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## Therapy or Pleiotropy? Analyzing the Connection Between Schizophrenia and Smoking

Sasank Isola • Aleyda M. San Hernandez • Chetana Singh •  
Danel J. Valero • Javariya Nisar • Jose I. Trujillo Ramirez • Karisma K. Kothari • Domonick K. Gordon

California Institute of Behavioral Neurosciences and Psychology (CIBNP), 4751 Mangels Blvd, Fairfield, United States  
[sasankisola@students.aucmed.edu](mailto:sasankisola@students.aucmed.edu)

**Abstract.** This study aimed to ascertain the reason for the widely observed prevalence of tobacco smoking among patients with schizophrenia. The reason for this line of inquiry is because in addition to causing malignancy, cardiovascular, and respiratory sequelae in smokers, tobacco smoking in patients with schizophrenia has been shown to cause unique neurologic, cognitive, and memory deficits. Therefore, investigating the reasons for this tendency could enable physicians to provide patients with schizophrenia with the means to effectively quit. The studies cited in this literature review were obtained by searching through Google Scholar, PubMed, and PubMed Central databases for full-text studies in the recent past conducted on human subjects, though no PRISMA checklist was created because this is not a systematic review. This review article highlights potential explanations for the association between schizophrenia and tobacco smoking. These include that tobacco smoking improves various symptoms of schizophrenia and that this may occur through the stimulation of specific receptors. Also, common genetic factors are identified, explaining the common neurologic abnormalities seen in both patients who smoke and those who have schizophrenia. In addition, this review highlights multiple shared specific genes that provide potential explanations for the link between schizophrenia and smoking. The results of the study therefore suggest that future researchers may find it productive to further investigate these neurologic, genetic, and receptor-based commonalities in the hopes of eventually creating schizophrenia medications that stimulate nicotinic acetylcholine receptors, or conversely, to eventually design screening tests or gene therapies geared towards one of the aforementioned genetic commonalities. Designing case-control or cohort studies to prove the utility of these drugs or tests may prove rewarding.

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### 1. Introduction:

While schizophrenia is the form of mental illness that is perhaps the most well-known to the public, many aspects of this disease are a mystery to both clinicians and the general public. The basic pathophysiology of schizophrenia itself, specifically its association with excessive levels of dopamine, and the use of antipsychotic medications to redress this imbalance, are widely understood and practiced by clinicians. However, among the most bizarre nuances of schizophrenia that continue to defy a straightforward explanation is the association between schizophrenia and tobacco smoking. Various studies of different populations from around the world suggest that patients with schizophrenia exhibit higher rates of tobacco use than patients without schizophrenia, a trend that can be observed across nationalities (Ohi et al., 2019). One study suggests that the prevalence of tobacco smoking in patients with schizophrenia is three times higher than in the general population (Castle et al., 2019).

While the precise reason for this association has eluded scientists and clinicians for decades, the stakes involved in understanding it remains higher than ever. In addition to the well-known damage that long term smoking can cause in patients, like malignancy, heart and lung disease, and stroke, there is evidence that smoking can impair cognitive function and memory in patients with schizophrenia (Cullen et al., 2012). Additional evidence suggests that a significant portion of the reduction in life expectancy seen in patients with schizophrenia can be attributed to smoking (Yokoyama et al., 2018)

There is also evidence that suggests that smoking adversely impacts brain structure in patients with schizophrenia, damaging the white and grey matter. Furthermore, it can also worsen the damage that has already been done due to schizophrenia (Lucatch et al., 2018). Most disturbing of all is the evidence that smoking enhances the metabolism of antipsychotic medications, which can make dosing medications with narrow



therapeutic indices particularly difficult (Hartz et al., 2018). Therefore, understanding why patients with schizophrenia feel the need to smoke more than the general population could help not only in developing smoking cessation strategies for these patients, but also in understanding the exact neurobiological causes and consequences of schizophrenia. This in turn could yield valuable information about its aggravating and alleviating factors, and comorbidities. Obtaining a more complete understanding of schizophrenia in this way would expand clinicians' understanding of the complex relationship between the neurological and psychological manifestations of mental illness. Additionally, it would enable the development of targeted pharmacological and behavioral interventions for patients with schizophrenia and improve the delivery of these interventions. Failure to comprehensively understand the association between smoking and schizophrenia would mean leaving potential avenues for smoking cessation in patients with schizophrenia, and potential treatments for schizophrenia, unexplored, and limiting our understanding of neurology and psychiatry. The goal of this literature review is to compile a selection of relevant studies on the cause of the increased prevalence of tobacco smoking in patients with schizophrenia by narrowing down the most likely reasons for this association. Finding the most likely reasons for this association will have significant implications for the therapeutic management of these patients.

