

DOI: <https://doi.org/10.17816/nb643639>



Malignant Comorbidity: Schizophrenia and Smoking

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ABSTRACT

The prevalence of smoking among individuals with schizophrenia is higher than in those with other mental disorders and several times greater than in the general population. Moreover, the severity of tobacco dependence in patients with schizophrenia significantly exceeds that in individuals without serious psychiatric illnesses. Schizophrenia is associated with an increased susceptibility to cardiovascular and metabolic diseases, as well as a high rate of premature mortality due to both medical causes and suicide. Smoking significantly magnifies the issue, contributing to both poor physical health and increased mortality rates. The decrease in tobacco use observed in many regions of the world over recent decades has only minimally affected individuals with schizophrenia. Standard smoking reduction strategies and tobacco dependence treatments have proven ineffective or insufficiently effective for individuals with schizophrenia, which highlights the need for the development of new preventive measures and therapeutic interventions.

Keywords: schizophrenia; schizophrenic spectrum disorders; positive symptoms; negative symptoms; depressive symptoms; dual diagnosis; smoking; cardiovascular diseases; metabolic disorders; malignancies; premature mortality; suicide; self-medication hypothesis.

To cite this article:

Sivolap YuP, Portnova AA. Malignant Comorbidity: Schizophrenia and Smoking. *Neurology Bulletin*. 2025;57(1):80–88. DOI: <https://doi.org/10.17816/nb643639>

Received: 05.01.2025

Accepted: 07.01.2025

Published online: 02.02.2025

DOI: <https://doi.org/10.17816/nb643639>

Злокачественная коморбидность: шизофрения и курение

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АННОТАЦИЯ

Распространённость курения у людей с шизофренией выше, чем у индивидов с другими психическими расстройствами, и в несколько раз превышает общепопуляционные показатели. Кроме того, тяжесть табачной зависимости у пациентов с шизофренией значительно превосходит таковую у людей без серьёзных психических расстройств. Шизофрения ассоциирована с особой подверженностью сердечно-сосудистым и метаболическим болезням и высокой частотой преждевременных смертей как по медицинским причинам, так и в связи с суицидами. Курение в значительной степени усугубляет проблему как неудовлетворительного физического здоровья, так и повышенной летальности. Уменьшение частоты курения, отмеченное за последние десятилетия во многих регионах мира, лишь в небольшой степени коснулось людей с шизофренией. Общепринятые стратегии снижения распространённости курения и лечения табачной зависимости оказываются неэффективными или недостаточно эффективными у людей с шизофренией, что определяет необходимость разработки новых профилактических мер и терапевтических вмешательств.

Ключевые слова: шизофрения; расстройства шизофренического спектра; позитивные симптомы; негативные симптомы; депрессивные симптомы; двойной диагноз; курение; сердечно-сосудистые болезни; метаболические болезни; злокачественные опухоли; преждевременные смерти; суицид; гипотеза самолечения.

Как цитировать:

Сиволап Ю.П., Портнова А.А. Злокачественная коморбидность: шизофрения и курение // Неврологический вестник. 2025. Т. 57, № 1. С. 80–88.

DOI: <https://doi.org/10.17816/nb643639>

DOI: <https://doi.org/10.17816/nb643639>

Яман сыйфатлы коморбидлык: шизофрения һәм тәмәке тарту

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АННОТАЦИЯ

Шизофренияле авырулар арасында тәмәке тарту башка психик тайпылышлы индивидларга караганда киңрәк таралган һәм гомумпопуляция күрсәткечләреннән берничә тапкырга артыграк. Моннан тыш, шизофрения белән авыручы пациентларда тәмәкегә бәйлелекнең кыенлыгы житди психик тайпылышлары булмаган кешеләрдәгедән шактый көчлөрәк. Шизофрения йөрәк-кан тамырлары һәм метаболизм авыруларына ешрак бирешү, вакытыннан алда үлемгә китерү (медицина сәбәпләре буенча да, суицидлар белән бәйле рәвештә дә) белән ассоциацияләнә. Тәмәке тарту физик яктан сәламәтлек проблемасын да, үлем очраklarын да шактый катлауландыра. Соңгы берничә дистә еллар эчендә дөньяның күп кенә төбәкләрендә тәмәке тарту күренешенең кимүе шизофрения белән авыручы кешеләргә бик аз дәрәжәдә генә кагылды. Тәмәке тартуны киметүгә, тәмәкегә бәйлелекне дәвалауга юнәлтелгән гомуми стратегияләрне шизофрения белән авыручы кешеләр белән эшләгәндә куллану житәрлек дәрәжәдә нәтижәле түгел, бу исә әлеге юнәлештә яңа профилактика чаралары һәм дәвалау алымнары булдыруның кирәклеге күрсәтә.

