

A selective literature review exploring the role of the nicotinic system in schizophrenia

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To cite: Kanniah G, Kumar R.

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General Psychiatry 2023;**36**:e100756. doi:10.1136/gpsych-2022-100756

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/gpsych-2022-100756>).

Received 20 January 2022

Accepted 16 February 2023

ABSTRACT

Nicotine use is more prevalent in patients with psychiatric disorders, especially those diagnosed with psychotic illnesses. Previously, this higher prevalence has been partially attributed to the potential ameliorative effects of nicotine on symptom severity and cognitive impairment. Some healthcare professionals and patients perceive there is a beneficial effect of nicotine on mental health. Emerging data show that the harm associated with nicotine in the population of patients with mental health conditions outweighs any potential benefit. This paper will review the evidence surrounding the nicotinic system and schizophrenia, with a focus on any causality between nicotine and psychosis.

INTRODUCTION

Psychosis is often described as the loss of contact with reality.¹ It is characterised by disordered thinking, hallucinations and delusions—termed ‘positive symptoms’ under the range of different psychotic presentations.² Such symptoms are associated with several psychiatric illnesses, most notably schizophrenia and related schizophrenia spectrum disorders.^{1,2} Risk factors for the spectrum of psychosis are well established, ranging from a history of genetic susceptibility, obstetric complications, childhood adversity and exposure to cannabis during adolescence and encountering stressful events during adulthood.¹

Recent literature has focused on elucidating the role of nicotine as a risk factor for either causing or exacerbating psychosis.^{3,4} Psychosis occurs two to three times more frequently in individuals with heavy nicotine use as compared with the general population.⁴ The prevalence rates of nicotine consumption through cigarette smoking in people with psychotic disorders are two to three times greater than in the general population.⁴ Patients with psychotic disorders demonstrate heavy smoking patterns⁵ and significant nicotine dependence⁴ and are less likely to quit than non-smokers.⁶ There is an increased risk of nicotine-related morbidity and excess

mortality in this population,⁷ a major contributor to health inequalities. Some studies show that daily nicotine consumption increases both the baseline risk of developing psychosis and places individuals at risk of developing symptoms at an earlier age.³ Higher rates of nicotine dependence are often associated with greater severity of mental health conditions.⁵ Additionally, patients consuming nicotine with psychotic disorders have decreased life expectancies and increased morbidity and mortality compared to the general population.⁶

The nature of this relationship, while extensively described in the literature, remains unclear.³ Some theorise that reverse causality can explain this phenomenon. Here, the distress or discomfort that mental health conditions impose on individuals is relieved by nicotine use. Additional benefits of nicotine, such as increased concentration and attention, may alleviate both symptoms of psychosis and adverse effects from antipsychotics.²

Established risk factors for mental illness, including lower socioeconomic status, unemployment and social adversity, are also associated with nicotine and other substance use, hence accounting for the higher rates seen.² Such confounding factors make it difficult to establish a causal relationship between nicotine use and psychosis. Some literature states that smoking itself may have neurobiological effects that can increase the risk of developing psychosis.⁸

As noted, rates of nicotine consumption are higher among the psychiatric population, in particular those with schizophrenia. This paper will examine the relationship between nicotine and the pathogenesis of psychosis, its effects on symptom relief and interactions with antipsychotic medications. Nicotine consumption has a multidimensional impact on patients with schizophrenia. Differential disease burdens, mortality and



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morbidity rates, prognoses and long-term complications are explored in this paper. Finally, there is an evaluation of the literature regarding system-based approaches to reduce nicotine consumption among psychiatric patients, as well as successful strategies and beneficial outcomes of such interventions.

