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The relationship between nicotine and psychosis

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Abstract: Cigarette smoking is strongly associated with psychotic disorders such as schizophrenia. For several decades it was assumed that the relationship could be explained by reverse causation; that smoking was secondary to the illness itself, either through self-medication or a process of institutionalization, or was entirely explained by confounding by cannabis use or social factors. However, studies have exposed that such hypotheses cannot fully explain the association, and more recently a bidirectional relationship has been proposed wherein cigarette smoking may be causally related to risk of psychosis, possibly *via* a shared genetic liability to smoking and psychosis. We review the evidence for these candidate explanations, using findings from the latest epidemiological, neuroimaging, genetic and preclinical work.

Keywords: nicotine, smoking psychosis, schizophrenia, psychotic disorder

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Introduction

Psychosis arises from difficulties establishing what is real and what is not, and is characterized by disordered thinking and speech, hallucinations and delusions, so-called positive psychotic symptoms or experiences. A psychotic disorder constitutes more persistent and pervasive psychotic symptoms, typically alongside a number of other deficits. One of the most severe psychotic disorders is schizophrenia. It has long been acknowledged that there is a strong relationship between cigarette smoking and psychotic disorders. More recently, smoking has also been found to be associated with psychotic experiences in the general population.[1–3] Rates of cigarette smoking in individuals with psychotic disorders are 2–3 times greater than those without.[4] Moreover, tobacco smokers with psychotic disorders display patterns of heavy smoking,[5] severe nicotine dependence[4] and are less likely to quit than nonsmokers.[6] There is an increased risk of tobacco-related morbidity and excess mortality in this population,[7] constituting a major contributor to health inequalities.

The reasons underlying the smoking–psychosis association are unclear. A number of explanations have been proposed, which are not necessarily mutually exclusive:

1. *Reverse causation*: high rates and intensity of smoking in individuals with psychotic disorders are secondary to the illness itself, whether through self-medication to alleviate symptoms or antipsychotic-induced side effects, to improve attention and working memory, or through a process of institutionalization.
2. *Shared liability*: psychotic disorders and cigarette smoking share some liability, likely genetic, and the high prevalence of tobacco smoking in this population is a manifestation of this common liability.
3. *Confounding*: tobacco smoking is associated with established risk factors for psychotic disorders, be they social (e.g. adversity) or biological (e.g. other drug use), which may be causally related to psychosis.
4. *Smoking itself is causally related to psychosis*: it is clear that smoking is neither a necessary nor a sufficient factor for the development of schizophrenia and related disorders. It can be inferred from temporality and dose-dependence effects, however, that smoking could be a primary causative factor for

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some cases of psychosis, or interact with other risk or precipitating factors.

In this paper we review the evidence for these hypotheses, using findings from the latest epidemiological, neuroimaging, genetic and preclinical work.

Effects of nicotine on the brain

The main components of tobacco smoke are nicotine, which is an alkaloid found in tobacco leaves and the neurologically active agent responsible for the addictive properties of cigarettes, and tars, the term given to the resinous, partially combusted particulate matter which includes polycyclic aromatic hydrocarbons, produced by the burning of tobacco. Inhalation of cigarette smoke distils nicotine from tobacco in the cigarette. Nicotine attaches to tar droplets and is absorbed by tissues in the mouth, nose and pulmonary alveoli, where it enters the pulmonary venous circulation.[8] Nicotine rapidly crosses the blood–brain barrier, reaching the brain 10–20 s after inhalation.[9]

The nicotinic cholinergic receptor and neurotransmitter release

Nicotine binds to nicotinic acetylcholine receptors (nAChRs). These are presynaptic receptors located throughout the brain, with the highest density in the thalamus, basal ganglia and caudate nucleus, followed by the frontal, parietal, temporal and occipital cortex, hippocampus and cerebellum.[10] Neuronal nAChRs exist as multiple subtypes of pentameric structures with unique combinations of at least 17 (α1–α10, β1–β4, γ, δ, ε) genetically distinct subunits; these have different distributions, functional properties and pharmacological profiles.[11] Nicotine demonstrates the highest affinity for nAChRs that contain α4 and β2 subunits; these are the most abundant nAChRs in the brain.[12] Nicotine binding opens an intrinsic ion channel in the receptor and allows the flow of cations (Na^+, $Ca2^+$, and K^+) through the cell membrane, activating voltage-gated calcium channels and leading to neurotransmitter release.[8] Nicotine is known to alter the release of virtually all major neurotransmitters, including dopamine, acetylcholine, endogenous opioid peptides, γ-aminobutyric acid (GABA), glutamate, noradrenaline and serotonin.[13]

