



The Effect of Cigarettes on Schizophrenia Patients

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ABSTRACT

Introduction: The prevalence of smoking in patients with schizophrenia is still high around 70-80%. While studies indicate that smoking may increase the risk of developing schizophrenia, the exact role of smoking in this connection still needs further exploration. The purpose of the study was to explain schizophrenia, dopamine, the etiology of cigarette use in patients with schizophrenia, the mechanism of action, the relationship between schizophrenia cases and cigarettes, the management of patients with schizophrenia and the relationship between the administration of antipsychotics to patients with schizophrenia and active smokers. The data collection method used is data derived from literature studies obtained from journals, books, and dissertations of Google Scholar and PubMed. The data collection tool used is documents.

Results: The nicotine in cigarettes interacts with nicotinic receptors in the brain, affecting the release of dopamine and serotonin. This can affect negative symptoms in schizophrenic patients, although the effect on positive symptoms still needs more research to be fully understood. Although the exact mechanism is not yet fully understood, some hypotheses indicate that smoking may play a role in managing negative symptoms and influencing impaired dopamine regulation in schizophrenia. Schizophrenia patients who are also active smokers face challenges in treatment with antipsychotics such as clozapine and olanzapine. Appropriate adjustment of antipsychotic doses is needed to optimize the management of schizophrenic symptoms without increasing the risk of unwanted side effects.

Conclusion: In patients with schizophrenia the production of the neurotransmitter dopamine is excessive. When dopamine levels are unbalanced, excessive or reduced, sufferers can experience both positive and negative symptoms. Although smoking may provide some benefits in reducing negative symptoms of schizophrenia, the overall impact is still complex and requires more research. Future studies are expected to better understand the mechanism of interaction between smoking and schizophrenia and develop better treatment strategies.

Introduction

The rate of smoking among individuals with schizophrenia remains high. Smoking is prevalent in psychotic disorders, with schizophrenia affecting around 70-80% of smokers. While some studies propose that smoking may raise the likelihood of

developing schizophrenia, the precise role of smoking in this connection still requires further exploration. Smokers with schizophrenia tend to experience more severe positive symptoms and cognitive impairments, although the intensity of extrapyramidal side effects is lower in

comparison with schizophrenia patients who are non-smokers (Mu et al., 2024).

Schizophrenia (SCZ) Schizophrenia (SCZ) is a long-term and serious mental illness that impacts 1% of the global population. Individuals with schizophrenia often have hallucinations, disorganized thoughts, and are susceptible to delusions and paranoia. The symptoms of schizophrenia are categorized into positive and negative symptoms (Mu et al., 2024).

Negative symptoms refer to a reduction in typical behaviors linked to everyday activities, including social interactions, motivation, and self-expression. These symptoms may be primary, arising from the underlying pathophysiology of schizophrenia, or secondary, arising from psychiatric or medical conditions, or the side impacts of medication.

Symptoms include reduced normal behaviors related to social interactions, motivation, and self-expression. These symptoms may be primary, arising from the underlying pathophysiology of schizophrenia, or secondary, arising from psychiatric or medical conditions, or the side impacts of medication. Negative symptoms consist of 5 main components: blunt affect, alogia (decrease in speech output), avolition (reduction in activities that lead to goals because of weakened motivation), asociality, and anhedonia (reduction in pleasure experiences). These

symptoms are central to Schizophrenia and are closely linked to chronic disability and unfavorable functional outcomes in patients. While available antipsychotic medications can frequently provide effective management of positive symptoms, the current approaches to treating negative symptoms are generally ineffective and continue to represent an unaddressed medical necessity. Interestingly, some studies show evidence of fewer negative symptoms of Schizophrenia patients who smoke, thus contributing to self-treatment of negative symptoms (Mu et al., 2024).

The study intends to explain schizophrenia, schizophrenia and dopamine, the etiology of cigarette use in patients with schizophrenia, the mechanism of action, the relationship between schizophrenia cases and cigarettes, the management of patients with schizophrenia and active smokers, the relationship between the administration of antipsychosis to patients with schizophrenia and active smokers.