EPIDEMIOLOGICAL INVESTIGATION ON SMOKING AND PSYCHOSIS IN NEW ZEALAND AND OTHER COUNTRIES

Smoking follows well-established sociodemographic trends observed worldwide. These trends are worth studying with respect to New Zealand. People living in the most socioeconomically deprived areas were 4.5 times as likely to be current smokers, compared with those living in less deprived areas, after adjusting for age, sex and ethnicity.⁹ In 2019/2020, approximately 535 000 adults (13.4%) were smokers.⁹ This represents a reduction from the estimates of 20.1% in 2006/2007.⁹ About 31.4% of all Māori adults were current smokers, again representing a decrease from 42% in 2006/2007.⁹ Māori, in general, were 2.8 times more likely to be current smokers, adjusting for age and gender, than non-Māori counterparts.⁹

Interestingly, the prevalence and incidence of schizophrenia in Māori assessed in 2019 is twofold to threefold higher compared with the remainder of the New Zealand population; this phenomenon did not exist prior to the turn of the century.¹⁰

This relationship between population-based trends of increased prevalence of psychosis and sustained elevated rates of smoking among Māori is worth exploring. Two meta-analyses found that people who smoke nicotine have a twofold increased risk of incident schizophrenia¹¹ or psychosis,³ even after adjusting for confounding factors. Eight longitudinal studies (seven cohort studies and one case-control study) were identified that examined nicotine exposure as an exposure and psychosis as an outcome. Of the eight studies, six reported a statistically significant positive association between nicotine consumption and incident psychosis.¹² These findings raise the possibility of a causal relationship between nicotine consumption and increased risk of psychosis.¹²

As stated above, the epidemiological trends of nicotine consumption are relevant in the healthcare setting. By understanding reasons for inequitable exposure, differential sociodemographic trends and population-level disparities, one can appreciate the broader implications of nicotine exposure on the set group of patients with schizophrenia. This phenomenon will be explored in depth in the following sections.

A meta-analysis of worldwide studies (10-year literature follow-up, 42 studies across 20 nations) found an association between schizophrenia and current smoking (weighted average OR=5.90). Heavy smoking and high nicotine dependence were more frequent in smokers with schizophrenia versus the general

population. Cessation rates were lower in smokers with schizophrenia versus the general population. People with schizophrenia had a higher prevalence of ever smoking than the general population.⁴

Another meta-analysis found that the prevalence of smoking was three times greater among people with schizophrenia compared with the general population and twice when compared with other major mental illnesses regardless of antipsychotic drug use.¹³ It has also been shown that patients with schizophrenia smoke cigarettes much more intensely, increasing their nicotine intake.¹⁴ Highly dependent smokers are generally those with more severe schizophrenic illness among patients taking antipsychotic drugs.¹⁵ Smoking and nicotine skin patches have a similar effect in improving attentional performance in people with schizophrenia who were taking antipsychotic drugs.^{16–18} Interestingly, higher smoking rates appear to precede the onset of schizophrenia.¹⁹ This may also be related to self-medication for cognitive deficits present before the first break into schizophrenia. Antipsychotic drugs which induce greater cognitive impairment, such as haloperidol, cause increases in smoking while those with less detrimental effects decrease smoking.^{17 20–22}

PSYCHOPHARMACOLOGICAL PROFILES OF NICOTINE IN THE CENTRAL NERVOUS SYSTEM

Nicotine is a highly addictive, neurologically active alkaloid. It crosses the blood-brain barrier as fast as 10–20 s postinhalation.²³ Here, it acts as a nicotinic acetylcholine receptor (nAChR) agonist, increasing the downstream release of dopamine in the ventral tegmentum of the midbrain³ and striatum.¹² These mediate a stimulant effect and enhance reward-seeking behaviours. Both positive reinforcement (eg, heightened vigilance, improved mood and weight loss) and negative reinforcement (alleviation of withdrawal symptoms, eg, anxiety, irritability, impaired concentration and increased appetite) mediate nicotine addiction.²⁴

The propensity of nicotine to peak and fall quickly contributes to its addictive potential. nAChRs become desensitised when nicotine levels in the brain are high. As these levels subsequently drop, the receptors resensitise, leading to withdrawal effects. Slower-release nicotine delivery systems, such as nicotine replacement therapies (NRTs), are less reinforcing, as the nAChRs do not rapidly resensitise, and the user has less control in titrating the dose to receive a rewarding effect when desired.²⁴ NRT lacks additional potentially addictive compounds, which could be why not all smokers like them. Some of these include menthol and acetaldehyde condensation products, which under normal circumstances lead to dopamine excess through the inhibition of monoamine oxidase.³ It must be acknowledged that NRT in different formulations (gum, transdermal patch, nasal spray, inhaler, sublingual tablet and lozenge) has been shown to relieve withdrawal

symptoms and to double abstinence rates compared with placebo. NRT forms deliver nicotine much slower than smoking, and the increase in blood nicotine levels is more gradual.