Addictive and cognitive effects

Nicotine stimulates dopamine release in broad target areas throughout the brain. The addictive properties of nicotine appear to be primarily associated with mesolimbic dopaminergic pathways; activation of nAChRs in the ventral tegmental area (VTA) results in the release of dopamine in the shell of the nucleus accumbens, which is important in the perception of pleasure and reward.[14] Nicotine also increases glutamate and GABA transmission in the VTA.[15] While nicotine-induced GABAergic transmission quickly desensitizes, the glutamatergic response does so to a lesser degree; there is therefore an overall shift where inhibitory GABAergic transmission is decreased and excitatory glutamatergic transmission is increased. This likely contributes to prolonged increases in dopamine release and the pattern of behavioural reinforcement seen in nicotine addiction. Interestingly, this mechanism has also been implicated in psychosis, with N-methyl-D-aspartate (NMDA) receptor hypofunction on GABAergic interneurons resulting in reduced inhibition of pyramidal glutamate, with excess glutamate release leading to activation of dopaminergic neurons.[16] The pro-cognitive properties of nicotine appear to be linked through the nicotine-induced release of dopamine in mesocortical pathways connecting the VTA with cortical regions, including the prefrontal cortex (PFC).[14]

Sensitivity to nicotine in the adolescent brain

Neural development is far from complete at birth, and continues into adolescence and early adulthood.[17] This is a period of critical vulnerability for the initiation of tobacco smoking, with uptake during adolescence associated with severe nicotine dependence.[18] There is variation in the relationship between nicotine exposure and neural structural characteristics across developmental epochs, and evidence suggests that nicotine may affect the trajectory of brain development, for example by modulating prefrontal cortical function.[19] In animal models, frontostriatal circuitry is particularly vulnerable to nicotine exposure in adolescence,[20] with ensuing cognitive deficits seen in later adulthood.[21,22] Nicotine appears to have a role in influencing neuronal growth,[23] and Nordman and colleagues show that stimulation of nicotinic receptors with nAChR agonists (such as nicotine) results in a decrease in axonal surface area.[24] Moreover, chronic exposure to nicotine is associated with upregulation of nAChRs,[25] and

preclinical data suggest that the adolescent brain is more vulnerable to nicotine-induced increases in nAChR expression than the adult brain.[26]

Of note, it has been suggested that psychotic disorders such as schizophrenia are neurodevelopmental in origin, with the emergence of prodromal symptoms typically occurring in adolescence and early adulthood. This has led to speculation that neurodevelopmental processes that take place during this period may be important in the expression of latent vulnerability for psychosis,[27] and may be susceptible to the influence of psychoactive substances such as nicotine.

In a recent study, Jobson and colleagues used a rodent model of adolescent neurodevelopment to show that exposure to nicotine during a critical period of adolescent neurodevelopment led to long-term behavioural, neuronal and molecular phenotypes consistent with mood and anxiety-related disorders, including an alteration in neuronal activity states in both dopaminergic neuronal populations in the mesolimbic VTA, and increased spontaneous neural activity in the PFC.[28] This suggests a convergence of nicotine-induced neuroadaptation in the mesocorticolimbic system, leading to neuropsychiatric phenotypes which persist into adulthood, and has implications for the development of pharmacological interventions to prevent or reverse the long-term effects of nicotine exposure, as well as in identifying those who may be at increased risk from nicotine exposure during select periods of neurodevelopment.

The smoking–psychosis association: candidate hypotheses

Reverse causation

Until recently it was widely assumed that the smoking–psychosis association could be explained by reverse causation and that cigarette smoking was a consequence of the psychotic disorder itself. This could arise through: (1) a process of institutionalization, whereby smoking habits are culturally transmitted *via* mental health settings; (2) due to psychotic individuals who smoke being less likely to give up due to more limited access to smoking cessation treatment and misguided attitudes regarding the supposed psychological benefits of smoking held by patients or mental health staff,[29] (3) through boredom, apathy or reduced motivation as part of a deficit syndrome; or (4) as a deliberate attempt to alleviate the symptoms of the disorder or the adverse effects of antipsychotic drugs (often referred to as self-medication).