This study uses a descriptive qualitative method that utilizes secondary data sources. This method aims to describe the phenomenon being studied without trying to test or measure certain variables statistically. The data used in this study were obtained from scientific articles, books, dissertations, and other academic

literature relevant to the research topic. In collecting data, researchers conducted searches through academic databases such as Google Scholar and PubMed, and used keywords related to smoking and schizophrenia. After the data was collected, researchers conducted a literature review to analyze the themes that emerged and conclude the impact of smoking on people with schizophrenia.

Inclusion and exclusion criteria were used to ensure that only relevant and high-quality data were used in this study. Inclusion criteria include data sources that are relevant to the research topic, such as journal articles and books that discuss the impact of smoking on people with schizophrenia. In addition, only literature published in the last five years will be considered to ensure that the data used is current and relevant. Exclusion criteria include articles or sources that are not relevant to the research topic, such as sources that discuss schizophrenia in general without linking it to smoking habits, or sources that are too old and not relevant to current phenomena.

In this study, the data collection tool used is documents. The documents used include journal articles, books, and dissertations that are relevant to the research topic. These documents provide systematic information and can be analyzed to find certain patterns or themes.

Data analysis is carried out by coding relevant information, looking for emerging themes, and interpreting the meaning of the data found. The results of the analysis are then presented in descriptive form to provide a clear picture of the relationship between smoking and its impact on schizophrenia sufferers. To obtain quality data sources, researchers use various leading academic databases such as Google Scholar, PubMed, and Scopus. Keywords used in the search include "smoking in schizophrenia", "the impact of smoking on mental health", and "schizophrenia and smoking habits". In addition, filters such as year of publication and type of publication are used to ensure that only current and credible sources are included in the study.

Results

Schizophrenia

Positive and Negative Symptoms of Schizophrenia

Schizophrenia is a severe mental disorder with manifestations in the form of disorders of the content of the mind, language, and perception (Fitri et al., 2022). Schizophrenia symptoms can be broadly categorized into two main types, which are positive and negative symptoms. Positive symptoms include delusions, hallucinations, confusion of mind, restless rows, and strange or hostile behavior. Negative symptoms are characterized by a

decrease in usual functions linked to interests such as anhedonia, asociality, avolition, or expressive functions i.e. blunt affective and alogia (Schooler, 2020).

Schizophrenia Diagnostic Guidelines and Symptom Criteria

According to PPDGJ-III, the diagnostic guideline for schizophrenia (F 20) is that there must be at least one of the following symptoms that are noticeable (and typically two or more symptoms if they are less sharp or less clear) including *thought echo*, *delusion of control*, auditory hallucinations and other types of persistent hallucinations or at least two of the following symptoms that must always be displayed including persistent hallucinations from Any sense, broken or *interpolated* thought flow, catatonic behavior, such as *excitement*, posture, or eccentric flexibility, negativism, mutism, and stupor, "negative" symptoms, such as extreme apathy, infrequent speech, and dull or unnatural emotional responses, usually result in Withdrawal from social associations and decreased social performance but it must be clear that all of these things are not caused by depression or neuroleptica medication (Maslim, 2019).

The existence of these typical symptoms has persisted for at least one month or longer. There must be a

consistent and consistent shift in the *overall quality* of various aspects of personal behavior, including a loss of interest, a lack of purpose in life, not doing something, *a tendency toward self-absorption*, and withdrawal from social interactions (Maslim, 2019).

Schizophrenia and Dopamine

Definition and Function of Dopamine

Dopamine is a neurotransmitter associated with RDS (*reward depletion syndrome*) and is formed from the amino acid tyrosine at the synaptic end of a neuron. This substance is then released into the synaptic slit to affect communication between neurons. Dopamine is a neurotransmitter that belongs to the catecholamine group. The function of Dopamine itself plays an important role in regulating motor control, arousal, cognition, and satisfaction as well as other functions. Dopamine is related to providing a feeling of pleasure and a source of motivation for a person to proactively do certain activities (Fitri et al., 2022).