Nicotinic cholinergic receptor and neurotransmitter release

Nicotine binds to nAChRs located throughout the brain, including the thalamus, basal ganglia, caudate nucleus, frontal, parietal, temporal and occipital cortices, hippocampus and cerebellum. Multiple subtypes of neuronal nAChRs with unique combinations of at least 17 ($\alpha 1$ – $\alpha 10$, $\beta 1$ – $\beta 4$, γ , δ , ϵ) genetically distinct subunits exist with diverse distributions, functional properties and pharmacological profiles.²⁵ Nicotine has the highest affinity for nAChRs $\alpha 4$ and $\beta 2$ subunits, especially in the brain.²⁶ On binding, nicotine opens intrinsic ion channels, allowing the influx of cations (Na^+ , Ca^{2+} and K^+), which activates voltage-gated channels. This leads to neurotransmitter release.²⁴ Nicotine alters the release of most neurotransmitters, including dopamine, acetylcholine, endogenous opioid peptides, γ -aminobutyric acid (GABA), glutamate, norepinephrine and serotonin.²⁷

NEUROBIOLOGICAL MECHANISMS UNDERLYING NICOTINE IMPLICATION IN PSYCHOSIS

Though nicotine stimulates dopamine release throughout the brain, its addictive properties are primarily associated with the mesolimbic dopaminergic pathways. Activation of nAChRs in the ventral tegmental area (VTA) releases dopamine in the nucleus accumbens, which is implicated in pleasure and reward perception. Nicotine, moreover, increases glutamate and GABA transmission in the VTA.²⁸ Though nicotine-induced GABAergic transmission quickly desensitises, the degree of glutamatergic response is less, resulting in an overall shift with a decrease in inhibitory GABAergic transmission and an increase in excitatory glutamatergic transmission. This shift contributes to prolonged increases in dopamine release and the pattern of behavioural reinforcement seen in nicotine addiction. A similar mechanism has been implicated in psychosis, with *N*-methyl-D-aspartate (NMDA) receptor hypofunction on GABAergic interneurons resulting in reduced inhibition of pyramidal glutamate, and with excess glutamate release leading to the activation of dopaminergic neurons.¹³

Some evidence from *in vivo* mice positron emission tomographic studies shows nicotine increases dopamine release in the dorsal ventral striatum and basal ganglia.¹⁴ Nicotine has a high affinity to the D2 receptor and was demonstrated to induce the proliferation of D2 receptors in these brain regions.¹⁴ Nicotine also releases a number of proinflammatory cytokines.^{15 16} This can lead to neuroinflammation, altered dopaminergic neurotransmission and dysregulated cortisol release. These models pertaining to the neural diathesis-stress model of schizophrenia² are relevant as they note discrete, neurobiological processes which can contribute to the development

of psychosis and then schizophrenia. The association between stimuli-related stressors and subsequent manifestation of psychosis sheds light on a previously poorly understood link between the two entities.

The relationship between nicotine and psychosis may especially be pertinent by examining the phenomena in the adolescent population. Psychotic disorders such as schizophrenia are neurodevelopmental in origin, with the emergence of prodromal symptoms typically occurring in adolescence and early adulthood.¹⁷ The developing brain may be more susceptible to the influence of nicotine, which causes upregulation of nAChRs¹⁸ compared with the adult brain, as evidenced in some rodent studies.¹⁹ In recent decades, a multifaceted relationship between nicotine use and psychosis has emerged that ranges from earlier disease onset,²⁰ increased disease severity,²¹ poorer prognoses⁴ and poorer quality of life.²⁹ This growing body of evidence supports both the neurobiological link between nicotine and psychosis and the idea that nicotine consumption itself may predispose individuals to worse overall outcomes. These ideas, although rudimentary at present, may highlight the importance of reducing nicotine exposure in susceptible populations for both disease prevention and severity mitigation.