The self-medication hypothesis assumes that individuals with psychotic disorders smoke to allay clinical symptoms or treatment side effects.[30] Indeed, smokers with schizophrenia more commonly attribute their motivation to the calming, mood enhancing, and pro-cognitive effects of smoking than smoking controls.[31] Nicotine has been shown to reduce sedating and other side effects of antipsychotic medication,[32] as well as diminish negative psychotic symptoms[33] and lessen distress. Use of nicotine prior to psychosis onset could be attributed to self-medication for anxiety in the prodromal phase of the illness.

Cigarette smoking in individuals with psychosis may be related to the type of antipsychotic. First generation antipsychotics (FGAs) such as haloperidol are associated with an increased risk of smoking.[34] This may be explained by nicotine-induced increases in dopaminergic activity, which compensate for the preferential D2 blockade produced by FGAs. Smoking has been associated with lower levels of antipsychotic-induced akathisia,[35] possibly suggesting an increased propensity for smoking in individuals exhibiting akathisia, though this is not a universal finding.[36] Interestingly, studies have reported that clozapine might reduce smoking in patients with schizophrenia.[37–39] Clozapine binds more strongly to D4 dopamine receptors than to D2 receptors and is associated with a lower incidence of extrapyramidal side effects; akathisia is also a rare side effect.[40] Constituents of tobacco smoke can increase the metabolism of some antipsychotic drugs through induction of cytochrome P450 enzymes,[41] thereby accelerating their metabolism.

Nicotine has been shown to improve cognitive deficits in individuals with psychosis, including working memory and attention,[42–45] and in this context nAChRs have emerged as targets for the treatment of cognitive and negative symptoms.[46,47] It is postulated that nicotine compensates a hypodopaminergic state in prefrontal brain regions, thought to underlie the negative symptoms and cognitive deficits seen in schizophrenia.[48] Indeed, a recent study by Koukouli and colleagues showed that chronic nicotine administration reversed hypofrontality in mouse models of schizophrenia.[49] There is a reduction in the density of $\alpha7$[50] and $\alpha4\beta2$ nicotinic receptors[51] in postmortem brain tissue of patients with schizophrenia, and

the degree of upregulation of α4β2 receptors in schizophrenia (for a given level of smoking) also appears to be impaired,[52] further strengthening a compensatory role for tobacco smoking in schizophrenia. Moreover, smoking may be implicated in improving a number of neurophysiological abnormalities associated with psychotic disorders, including sensory gating deficits,[53,54] pre-pulse inhibition,[55] and abnormal smooth pursuit eye movement.[56]

The fundamental principle of the self-medication hypothesis is that psychotic individuals seek out nicotine to alleviate the symptoms associated with the illness or side effects of treatments, that is smoking is initiated upon development of the illness, or initiation of antipsychotic medication. Evidence for this, however, is scarce.[57] Furthermore, symptoms of psychosis do not appear to be exacerbated by smoking cessation.[58] Not all studies have found an improvement in cognition with nicotine use in individuals with psychotic disorders,[59–61] and many of those that did failed to match groups on smoking severity, thus the greater nicotine effects in individuals with psychosis may reflect more pronounced withdrawal-induced deficits, as a result of heavier smoking.[61] A review conducted by Prochaska and colleagues exposed that the tobacco industry monitored or directly funded research promoting the idea that individuals with schizophrenia need tobacco to self-medicate, and that they are less susceptible to the harms of tobacco smoking.[62] Such revelations have stimulated further empirical research and novel and alternative hypotheses to the notion of self-medication.[63,64]

Shared genetic liability

Shared genetic liability to both smoking and psychosis has been suggested based on findings from discordant twin and sibling studies of schizophrenia.[65,66] A Swedish study by Kendler and colleagues found, in a co-relative analysis, that heavy smokers in discordant monozygotic twin pairs were approximately 1.7-times more likely to develop psychosis compared with the nonsmoking twin, however, there was only a modest decrease in the hazard ratio when comparing full siblings to half-siblings, cousins or the general population,[67] suggesting that genetic factors cannot fully explain the relationship between smoking and risk of psychosis.