Dopaminergic Pathways in the Central Nervous System

Important dopaminergic pathways that have been known in the central nervous system, especially the brain, include (Maslim, 2019): 1. The mesocortical

pathway connects the ventral tegmental area to the prefrontal cortex. 2. The mesolimbic pathway carries dopamine from the ventral tegmental region to the nucleus of the accumbens through the amygdala and hippocampus. 3. The nigrostriatal pathway runs from the substantia nigra to the neostriatum. Soma in substantia nigra projects axons into the nucleus of caudatus and putamen. This path is involved in the motor loop of the basal ganglia. 4. The tuberoinfundibular pathway from the hypothalamus to the dopamine glands.

Dopamine Theory in Schizophrenia

The theory of dopamine pathways that are influential in schizophrenia is

1. The hypoactivity pathways of dopamine pathways from this area cause negative symptoms and cognitive impairment.
2. Mesolimbic dopamine pathways. Hyperactivity in this area causes positive symptoms of schizophrenia.

Etiology of Cigarette Use in Patients with Schizophrenia

The underlying factors for the high rate of smoking in schizophrenic patients are still unclear, although there are several hypotheses. One of them is the self-treatment hypothesis:

1. The self-treatment theory proposes that nicotine affects central nicotinic

acetylcholine receptors (nAChRs), leading to the release of dopamine and serotonin. This results in a secondary stimulant effect driven by dopaminergic activity, which in turn reinforces the person's urge to smoke. (Ding & Hu, 2021).

2. Alternative Theory Alternative theories state that smoking plays a role in the development of schizophrenia. This theory is in line with the high prevalence of smoking in first-generation psychosis patients of 58%. An Israeli cohort study of 14,248 military recruits without severe mental illness was followed over a period of 4 to 16 years (Ding & Hu, 2021).
3. Genetic predisposition is the same in smoking and the development of schizophrenia. A study investigated genetic variants associated with tobacco use and schizophrenia with data taken from genome association studies (Ding & Hu, 2021).

Nicotine Working Mechanism

Effect of Nicotine on nAChR (Nicotinic Acetylcholine Receptor)

Nicotine is a highly addictive substance and helps people start and continue their smoking habits. Nicotine's ability to quickly reach the brain after being inhaled from cigarettes may explain its benefits. Nicotine works through nAChRs, which

are ion channels made up of α and β subunits, regulating the flow of ions such as calcium, sodium, and potassium.

In the brain, nAChR is involved in triggering the release of neurotransmitters like norepinephrine, dopamine, serotonin, glutamate, GABA, and acetylcholine before nerve impulses pass through synapses.

Desensitization and Antagonism at nAChR

The sensitivity of nAChRs to desensitization varies, which can affect the release of different neurotransmitters such as glutamate and GABA. The increased release of dopamine in the nucleus accumbens may affect the tendency to use tobacco.

High doses or prolonged exposure to nicotine can turn nAChR into an antagonist, reducing its effectiveness. Although the effects of nicotine on nAChR regulation and desensitization are well known, their impact on cognition is still complex and poorly understood. Nicotine appears to have the opposite effect depending on the dose. Low doses may improve cognitive function, while high doses may have the opposite effect (Spasova et al., 2022).

The Relationship between Schizophrenia Cases and Cigarettes

Barriers to Quitting Smoking in Schizophrenia Patients

Patients with schizophrenia face additional barriers in achieving smoking cessation goals compared to patients without schizophrenia. A study showed that dopamine D2 receptor antagonists attenuate the effects of nicotine rewards. These pharmacological interactions may partly explain why schizophrenic patients smoke more and inhale more deeply than other patients. There is also evidence that there is an increase in the connection from the nucleus accumbens to the middle temporal gyrus and precuneus amid episodes of smoking cravings (Ding & Hu, 2021).

The Role of Nicotine in Increasing Schizophrenia Symptoms

Schizophrenia patients tend to smoke more because nicotine can increase the release of dopamine and serotonin, providing a stimulant effect that encourages the desire to smoke. In addition, nicotine also inhibits the activity of monoamine oxidase (MAO) A and B, thereby decreasing dopamine degradation and increasing dopaminergic activity. Another theory states that patients try to alleviate the negative symptoms of schizophrenia by taking nicotine which can increase dopamine and glutamate in the prefrontal cortex. Smoking has also been

found to reduce extrapyramidal symptoms caused by antipsychotic treatment, which is believed to be related to the interaction of nicotine with nicotinic receptors in the ventral tegmental area, leading to an increase in dopamine levels in the striatum. Overall, smoking behavior in schizophrenia patients is their effort to improve the symptoms and side effects of the treatment experienced.