Emphasis will be placed on the possibility of a shared genetic predisposition for smoking and schizophrenia, and the possibility that smoking may ameliorate the symptoms of schizophrenia

## 2. Methods:

The studies in this traditional literature review were compiled by reviewing the Pubmed, Pubmed Central, and Google Scholar databases using the keywords "smoking and schizophrenia" and "smoking and schizophrenia pathophysiology." The inclusion/exclusion search criteria limited the search to the years 1990-2020, limited the studies used to free full text studies, and limited the species of the study participants to humans only. This was done to ensure that the studies cited were relatively recent, and therefore more relevant to readers, accessible to all without financial constraints, and most useful for the investigation of future medical treatments for humans. 45 studies were originally identified and those that did not meet all the aforementioned inclusion criteria were excluded. As this study was intended to be a traditional literature review, not a systematic literature review, no PRISMA flowchart was generated, nor was a PICOS process utilized.

## 3. Results:

Table 1 below shows a summary of the included studies that establish a positive link between tobacco smoking and schizophrenia.

Table 2 below shows a summary of the included studies that illustrate how tobacco smoking ameliorates certain symptoms of schizophrenia.

Table 3 below shows a summary of the included studies that establish a genetic link between tobacco smoking and schizophrenia.

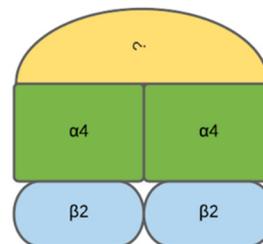
## 4. Discussion:

The analysis of the scientific literature completed in light of the established connection between schizophrenia and smoking revealed that there were two widely accepted possible explanations for the unusual prevalence of tobacco smoking among patients with schizophrenia. One possibility was that tobacco smoking ameliorated the various symptoms of schizophrenia. The other was that schizophrenia and tobacco smoking shared a common genetic origin, meaning that a genetic predisposition for the former made the latter more likely as well.

### 4.1. Smoking Ameliorates Symptoms of Schizophrenia

Of those studies that concluded that tobacco smoking ameliorated various symptoms of schizophrenia, some concluded that tobacco smoking specifically ameliorated the negative symptoms of schizophrenia. Jiang et al found this among Chinese patients, which resembled the results of previous work by Moran et al., (2012). Other studies, like that of Moran et al concluded that tobacco smoking ameliorated cognitive deficits associated with schizophrenia, which echoed previous work by Smucny & Tregellas, (2017). Lucatch et al furthered this line of inquiry, concluding that tobacco smoking ameliorated both the negative symptoms of schizophrenia as well as cognitive deficits, echoing previous work by Hashimoto (Yokoyama et al., 2018)

Some of those studies that focused on the amelioration of cognitive deficits postulated that this was achieved through the stimulation of nicotinic acetylcholine receptors. These include the aforementioned studies by Moran et al, Sacco et al, Lucatch et al, and Hashimoto. Other studies that came to similar conclusions were those by Ochoa and Lesalle-Dominicci, as well as that of Chen et al., (2016). One potential configuration of the specific nicotinic receptor involved in this process, consisting of two  $\alpha 4$  and two  $\beta 2$  subunits, as well as one unidentified subunit represented by a question mark, is shown in Figure 1 below.



**Figure 1.** Showing a Potential Configuration of a Nicotinic Acetylcholine Receptor

Table 1: Showing the Summary of the Included studies that Establish a Positive Link Between Tobacco Smoking and Schizophrenia