Large scale genome-wide association studies (GWASs) have identified risk genes for many complex human diseases and traits, including schizophrenia[68] and smoking behaviour phenotypes,[69] which provide an opportunity to examine the genetic relationship between correlated traits, as well as identify shared risk genes. The Schizophrenia Working Group of the Psychiatric Genomics Consortium identified 108 genome-wide significant loci associated with an increased risk of schizophrenia, and one of these is located in a cluster of genes, *CHRNA5-A3-B5* which code for the α5-α3-β4 nicotinic receptor subunit, the strongest genetic contributor to nicotine dependence.[69–71] There are three further genetic studies that have also cast nicotine dependence as a phenotype that shares genetic liability with schizophrenia.[72–74] For example, Reginsson and colleagues use polygenic risk scores for schizophrenia to predict smoking and nicotine dependence in an Icelandic sample, suggesting shared genetic aetiology, and show that as smoking rates decline, genetic risk appears to gain importance as a determinant of smoking behaviour.[74] A shared genetic architecture could suggest biological pleiotropy, in which a single locus affects multiple traits; however, alternate explanations are possible, involving mediated pleiotropy wherein one phenotype is itself causally influenced by the second phenotype, consistent with causal or reverse-causal effects.[75]

Causality can be studied in observational epidemiological studies using Mendelian randomization (MR), whereby randomly assorted genetic variants that are associated with an environmental exposure are used as proxy measures for the exposure itself. Subject to certain assumptions, MR has the potential to overcome many of the biases that impact the validity of traditional approaches such as confounding and reverse causation.[76] A MR study by Wium-Andersen and colleagues found that a single nucleotide polymorphism (SNP) in the *CHRNA3* gene associated with smoking intensity and the likelihood of receiving a prescription for antipsychotic medication (considered a proxy for risk of psychotic illness), suggesting that smoking could have a causal influence on the development of psychosis.[77] Two-sample MR has recently been developed, in which data on the gene-risk factor and gene-outcome associations are taken from different data sources to conduct MR analyses.[78] Using this technique, Gage and colleagues combined SNPs associated with smoking initiation (from the Tobacco and Genetics Consortium[69]) and schizophrenia (from the Psychiatric Genetics Consortium[68]) and show

little evidence of a causal association between smoking initiation and schizophrenia in either direction,[79] which supports a possible pleiotropic effect. However, the authors emphasize that this does not rule out a causal effect of smoking on schizophrenia related to heavier, lifetime exposure. In a recent study, Wootton and colleagues describe the development of a novel genetic instrument for lifetime exposure that can be used in two-sample MR without the need to stratify by smoking status, and using this instrument the authors report evidence that the association between smoking and schizophrenia is due, at least in part, to a causal effect of smoking.[80]

Confounder, mediator, or a special relationship with cannabis?

To further complicate matters, tobacco smoking is associated with established environmental risk factors for psychosis such as adversity and childhood trauma,[81] and illicit substance use.[82]

Cannabis is the most commonly studied illicit substance and its association with psychosis is widely accepted to be at least partly causal in nature, and related to its potency.[83] Cannabis and tobacco smoking are highly correlated with one another,[84] and while many cigarette smokers do not use cannabis, a high proportion of cannabis users smoke tobacco,[85] either concurrently as cigarettes (co-use) or as a component of cannabis joints (simultaneous use).

The relationship between these two substances is complex and challenging to disentangle. The 'gateway' hypothesis suggests that tobacco smoking acts as a gateway to the use of cannabis,[86] however, there is evidence for the 'reverse gateway', whereby cannabis smoking paves the way for tobacco initiation,[87] as well as evidence implicating genetic factors associated with the use of both drugs.[84] Tobacco smoking increases the amount of tetrahydrocannabinol inhaled per gram,[88] thus enhancing the subjective effect of cannabis. In a naturalistic study of cannabis and tobacco co-users, tobacco smoking has been shown to mediate the relationship between cannabis use and cannabis dependence, even when controlling for psychological and demographic correlates that could explain this relationship, perhaps due to the more addictive properties of nicotine.[89] Preliminary experimental evidence also suggests that tobacco may offset the effects of cannabis on delayed verbal recall and working memory.[90] Co-use of tobacco and cannabis also leads to poorer psychosocial, cessation and physical health outcomes.[91,92] Thus, it is plausible that tobacco smoking might directly perpetuate cannabis dependence and relapse in co-dependent users, in this way mediating the risk of developing psychosis. Evidence also exists to suggest a possible synergistic effect whereby the combination of tobacco and cannabis gives rise to psychotic symptoms.[2] There might be implications for clinical practice here, given the lack of empirical research guiding treatments for simultaneous and co-use of tobacco and cannabis,[84,93] particularly in those with psychotic disorders.