Although the treatment hypothesis itself states that schizophrenia patients smoke to alleviate negative symptoms, some studies show the opposite results. Cross-sectional studies found that patients with mild-moderate nicotine dependence, rather than heavy dependence, had higher PANSS (*Positive and Negative Syndrome Scale*) scores, indicating worse negative symptoms compared to non-smokers. However, the design of cross-sectional studies is limited in determining the direction of the relationship, whether smoking causes more severe negative symptoms or patients with negative symptoms are more likely to smoke. In addition, a systematic review concluded that smoking was associated with an increase in the severity of psychiatric symptoms in schizophrenia, contrary to the self-medication hypothesis. Therefore, further longitudinal studies comparing negative symptoms when patients quit smoking versus when smoking is needed to

strengthen the evidence related to the self-treatment hypothesis.

Self-medication hypothesis and research showing that smoking relieves symptoms of schizophrenia

The self-medication hypothesis and research showing that smoking worsens schizophrenia symptoms reveal two conflicting views:

- a) The self-medication hypothesis argues that some individuals with schizophrenia smoke to reduce anxiety or as a way to cope with their symptoms, with smoking thought to provide a temporary calming effect due to the increase in dopamine (Hilmy et al., 2018).
- b) Conversely, research shows that smoking causes symptoms and has negative long-term impacts, such as decreased effectiveness of treatment and increased risk of cognitive impairment, which can improve the quality of life of schizophrenia sufferers (Kurniasih, et al., 2017).

Nicotine can provide a temporary relaxing effect, especially in increasing dopamine levels associated with feelings of euphoria or satisfaction, the long-term effects of smoking on cognitive and mental function tend to be detrimental.

Nicotine can also interfere with antipsychotic medications, reducing their

effectiveness, and worsening the long-term condition. In addition, smoking is associated with biological and psychological factors that vary widely between individuals, making responses to smoking different, depending on the severity of schizophrenia symptoms and factors such as stress, social support, or the presence of appropriate treatment.

The Role of Nicotine in Increasing Schizophrenia Symptoms

Prospective studies provide strong evidence that tobacco smoking raises the risk of developing schizophrenia, with the risk increasing with smoking intensity. These studies show that heavy smokers have a 2-4 times higher risk of developing schizophrenia than those who do not smoke. However, there are still limitations because it has not adjusted to the use of marijuana as a potential disruptive factor.

Another theory argues that smoking and the development of schizophrenia may be influenced by genetic factors. Although some studies found a causal effect of smoking on schizophrenia or genetic overlap, other studies showed a decreasing association between smoking and schizophrenia in identical twins, indicating genetic factors alone do not fully explain this link. More research is needed to understand the interaction between

genetics, smoking, and the risk of schizophrenia (Ding & Hu, 2021).

Management of Patients with Schizophrenia and Active Smokers

Types of Antipsychotics in the Treatment of Schizophrenia

Management of pharmacotherapy in patients with schizophrenia by means of the use of antipsychotics, either alone or in combination. Antipsychotics are clarified into atypical antipsychotics and typical antipsychotics. Both groups of antipsychotics have the same pharmacological activity, namely blocking dopamine D2 receptors. First-generation antipsychotics can improve positive symptoms but generally do not improve negative symptoms. Meanwhile, second-generation antipsychotics can improve positive and negative symptoms and more effectively treat resistant patients (Rissa & Darmawan, 2021).

Antipsychotic Side Effects

Typical and atypical antipsychotics, both have the potential to cause side effects in the form of sedation, autonomic disorders, extrapyramidal disorders, and disorders of the metabolic system (Meilina et al., 2022).

Antipsychotics are divided into two first-generation Antipsychotics (Typical) and also second-generation antipsychotics

(Atypical). Typical antipsychotics have a better effect on positive symptoms and have side effects. Examples of first-generation or typical antipsychotics, such as haloperidol, trifluoperazine, chlorpromazine, and fluphenazine, have greater side effects compared to second-generation or atypical antipsychotics. Examples of atypical antipsychotics include risperidone, aripiprazole, quetiapine, and olanzapine, which are known to have a lower risk of side effects (Putra et al., 2023).