Төп сүзләр: шизофрения; шизофрения спектры тайпылышлары; уңай симптомнар; тискәре симптомнар; депрессия симптомнары; икеле диагноз; тәмәке тарту; йөрәк-кан тамырлары авырулары; метаболизм авырулары; яман шешләр; вакытыннан алда үлү; суицид (мордар китү); үз-үзеңне дәвалау гипотезасы.

Өземтәләр ясау өчен:

Сиволап Ю.П., Портнова А. А. Яман сыйфатлы коморбидлык: шизофрения һәм тәмәке тарту // Неврология хәбәрләре. 2025. Т. 57, № 1. 80–88 б.

DOI: <https://doi.org/10.17816/nb643639>

Schizophrenia is a serious mental disorder characterized by adverse physical health outcomes and significantly higher rates of premature mortality compared with the general population.

According to various estimates, people with schizophrenia live 10–25 years less than those without severe mental disorders¹ [1].

A study in Ontario (Canada) of 13,385 individuals aged 16–45 years with schizophrenia spectrum disorders (SSDs) found that 1/25 inpatients and 1/40 outpatients died within five years of initial diagnosis. This mortality rate is 9–13 times higher than expected for this age group [2].

Premature mortality in those with SSDs is primarily attributed to natural causes such as cardiovascular and other diseases, including malignancies, cardiometabolic changes induced by antipsychotic medications, and suicide, which is the predominant cause of unnatural death² [3].

Cardiovascular and other diseases are thought to account for approximately 60%, whereas suicides and accidents account for about 40% of premature deaths in schizophrenia [4].

The critical gap in mortality rates affects all age groups, indicating that the causes of death are not limited to age-related diseases. This phenomenon is not regarded as a stable indicator and may potentially increase in the future³ [5].

Comorbid substance abuse plays a significant role in poor health and increased mortality (including cardiovascular disease, malignancy, and suicidality) in people with schizophrenia.

According to the summary data, 40% to 60% of people with SSDs (one in two on average) have substance abuse of some kind [1].

Dual diagnosis — the co-occurrence of psychiatric and addictive disorders, such as schizophrenia and nicotine dependence — is a complex problem in clinical medicine.

The particular drama of this comorbid pair is that schizophrenia is a severe mental disorder that often has an unfavorable course, leads to disability, has a devastating impact on the individual and their family, and is associated with a significant reduction in life expectancy. Conversely, tobacco and nicotine dependence is one of the leading causes of premature mortality. The combination of these disorders significantly increases the risk of medical death.

Smoking is more frequent in individuals with schizophrenia than in the general population and more common than in any other psychiatric disorder.

According to Myles et al. [6], the prevalence of smoking among individuals with a first episode of schizophrenia is 58.9%, increasing subsequently up to 70%–80% [7].

A survey of 1938 individuals revealed that 62% of those with schizophrenia, 37% with bipolar disorder, and 17% without a psychiatric disorder were current smokers.

The prevalence of smoking in the sample exhibited a decline over time, primarily attributable to a decrease in smoking observed in the control group. Patients with schizophrenia and bipolar disorder smoked more cigarettes per day compared with smokers in the control group. However, the number of cigarettes smoked per day decreased significantly in all groups during the study period. The frequency and severity of nicotine dependence were significantly associated with older age, limited education, white race, and male sex.

The authors note that the prevalence of smoking among people with schizophrenia and bipolar disorder remains “alarmingly high” and that the gap between psychiatric patients who smoke and those without psychiatric disorders is widening, suggesting that additional measures are urgently needed to address this serious public health problem [8].

Freudenreich [9] has reported that the prevalence of smoking among patients diagnosed with schizophrenia ranged from 80% to 90% prior to the 1990s, decreased to 62% in 2016, yet remains at 80% in certain medical facilities. In contrast, the prevalence of smoking in the general population of Massachusetts reached an all-time low of 14% in 2015, which is approximately average for the United States.