Recent lines of evidence suggest that the endocannabinoid system, which is implicated in a host of physiological processes and the system through which cannabis exerts its psychological and physical effects, may play a role in the rewarding and reinforcing effects of nicotine.[94] For example, genetically deleting or pharmacologically blocking CB1 cannabinoid receptors reduces or eliminates many of the behavioural and neurobiological effects of nicotine that are responsible for its addictive potential.[95] There is current interest in the endocannabinoid system as a therapeutic target for nicotine addiction,[96] as well as in the treatment of psychosis.[97]

Causal effect

More recently, attention has been directed towards the possibility that tobacco smoking might be causally related to risk of psychosis. There are two meta-analyses that have reported strong associations between tobacco smoking and an increased risk of having a psychotic disorder estimating odds ratios in smokers *versus* nonsmokers of 6.04 [95% confidence interval (CI) 3.03–12.02][57] and 3.22 (95% CI 1.63–6.33).[98] The latter study showed that daily smokers experienced their first psychotic episode at an earlier age than nonsmokers (weighted mean difference −1.04 years, 95% CI −1.82 to −0.26), and for prospective studies, calculated an overall relative risk of new psychotic disorders in daily smokers *versus* nonsmokers of 2.18 (95% CI 1.23–3.85). Moreover, those with psychosis started smoking at a nonsignificantly earlier age than did healthy controls (−0.44 years, 95% CI −1.21 to 0.34). These meta-analyses were not able to adjust for substances other than tobacco (e.g. cannabis use) as very few studies measured or controlled for these variables objectively; they are further limited by comparatively

small numbers of longitudinal prospective studies. Of note, early initiation of daily smoking is also associated with greater risk of later developing a psychotic illness, consistent with the hypothesis that exposure during a critical period of brain development may be specifically associated with psychosis risk.[63,99]

The Bradford Hill criteria can be useful in establishing epidemiologic evidence of a causal relationship between a presumed cause and an observed effect, and constitute the strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy of an association.[100] In relation to strength, the association reported in prospective studies undertaken in the general population identifies a modest increase in relative risk. Moreover, the association has persisted after adjustment for smoking onset during a prodromal period, and other risk factors such as socioeconomic status, other drug use, baseline psychotic experiences and parental psychosis and drug use.[63,67] The findings appear to be consistent between different populations.[101,102] With the exception of one sample, wherein cigarette smoking reduced risk of later developing schizophrenia,[103] cigarette smoking typically predates psychosis onset, thereby satisfying temporality criteria, and prospective studies demonstrate a dose–response effect, suggesting that a biological gradient exists.[67,104,105] Further, daily smoking appears to have a greater effect on the positive symptoms of psychosis,[106] and there is evidence that schizophrenia with comorbid nicotine dependence is more severe and has worse clinical and functional outcomes.[104,107,108] Smoking affects a number of disease processes, therefore limiting the applicability of the specificity criterion, while experimental animal models of psychosis do not exist.

If cigarette smoking is causally related to psychosis, we must consider how this might plausibly fit with our current understanding of the neurobiology of psychosis, which implicates excess subcortical dopamine synthesis and release.[109] Nicotine appears to increase dopamine release directly and to a similar extent as other misused substances, as measured *in vivo* by positron emission tomography (PET) in the dorsalventral striatum and basal ganglia.[110,111] Bloomfield and colleagues, however, show that moderate smoking does not appear to be associated with marked effects on striatal dopamine synthesis capacity, in contrast with previous findings of elevated dopamine synthesis capacity in heavy smokers.[112] Nicotine alters the release of almost all major neurotransmitters, many of which have been implicated in the pathogenesis of psychotic symptoms.[13] There is also an inverse relationship between smoking and risk of Parkinson's disease,[113] a dopamine deficiency disorder. Work in animal models shows that nicotine exposure might increase D2 high-affinity receptors[114] thus supporting a role for nicotine in the induction of supersensitive D2 receptors, which has been posited as an underlying mechanism for a number of schizophrenia risk factors, and as a common pathway for symptoms of psychosis.[115]