PROS AND CONS OF NICOTINE IN PSYCHOSIS

The relationship between smoking and antipsychotic medications is worth examining in detail. Some early reports state that smoking ameliorates previously noted psychomotor slowing seen with first-generation antipsychotics (FGA) such as haloperidol.³⁰ The basis of this association arises from nicotine's potential to increase dopaminergic activity and to compensate for the preferential D2 blockage caused by FGA.² Nicotine use has been associated with lower levels of antipsychotic-induced akathisia.³¹ This could explain the increased propensity for smoking in patients exhibiting akathisia, although this is not a universal finding.³² Clozapine has a higher affinity for D4 than D2 receptors, lowering the baseline risks of extrapyramidal side effects and akathisia.³³ As a result, smoking may confer little symptomatic relief in patients on clozapine, compared with those on FGA.³⁴ Nicotine induces cytochrome P450, thus increasing the metabolism of some antipsychotic drugs. This lowers their plasma levels and reduces the antipsychotic efficacy.³⁵ As such, continued nicotine consumption may have adverse effects on the efficacy of antipsychotic regimes. This may increase the risk of psychosis relapse, worsening disease progression and complications from antecedent pathology.

Some positive effects associated with nicotine warrant acknowledgement and possibly even exploitation. The relative hypodopaminergic state in the prefrontal brain is thought to contribute to the negative symptoms and cognitive deficits seen in schizophrenia. Koukoli *et al.*³⁶ showed that chronic nicotine administration reversed

this hypofrontality in mouse models of schizophrenia. In humans, nicotine has been shown to improve cognitive deficits in individuals with psychosis, including working memory and attention.^{37 38} In this context, nAChRs have emerged as targets for the treatment of cognitive and negative symptoms of psychosis.^{39 40}

It is important to examine the positive effects of nicotine on any health condition, including schizophrenia, with a considerable degree of scepticism. This is due to the nefarious history of the tobacco industry and its influences on published literature. Prochaska *et al*⁴¹ exposed instances of the tobacco industry directly funding research, which encourages self-medication of tobacco among those individuals with schizophrenia. Such revelations have stimulated further empirical research and novel hypotheses surrounding self-medication.^{41 42} Despite these potentially meddling influences, there is, arguably, a scope for the exploitation of nicotine consumption among some patients with schizophrenia. Ameliorating negative and mitigating cognitive symptoms of schizophrenia certainly may be viewed as beneficial and appropriate adjuvant therapy in these populations. The risks of such consumption, in the context of broader health-related outcomes and the above-documented effects on schizophrenia itself, must be weighed against the potential benefits of nicotine exposure. It would be pertinent to evaluate such benefits against other available therapeutic options for relieving both cognitive and negative symptoms in the given population. The harm associated with nicotine is further explored below.

COMORBIDITIES BETWEEN PSYCHOSIS AND SMOKING

Nicotine, alcohol and other drugs of abuse target dopaminergic, glutamatergic and GABAergic transmission, which are also involved in the pathophysiology of severe mental illness, and smoking precedes the onset of symptoms of mental illness.⁴³

The strongest associations between severe psychotic illness and substance use were seen with cigarette use. This is notable because most mortality seen in severe psychiatric illnesses is due to smoking-related disorders. In addition, it appears that recent public health efforts that have successfully decreased smoking in the general population have not been effective in individuals with severe psychotic disorders.⁴⁴

Factors like male gender, being in treatment for more than 5 years, having a history of admission and having a family history of mental illness were found to have a significant positive association with tobacco dependence. Hence, there is a need for coordinated and comprehensive clinical management to address tobacco dependence along with identified risk factors in patients with schizophrenia.⁴⁵ It is also worth noting that many antipsychotics interact with nicotine and vice versa. Pinniti *et al*⁴⁶ reviewed this relationship, as presented in [table 1](#).