Men with schizophrenia smoke more often than women, reflecting patterns in the general population; however, women smoke more cigarettes per day than men [10].

Although the prevalence of smoking in schizophrenia is higher than in other psychiatric disorders and significantly higher than in the general population, people with schizophrenia are particularly prone to heavy nicotine dependence: in fact, they smoke more cigarettes per day than smokers without psychiatric disorders [11–13].

Smokers with schizophrenia take more frequent and deeper drags on a cigarette compared with the control group, thereby increasing their exposure to the harmful components of tobacco and tobacco smoke [14].

Remarkably, individuals who subsequently develop schizophrenia exhibit a higher prevalence of smoking prior to the onset of the disease when compared with the general population. This increased smoking prevalence before the onset of schizophrenia is not related to its prodromal manifestations, and therefore cannot be explained by the self-medication hypothesis [15].

The high comorbidity of schizophrenia and smoking suggests a mutual conditioning of the two disorders. Schizophrenia obviously contributes to the need for nicotine;

¹ Similar shortening of life expectancy rates are reported for patients with bipolar disorder.

² Contemporary terminology includes the concepts of natural and unnatural causes of death. The former include diseases and other medical factors, whereas the latter include suicide, homicide, and accidents.

³ The cited article was published in 2014.

however, it is legitimate to pose the question of whether heavy tobacco use contributes to the symptoms of schizophrenia.

Observational studies using methods that allow causal inference (e.g., instrumental variable methods or appropriately adjusted longitudinal observational studies) indicate that smoking is a likely causal risk factor for depression, bipolar disorder, and schizophrenia [16].

The frequent association of schizophrenia and smoking suggests a common genetic predisposition to both disorders, which has been confirmed in several studies.

Genomic studies of the association between schizophrenia and smoking have revealed biological pleiotropy, with the 15q25 locus influencing both traits.

In particular, Ohi et al. [17] conducted a quantitative analysis of trait expression loci in ten postmortem brain regions using the BRAINEAC dataset from 134 healthy individuals and demonstrated that 22 genetic variants in 15q25 locus were associated with both the number of smokers and schizophrenia. The major alleles of all genetic variants associated with a greater number of smokers and risk of schizophrenia were found to be associated with *PSMA4*, *CHRNA3*, and *CHRNA4* expression.

The authors suggest that variants associated with nicotine dependence and schizophrenia may share a common pathophysiological basis, including altered *CHRNA5* expression in the brain [17].

In addition to a common genetic predisposition, possible reasons for the high prevalence and severity of tobacco dependence in schizophrenia include the use of smoking as an available coping strategy for anxiety and other psychological distress, as well as for improving cognitive function and reducing extrapyramidal symptoms induced by antipsychotics.

When nicotine acts on neuronal⁴ nicotinic acetylcholine receptors projecting to the ventral tegmental area and mesolimbic pathways, the reward system is activated. This is manifested by dopamine release from mesolimbic neurons, as well as enhanced cholinergic transmission in the nucleus accumbens, amygdala, and hippocampus, and the resulting reinforcing effect that underlies substance dependence [18].

In addition to dopamine and acetylcholine, nicotine modulates the neurotransmission of serotonin, noradrenaline, glutamate, opioids, and gamma-aminobutyric acid. Notably, in addition to the stimulation of dopamine release, nicotine exhibits the properties of an inhibitor of both types of monoamine oxidase (A and B), which promotes the conversion of dopamine to inactive metabolites [19].

The increase in dopaminergic activity that occurs under the influence of nicotine may be considered a counterbalance

to the hypofunction of the central nervous system described in the published studies [7, 20]. This hypofunction is reflected in apathetic states and other negative manifestations of schizophrenia that are well known to clinicians.

Apparently, the ability of nicotine to reduce extrapyramidal disorders induced by antipsychotics and to improve the mental state of people with schizophrenia, including by reducing depressive symptoms, is related to these effects, partially confirming the validity of the self-medication hypothesis mentioned above.

The enhanced tolerability of antipsychotics in the presence of nicotine may be attributable to a combination of factors, including a reduction in extrapyramidal symptoms, an acceleration of medication metabolism, and a decline in plasma concentrations⁵ [21].

Data from different studies on the effect of smoking on the symptoms of schizophrenia (especially its negative manifestations) are contradictory.