Thus far, we have primarily focused on the relationship between nicotine and dopamine. A number of other factors, however, have relevance in terms of their relationship with both cigarette smoking and the pathoaetiology of psychosis. First, much attention has recently been directed towards inflammation and the neural diathesis-stress hypothesis of schizophrenia,[116] and cigarette smoking is highly associated with both the release and inhibition of proinflammatory and anti-inflammatory mediators.[117] Indeed, inflammatory processes underlie a number of the physical health consequences of smoking, and preclinical studies show that peripheral inflammation can induce neuroinflammation.[118] Inflammatory cytokines may also modulate dopaminergic and glutamatergic neurotransmission directly.[119,120] Second, constituents of cigarette smoke have significant effects on the endocrine system, for example altering production and metabolism of estradiol,[121] which is thought to contribute to the sex differences in schizophrenia incidence,[122] as well as cortisol,[123] which has also been implicated in psychosis.[124] Finally, epigenetic processes may mediate the relationship between genetic risk burden, environmental exposure, and phenotype, and increasing emphasis has been placed on the potential role of epigenetic dysfunction in the aetiology of psychosis.[125] Smoking is strongly associated with DNA methylation in a distinct set of loci,[126] thus investigation of the tobacco epigenetic signature in individuals with psychosis may provide insight into mechanisms by which tobacco smoking and psychosis are associated.

There is increasing acceptance that schizophrenia is not a homogenous disorder; instead, it is likely that subtypes of schizophrenia exist, reflecting distinct neurobiological aetiologies. As the risk that smoking confers in the development of

cancer varies as the subtype of cancer becomes more specific, so too might parallels exist with subtypes of schizophrenia.

Discussion

In this review we have compared the evidence for four possible explanations for the relationship between smoking and psychosis. The elevated smoking rates found in those with psychosis led to the supposition that these individuals smoke to self-medicate, and a self-medication hypothesis put forward almost 40 years ago remained the default explanation for the association between smoking and psychosis. However, over recent years, studies have exposed that self-medication and reverse causation cannot fully explain the association. The jury is out on whether tobacco might be causally related to the risk for psychosis, or whether the association manifests through a shared genetic vulnerability, or is confounded by use of illicit substances or other social factors. Of course, if smoking is a causal risk factor for psychosis, this does not preclude the possibility that smoking is also used as a form of self-medication, and indeed the dopaminergic effects of nicotine on the mesocorticolimbic pathway might support this.

Of growing relevance is the increasing use and popularity of nicotine-containing products, particularly electronic cigarettes (which typically contain high levels of nicotine). By encouraging the use of such products as part of smoking cessation programmes, clinicians may be inadvertently increasing psychotic symptoms. To our knowledge this has not been studied directly; however, Munafo and colleagues reported a modest association with using 'snus', a form of buccally absorbed moist tobacco, and risk for nonaffective psychosis in a large Swedish registry data set.[127] These results suggest that any causal mediator is present in unburned tobacco products, and although perhaps the most plausible and widely studied culprit is nicotine, there are other possible mechanisms such as inhibition of monoamine oxidase, which is involved in the degradation of dopamine.[128] It might be that different constituents account for different neurobiological effects; some might improve symptoms, while others might exacerbate them. Determining which constituents are responsible may have important public health implications.

Nevertheless, the dramatic declines in cigarette smoking seen in the general population have not been reflected in individuals with psychotic disorders,[129] and there is also stark evidence that the mortality gap is widening.[130] Establishing smoke-free inpatient psychiatric units is a goal that hospitals and policymakers are increasingly supporting, however the impact on long-term patterns of smoking in this population remains to be elucidated. While science continues the challenging task of unravelling this complex relationship, every effort should be made to implement change in smoking behaviours in this population, with initiation of counselling and treatment for nicotine dependence alongside treatment for the primary psychotic disorder.

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