkvicova V, Paulova H, Novakova M. Haloperidol affects coupling between QT and RR intervals in guinea pig isolated heart. J Pharmacol Sci. 2019;139:23-28. https://doi.org/10.1016/j.jphs.2018.11.004
115. Tarabová B, Nováková M, Lacinová L. Haloperidol moderately inhibits cardiovascular L-type calcium current. Gen Physiol Biophys. 2009;28:249-259. https://doi.org/10.4149/gpb_2009_03_249

116. Bébarová M, Matejovic P, Pásek M, Nováková M. Effect of haloperidol on transient outward potassium current in rat ventricular myocytes. Eur J Pharmacol. 2006;550:15-23. https://doi.org/10.1016/j.ejphar.2006.08.046
117. Novakova M, Sedlakova B, Sirova M, Fialova K, Krizanova O. Haloperidol increases expression of the inositol 1,4,5-trisphosphate receptors in rat cardiac atria, but not in ventricles. Gen Physiol Biophys. 2010;29:381-389. https://doi.org/10.4149/gpb_2010_04_381
118. Nguyen EC, McCracken KA, Liu Y, Pouw B, Matsumoto RR. Involvement of sigma (sigma) receptors in the acute actions of methamphetamine: receptor binding and behavioral studies. Neuropharmacology. 2005; 49:638-645. https://doi.org/10.1016/j.neuropharm.2005.04.016
119. Chen Y, Hajipour AR, Sievert MK, Arbabian M, Ruoho AE. Characterization of the cocaine binding site on the sigma-1 receptor. Biochemistry. 2007;46:3532-3542. https://doi.org/10.1021/bi061727o
120. Quadir SG, Cottone P, Sabino V. Role of sigma receptors in alcohol addiction. Front Pharmacol. 2019;10. Accessed March 15, 2023. https://doi.org/10.3389/fphar.2019.00687