Author	Year of Publication	Purpose of the Study	# of Patients	Intervention Studied	Result/Conclusion
Ohi et al	2019	To evaluate the smoking status in a large Japanese cohort of patients with schizophrenia	200,298	Tobacco Smoking	Schizophrenia patients are about twice as likely to smoke than the general population and the healthy control group
Castle et al	2019	To examine the established literature on the relationship between smoking and schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco Smoking	The association between schizophrenia and smoking is strongly established in the medical literature, though understanding the reason for this association would enable the development of targeted treatment modalities with improved methods of treatment delivery.
Yokoyama et al	2018	Examining the effects that cigarette smoking has on gray matter in patients with schizophrenia	100	Tobacco Smoking	There is a high prevalence of smoking in patients with a history of schizophrenia, which may cause abnormalities in the left prefrontal cortices of these patients
Kendler et al	2015	To clarify the causes of the smoking-schizophrenia association	1,647,728	Tobacco Smoking	Smoking predicts risk for schizophrenia
Schneider et al	2013	Examining whether gray matter reductions in the brains of schizophrenia patients may be attributed to smoking rather than to schizophrenia alone.	189	Tobacco smoking	A proportion of the volume reduction seen in the hippocampus and dorsolateral prefrontal cortex in schizophrenia is associated with smoking rather than with the diagnosis of schizophrenia.
Cullen et al	2012	Examining the effects that cigarette smoking has on white matter microstructure in patients with schizophrenia	83	Tobacco Smoking	Most patients with schizophrenia smoke cigarettes, a habit that may contribute to the atrophy of the white matter in the brains of these patients
Moran et al	2012	Examining the effect that smoking has on the insular and anterior cingulate circuits on patients with schizophrenia vs patients without	20	Tobacco Smoking	Schizophrenia is associated with increased likelihood to smoke, and smokers with schizophrenia demonstrated additive reductions in circuit strength between the dorsal anterior cingulate and insula compared to normal control smokers independent of smoking severity
Zhang et al	2010	To determine if smoking and schizophrenia are both associated with white matter abnormalities that could be biomarkers for the high rates of smoking in patients with schizophrenia	115	Tobacco smoking	Both smoking and schizophrenia are independently associated with reductions in whole brain white matter integrity

Table 2: Showing the Summary of the Included studies that Illustrate how Tobacco Smoking Ameliorates Certain Symptoms of Schizophrenia

Author	Year of Publication	Purpose of the Study	# of Patients	Intervention Studied	Result/Conclusion
Lucatch et al	2018	To understand the neurobiology of tobacco smoking in schizophrenia and how to manage this comorbidity	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	Tobacco smoking may ameliorate negative and positive symptoms of schizophrenia, as well as cognitive deficits
Moran et al	2018	To examine the effects of nicotine on the cognitive abilities of patients with schizophrenia	29	Tobacco smoking	Nicotinic agents may be used to ameliorate cognitive deficits in patients with schizophrenia
Smucny and Tregellas	2017	Examining the possibility that nicotinic agonists may effectively target dysfunctional neuronal circuits in patients with schizophrenia.	Numbers are not mentioned because the study does not have a distinct methods section	Nicotine use	Nicotine effectively modulates dysfunctional neuronal circuits in patients with schizophrenia
Hashimoto	2015	Examining the potential of $\alpha 7$ nicotinic acetylcholine receptor agonists as therapeutic drugs in schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Nicotinic receptor stimulation	$\alpha 7$ nicotinic acetylcholine receptor presents as an extremely attractive therapeutic target for schizophrenia
Boggs et al	2014	To determine if nicotinic acetylcholine receptor based treatments for schizophrenia improve cognitive impairment in patients with schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	Nicotinic acetylcholine receptor-based treatments for schizophrenia improve attention deficits and information processing deficits in patients with schizophrenia
Strube et al	2014	To investigate the impact of nicotine on LTD-like plasticity in patients with schizophrenia.	75	Tobacco smoking	Chronic smoking restores the impaired LTD-like plasticity in schizophrenia patients
Jiang et al	2013	To show that smokers have higher rates of schizophrenia and explore the mechanism of action behind this	1,674	Tobacco smoking	Male Chinese patients with schizophrenia have higher rates of smoking, lower rates of cessation, and improved negative symptoms of schizophrenia
D'Souza and Markou	2012	To examine the beneficial effects of nicotine and subtype-selective nicotinic receptor agonists in schizophrenia-associated cognitive deficits	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	The administration of nicotine or nicotinic acetylcholine receptor subtype-selective agonists results in beneficial cognitive effects on attention and working memory

Table 2: Showing the Summary of the Included studies that Illustrate how Tobacco Smoking Ameliorates Certain Symptoms of Schizophrenia