There is an association between smoking in schizophrenia and depression (positive and negative symptoms), and lower quality of life [22].

However, there are some open issues regarding explanations for the observed correlation. These include the following: whether tobacco dependence may be considered as an indicator of the severity of psychiatric disorders; whether smoking is a non-specific manifestation of the general high addictive comorbidity typical of schizophrenia; and whether smoking in patients with schizophrenia reflects the need for nicotine as a means of mitigating psychiatric disorders in proportion to the degree of their clinical expression.

Ding and Hu [7] cite various study data on both the mitigation of negative symptoms of schizophrenia under the influence of smoking [23] and their intensification [12, 24].

A systematic review of 8 morphological and 14 functional studies provides evidence of widespread gray matter reduction associated with SSDs and smoking, with no evidence of a correlation between the two, and notes the possibility of mitigation of neuronal connectivity deficits⁶ under the influence of smoking.

The authors emphasize the limited number of works, with the predominance of cross-sectional studies, as well as a considerable overlap of samples between different studies. This limitation does not allow for the determination of the nature and extent of the effect of smoking on brain function in patients with SSDs. The authors suggest the presence of a specific neurobiological basis of tobacco dependence in this patient category, which may be due to differences in the level of nicotinic acetylcholine receptors [22].

⁴ In addition to neuronal, there are also muscle nicotinic receptors.

⁵ A potential adverse outcome of the observed effect may be a reduced effect of antipsychotic therapy.

⁶ The observed neurophysiological characteristic of patients with schizophrenia is often attributed to, the negative symptoms of this disease, among other things.

Follow-up of 145 treatment-naïve men with a first episode of schizophrenia showed no differences in positive and negative symptoms between smokers and non-smokers at baseline, as measured by the Positive and Negative Syndrome Scale (PANSS). However, after 12 weeks of antipsychotic monotherapy, smokers showed a greater reduction in negative symptoms in relation to age, years of education, age at smoking initiation, and baseline body mass index [25].

Some evidence supports the hypothesis that nicotine, as an agonist of nicotinic-type acetylcholine receptors, may improve cognitive function. However, this view is somewhat contradicted by the finding that smoking is associated with worse cognitive performance in patients with schizophrenia than in non-smokers [26].

Kanniah and Kumar, commenting on the idea of some mental health professionals that nicotine improves the mental state of people with schizophrenia, showed that the harm associated with smoking outweighs any potential benefits of nicotine for psychiatric patients [27].

Psychosis occurs 2–3 times more frequently in individuals with severe nicotine dependence compared with the general population [11].

Tobacco-related illnesses are among the leading causes of preventable death in patients with schizophrenia, and smoking is associated with a worse course of schizophrenia, including exacerbation of psychosis and repeated hospitalizations [22].

Smoking contributes to the development of cardiovascular disease. Since cardiovascular causes account for up to 50% of excess deaths in schizophrenia [28], tobacco dependence in patients with this disorder is particularly dramatic.

The prevalence of smoking among 1213 patients with SSDs observed during 1994–2000 was 55%, whereas the incidence of illicit drug abuse was as high as 71%.

An association between age and smoking ($\chi^2=14.6$; $df=1$; $p=0.0001$) was found for mortality, with calculated hazard ratios for smokers and non-smokers of 2.1 for those aged 35 to 54 years and 0.7 for those aged 55 to 69 years. The five- and ten-year mortality rates for smokers aged 35–54 years were 7.0% and 14.2%, respectively, compared with 3.3% and 10.0% for non-smokers ($\chi^2=5.53$, $df=1$, $p=0.019$). Cardiac causes were identified in 43% of smoker deaths and only 19% of non-smoker deaths ($p<0.006$). Smokers aged 35–54 years were 12 times more likely to die from cardiovascular causes than non-smokers (odds ratio [OR]=12.4; $\chi^2=12.0$; $df=1$; $p=0.0005$). People aged 35–54 years who smoked more than one pack of cigarettes per day had a significantly higher risk of all-cause mortality (OR=2.7) compared with non-smokers.

The authors conclude that cigarette smoking, especially among individuals aged 35–54 years, contributes significantly to the risk of mortality. They further state that the most serious efforts should be applied to identify strategies to reduce smoking in people with schizophrenia [29].

Additionally, smoking appears to be the underlying factor contributing to the high prevalence of cardiovascular and respiratory diseases and malignancies as primary causes of early death in people with schizophrenia [26].