Table 1 Interaction between antipsychotics and nicotine

Possible effect of nicotine on antipsychotic drug levels (P450)	
Antipsychotic medication	Nicotine
Clozapine	Decreases drug levels
Olanzapine	Decreases drug levels
Haloperidol	Possibly decreases drug levels
Phenothiazines	Decreases drug levels
Risperidone	None reported
Ziprasidone	None reported
Quetiapine	None reported
Aripiprazole	None reported
Data adapted from Mago <i>et al</i> . ⁴⁶	

NICOTINE REPLACEMENT THERAPIES IN PSYCHOSIS

The World Health Organization (WHO)⁴⁷ recommends that all healthcare premises and immediate surroundings should be smoke-free. The last two decades have seen a clear transition towards smoke-free mental health settings in many countries with the goal of improving the health outcomes for both patients and staff.⁴⁸ The no-smoking policy in hospitals and mental health facilities was driven by public health advocates. These changes led to extensive debates. Questions were raised about the capacity of people with mental disorders to tolerate such policy changes while being unwell. Others noted the infringements on human rights by banning a legal, although psychoactive, substance. Removal of patient choice, risk of decompensation secondary to dependence/withdrawal^{49–51} and harm avoidance were among other areas of concern raised over this time period.^{52 53}

Most psychiatric units do not allow smoking indoors, with some exceptions for outdoor areas. A growing body of evidence indicates that a total smoking ban can be successfully implemented in psychiatric hospitals. This topic remains contentious.⁵⁴ Some facilities allow psychiatric patients to smoke outdoors on hospital grounds, despite total smoking bans (indoor and outdoor) being in place for non-psychiatric patients. The argument is that allowing patients to smoke may have beneficial effects on their condition or at least prevent decompensation.⁴⁸ These practices directly contraindicate evidence that clearly states that universal smoking bans do not increase patient aggression and assist all patients in smoking cessation.⁵⁵

Globally, e-cigarettes and vaping products are increasingly being seen as aids for smoking cessation. Their use in the psychiatric population is increasing. This increased use, popularity and higher concentration of nicotine delivery seen with e-cigarettes and vapes have the risk of worsening outcomes of schizophrenia.⁵⁶ The notion that vaping or e-cigarettes may be effective in smoking cessation needs to be critically examined among medical

bodies.⁵⁷ By encouraging the use of such products as part of smoking cessation programmes, clinicians may inadvertently increase psychotic symptoms. This would serve as a detriment to an already susceptible population, with noted adverse outcomes when considering the impacts of nicotine exposure. Keeping this in mind, it becomes clear that healthcare premises should indeed work towards achieving smoke-free statuses. This is even more relevant in the schizophrenia population, with a differential disease burden, psychopharmacological profile and a unique, emerging causal relationship.

CONCLUSIONS

Higher levels of nicotine use among people with psychosis led to the self-medication hypothesis almost 40 years ago. This idea of reverse causality has remained the default explanation for the association between psychosis and smoking. Notable benefits of symptom relief, cognitive improvement and mitigation of adverse antipsychotic effects seen in nicotine use form the backbone of why it is generally believed that nicotine use is markedly increased in these populations. Emergent data demonstrate some causal associations between nicotine and the development of psychosis. However, there remains limited evidence in this area, which needs to be explored further. Despite the uncertainty surrounding nicotine's role as a contributor or ameliorator of psychosis, nicotine exposure remains a poor prognostic factor in terms of onset, severity, duration and complications of psychosis and its spectrum of disorders. Continued efforts to reduce smoking in psychiatric populations are agreed to be a beneficial intervention in terms of mental health-related and systemic outcomes.

Contributors GK identified the topic, planned the review, did the reference search, extracted data and drafted the manuscript and responsible for the overall content of the manuscript and submission of manuscript. RK undertook the literature review, extracted data, contributed to the writing and prepared bibliography for this paper formatting in line with *General Psychiatry* referencing requirements.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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