The Role of CYP Enzymes in Drug Metabolism and the Effects of Smoking

Cytochrome P450 enzyme (CYP) is a family of enzymes that are heavily involved in drug metabolism, accounting for up to 75% of these processes. CYP1A2 members play an important role in the metabolism of antipsychotic drugs such as clozapine and olanzapine used for the treatment of schizophrenia.

Tobacco contains polycyclic aromatic hydrocarbons that have been shown to increase CYP1A2 activity, thereby increasing the metabolism of clozapine and olanzapine. This causes a decrease in plasma concentrations of these drugs in smoking patients. Meta-analyses showed the need for a 30% and 50% reduction in olanzapine and clozapine doses, respectively, in non-smoking

schizophrenia patients compared to smokers.

In addition, smoking also increases caffeine metabolism through CYP1A2 induction. The combination of smoking and high coffee consumption was associated with reduced effectiveness but increased safety of olanzapine. In smoking cessation, it is recommended to reduce the dose of clozapine and olanzapine by 30-40% to restore serum concentrations to previously stable levels (Ding & Hu, 2021).

The Relationship Between Administering Antipsychotics to Patients with Schizophrenia and Active Smokers

The Effect of Smoking on Schizophrenia Treatment

Smoking in individuals with schizophrenia can impact the treatment process, potentially hindering the reduction of symptoms or behavioral changes in people with the condition (Kurniasih et al., 2017). This is crucial in clinical practice because without dose adjustment, smokers may face the risk of undergoing subtherapeutic psychopharmacological management. A meta-analysis of seven studies conducted in 2014, indicated a 30% and 50% reduction in olanzapine and clozapine doses, respectively, in non-smoking schizophrenia patients compared to smokers (Ding, 2021).

The Role of CYP1A2 Enzymes in Antipsychotic Drug Metabolism

Schizophrenia patients who are also active smokers have particular challenges in treatment with antipsychotics. This is because cytochrome P450 enzymes (CYP), especially CYP1A2, play an important role in the metabolism of antipsychotic medications like clozapine and olanzapine.

Compounds in tobacco, namely polycyclic aromatic hydrocarbons, have been demonstrated to enhance CYP1A2 activity. This increase in CYP1A2 activity results in an enhanced metabolism of clozapine and olanzapine in smoker patients. As a result, plasma concentrations of these drugs are lower in smoking patients than in non-smokers.

Antipsychotic Dose Adjustment in Schizophrenia Patients Who Are Active Smokers

The meta-analysis study found that non-smoking patients required higher doses of olanzapine and clozapine by about 30% and 50% than smoking patients to achieve the same therapeutic effect. This is crucial in clinical practice because, without proper dose adjustment, smoking patients are at risk of subtherapeutic psychopharmacological management.

In addition, smoking also increases caffeine metabolism through CYP1A2

induction. The combination of high coffee consumption and smoking is associated with reduced effectiveness but enhanced safety profile of olanzapine.

At the time of smoking discontinuation, it is necessary to reduce the dose of clozapine and olanzapine by about 30-40% to restore the concentration of the drug to a stable previous level. So, strict monitoring and adjustment of antipsychotic doses are essential in schizophrenia patients who are also active smokers to ensure the effectiveness and safety of treatment (Ding & Hu, 2021).

Conclusion

The pervasiveness of smoking in schizophrenic patients reaches 70-80%. Smoking appears to reduce negative symptoms such as low motivation in schizophrenia patients, although its effects on positive symptoms and cognitive function are still unclear. The interaction of nicotine with brain receptors such as nAChRs and dopamine pathways provides the basis for the hypothesis of self-medication, in which smoking may be used to reduce symptoms.

The management of schizophrenia in active smokers poses challenges in terms of pharmacotherapy due to interactions with antipsychotic drugs such as clozapine and olanzapine. Drug metabolism is affected by smoking, so it is necessary to

adjust the dosage to maintain optimal therapeutic efficacy.

Overall, although smoking appears to provide some benefits in managing schizophrenia symptoms, the overall effects are still complex and more research is needed to better understand the mechanisms and treatment strategies.

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