Author	Year of Publication	Purpose of the Study	# of Patients	Intervention Studied	Result/Conclusion
Sagud et al	2009	To explore the potential reasons for high smoking prevalence in patients with schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	There is evidence that smoking can reduce deficits associated with dopamine hypofunction in the prefrontal cortex in patients with schizophrenia
Leonard et al	2007	What is the evidence for self-medication in smokers with schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	Targeting the $\alpha 7^*$ nicotinic receptor can cause improvements in cognition in patients with schizophrenia
Sacco et al	2005	To determine the effects that cigarette smoking has on the cognitive abilities of patients with schizophrenia and establish the role of nicotinic acetylcholine receptors in this	50	Tobacco smoking	Cigarette smoking may selectively improve visuospatial working memory in smokers with schizophrenia, which may require nicotinic acetylcholine receptor stimulation
Ochoa and Lasalle-Dominicci	2005	To examine the role of smoking as a cognitive remediator in patients with schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	Stimulating nicotinic acetylcholine receptors may ameliorate cognitive deficits in patients with schizophrenia
Sacco et al	2005	To examine the role of central nicotinic acetylcholine receptor systems with respect to cognitive dysfunction in different neuropsychiatric diseases	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	Nicotine may enhance cognitive performance in patients with schizophrenia
Smith et al	2002	To examine the effects of acute smoking on negative symptoms and neurocognitive function in patients with schizophrenia	31	Tobacco smoking or nicotine spray	Acute smoking of cigarettes may transiently decrease negative symptoms in patients with schizophrenia
Dalack et al	1998	To examine the potential implications of the high prevalence of smoking in schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	Chronic nicotine treatment is associated with increased dopamine levels in the cortical regions of the brain, as well as increased glutaminergic activity in the frontal cortex and hippocampus, which are affected by schizophrenia, thereby ameliorating hypo frontality

Table 3: Showing the Summary of the Included studies that Establish a Genetic Link between Tobacco smoking and Schizophrenia

Author	Year of Publication	Purpose of the Study	# of Patients	Intervention Studied	Result/Conclusion
Ma et al	2020	To identify shared genetic vulnerabilities for schizophrenia and smoking behaviors	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	34 genes with various single nucleotide polymorphisms which convey susceptibility to the comorbidity of schizophrenia and smoking were identified
Ohi et al	2019	To investigate a common genetic pathophysiology linking smoking and schizophrenia	134	Tobacco smoking	There is a common genetic pathophysiology linking smoking and schizophrenia involving alterations in the CHRNA5 gene
Hatz et al	2017	To determine if there is a genetic correlation between smoking and schizophrenia	Numbers are not mentioned because the study does not have a distinct methods section	Tobacco smoking	There is some common genetic basis for both smoking and schizophrenia
Chen et al	2016	Examining the genetic relationship between schizophrenia and nicotine dependence	Numbers are not mentioned because the study does not have a distinct methods section	Nicotine dependence	Nicotine dependence and schizophrenia share genetic liability
Moran et al	2013	To examine whether dorsal anterior cingulate functional circuits are the paths for the high risk of smoking in patients with schizophrenia	119	Tobacco smoking	There is a brain circuit mechanism that contributes to the high prevalence of smoking in patients with schizophrenia
De Luca et al	2004	Examining the Association between Smoking and $\alpha 7$ Nicotinic Receptor Subunit Gene in Schizophrenia Patients	177	Tobacco smoking	There is an association between the homozygous 113 bp allele of the D15S1360 marker in the CHRNA7 gene and smoking

Other studies that focused on the salutary effect that stimulating nicotinic receptors has on cognition in patients with schizophrenia specifically concluded that tobacco smoking improved their memory. These include studies by Sacco et al, and D'Souza and Markou (Smith et al., 2002; Ma et al., 2020). In contrast, Boggs et al concluded that nicotinic receptor-based treatments improved attention and information processing deficits in patients with schizophrenia (Ohi et al., 2019).

In addition to these, other studies focused on the beneficial effects that tobacco smoking had on the function of various specific areas of the brain in patients with schizophrenia. For instance, Sagud et al concluded that tobacco smoking increased dopamine activity in the prefrontal cortex, much like how Dalack et al had previously concluded that tobacco smoking increases dopamine levels and glutamergic activity in the prefrontal cortex and hippocampus (Hartz et al., 2018; Strube et al., 2015). In contrast, Smucny and Tregellas concluded that nicotine regulates dysfunctional neuronal circuits in patients with schizophrenia, while Strube et al concluded that chronic tobacco use restores long term

depression (LTD) like plasticity in the brains of patients with schizophrenia (Moran et al., 2013; Sacco et al., 2004).