The issue of schizophrenia and smoking comorbidity is exacerbated by a significant dissociation. On the one hand, the prevalence of nicotine dependence in individuals with SSDs, as has been repeatedly emphasized, is considerably higher than in the general population. On the other hand, only a limited number of patients successfully cease smoking.

A meta-analysis of 14 comparative and observational studies, including 5062 patients with schizophrenia and 3511 controls, found that smoking cessation rates in schizophrenia do not exceed 14%, which is significantly lower than the rates in healthy participants and patients with other psychiatric disorders [30].

Approaches used in the treatment of nicotine dependence in individuals without severe psychiatric disorders have not been as effective as expected in smokers with schizophrenia. This may be partially due to the particular predisposition of individuals with SSDs to addictive behavior (including tobacco use) and increased nicotine cravings.

Recent public health initiatives⁷ aimed at reducing smoking among individuals under 30 years of age have not yielded the expected outcomes in those with severe psychotic disorders [31].

Johnstone et al. [32], based on a systematic review and meta-analysis of 16 laboratory studies of acute nicotine withdrawal in patients with schizophrenia, found a marked predominance of reward-related cravings for the substance over more moderate cravings reflecting the need for relief. The authors conclude that the first type of craving should represent a key target for therapeutic interventions in patients attempting to stop smoking. They emphasize that influencing the second type of craving with the identification of specific therapeutic targets (memory impairment, negative affect, anxiety, restlessness, and irritability) is also relevant to clinical practice.

A significant barrier to formulating guidelines on the treatment of nicotine dependence in patients diagnosed with schizophrenia is the exclusion of individuals with this condition from laboratory and intervention studies⁸ [32].

One of the reasons cited for the lack of support for patients with severe psychiatric disorders and comorbid tobacco dependence is physicians' concern that smoking cessation might worsen patients' disease course or quality of life.

⁷ The cited article was published in 2014.

⁸ The lack of treatment protocols is a common problem with dual diagnosis. For many decades, comorbid addictions served as a criterion for excluding patients from psychiatric research. Conversely, psychiatric diagnoses prevented patients from participating in research on addictive disorders, although this deficit has recently begun to be overcome, with an increasing number of papers focusing specifically on dual diagnosis.

In a 12-week study of 178 patients with severe psychiatric disorders⁹, each additional pack of cigarettes smoked per day was associated with a 0.83-point increase in negative symptoms on the Brief Psychiatric Rating Scale. Conversely, a reduction in the number of cigarettes smoked per day by one pack was associated with a 0.32-point improvement in health-related quality of life, as measured by the Lehman Quality of Life Interview–Short Version.

Researchers conclude that people with severe mental disorders and their treating physicians should strive to quit smoking without fear of worsening their mental health or reducing their quality of life [33].

The possibility of effective treatment of nicotine dependence without the risk of worsening schizophrenia symptoms has been confirmed by other authors [7, 32].

Based on the data from many studies, including their own, Taylor and Treur [16] state that smoking cessation is not harmful to mental health but, on the contrary, is highly likely to improve patients' condition. This is indirectly supported by the reduction in prescriptions for antidepressants and anxiolytics in tobacco dependence remission¹⁰.

Despite the inadequate efficacy of commonly accepted therapeutic protocols for treating nicotine dependence

in patients with schizophrenia, the search for ways to at least partially address this problem should continue. This is important because smoking is a modifiable¹¹ factor for premature mortality in schizophrenia.

A synthesis of the aforementioned data indicates the need for emphasizing the complexity and ongoing challenges associated with schizophrenia complicated by smoking. This multifaceted medical problem necessitates substantial efforts from psychiatrists and other healthcare specialists to identify effective solutions.

ADDITIONAL INFORMATION

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that there is no potential conflict of interest requiring disclosure in this article.

Authors' contribution. Yu.P. Sivolap, A.A. Portnova — concept development, research, collection and analysis of literature, writing an article. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conducting the study and preparing the article, read and approved the final version before publication).

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⁹ Apparently, the authors use this term to avoid stigmatizing concepts, although the clinical descriptions given in the paper are clearly consistent with schizophrenia.

¹⁰ The above data were obtained from patients with affective disorders as well as schizophrenia.

¹¹ Modifiable factors are defined as factors that may be changed, as opposed to non-modifiable factors such as age or race.

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