What these findings suggest is that the reason that patients with schizophrenia are increasingly likely to engage in tobacco smoking is that doing so can improve various symptoms of schizophrenia, ranging from negative symptoms and cognitive deficits to memory, attention, dopamine activity, brain plasticity, and the activity of neuronal circuits. This would suggest that exploring pharmaceutical treatments for schizophrenia based on the stimulation of nicotinic acetylcholine receptors would be a potentially fruitful line of inquiry.

#### 4.2. The Common Genetic Cause of Smoking and Schizophrenia

In contrast to the studies investigating the various ways in which tobacco smoking ameliorates the symptoms of schizophrenia, several studies concluded that smoking and schizophrenia were linked through a common genetic root, rather than the former being used as a treatment for the latter. While Hatz et al merely concluded that there was some common genetic basis for both conditions, some



studies went further, attempting to identify the specific genes or areas of the brain involved (De Luca et al., 2004). For instance, Chen et al identified specific non-coding RNAs and RNA binding proteins, protein modification genes, and energy production genes in both smokers and patients with schizophrenia, while Ma et al identified genes associated with axon guidance, long term depression, cadherin binding, dendritic spine, and postsynaptic density in common in both populations (Hashimoto, 2015; Leonard et al., 2007). Moran et al identified overlap between the abnormalities in the dorsal anterior cingulate and limbic systems of patients with schizophrenia and a circuit associated with nicotine dependence (Dalack & Meador-Woodruff, 1996). In contrast, both Ohi et al and De Luca et al concluded that the association between the two was based on alterations in genes that coded for nicotinic cholinergic receptor alpha subunits five and seven, respectively, with the former seeing this as evidence of pleiotropy (Schneider et al., 2014; L Boggs et al., 2014). Given the wide variety of genetic overlap between the two conditions, it is possible that future treatments to manage schizophrenia might involve screening for these sources of genetic commonality or pursuing gene therapy that targets them.

Despite the wide range of studies cited in this traditional literature review, it has some limitations that must be mentioned. The search criteria limited the years of publication of the papers cited to 1990-2020, depriving the analysis of any potentially useful studies from before this period. Additionally, only free full-text studies, written in English, that involved human participants were used, meaning that no insight from studies hidden behind paywalls, written in other languages, or involving animals could be utilized. This literature review could also be strengthened through a comprehensive quality assessment, as well as a PRISMA checklist.

#### 4. Conclusions:

The goal of this literature review was to better understand the reasons for the higher prevalence of tobacco smoking among patients with schizophrenia. The reviewed studies showed that tobacco smoking either ameliorated some symptoms of schizophrenia, or that the tendency to engage in tobacco smoking and the tendency to develop schizophrenia shared a common genetic cause. The former group of studies showed that tobacco smoking ameliorated various symptoms of schizophrenia, including negative symptoms and deficits in cognition, memory and attention, and information processing. The primary proposed mechanism of action for this was the stimulation of nicotinic acetylcholine receptors. Additionally, some of these studies showed that tobacco smoking provided neurologic, as well as psychiatric benefits for patients with schizophrenia, increasing neurotransmitter activity and neuroplasticity.

In contrast, the latter group of studies identified various areas of potential genetic commonality between tobacco smoking and schizophrenia. These included genes associated with RNA, protein modification, energy production, and building various neuronal components. One study identified common neurologic abnormalities in patients with schizophrenia in various parts of the brain, including one area associated with nicotine dependence. Some studies found that the connection between smoking and schizophrenia lies in modified genes that code for nicotinic cholinergic receptor subunits.

Collectively, the findings of this literature review suggest that researchers should investigate formulating drugs that stimulate nicotinic acetylcholine receptors, or perhaps develop screening tests or gene therapies that target the genetic commonalities identified above. Case-control or cohort studies could measure the efficacy of these medications or tests.

#### Conflict of Interest:

There was no conflict of interest by authors.

#### Corresponding Person CIBNP:

Syeda Sidra Hasnain, Pharm-D.

California Institute of Behavioral Neurosciences and Psychology (CIBNP), 4751 Mangels Blvd, Fairfield, CA, 94533, United States.

E-mail: [neurocalcibnp@gmail.com](mailto:neurocalcibnp@gmail.com)

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