

Why do patients with schizophrenia smoke?

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Purpose of review

Among the mentally ill, smoking prevalence is highest in patients with schizophrenia (~70–80%). This can impose a significant financial burden on patients, not to speak of increased smoking-related morbidity and mortality. Therefore, it is critical for clinicians to understand why patients with schizophrenia smoke in order to adapt treatment schemes. Understanding the reasons may also help to develop new drugs that target the nicotinic system in the brain as well as smoking cessation programs that are specifically designed for this particular patient population.

Recent findings

So far, several reasons have been identified which are believed to explain tobacco consumption in patients with schizophrenia. Originally, it was widely believed that patients with schizophrenia smoke to increase hepatic clearance and to restore the dopamine blockade of certain antipsychotic drugs to diminish their side effects. However, more recently it became obvious that cigarette smoking may also be reinforcing for patients because it improves psychiatric symptoms, most notably negative and cognitive symptoms. The underlying molecular mechanisms of these nicotine effects are currently under intensive investigation.

Summary

Heavy smoking in schizophrenia cannot simply be viewed as a 'bad habit'. Rather, self-medication of clinical symptoms and side effects of antipsychotic drugs appear to play a major role.

Keywords

nicotine, schizophrenia, self-medication, smoking

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Introduction

Among the mentally ill, smoking prevalence is highest in patients with schizophrenia (70–80%), whereas it is 20–30% in the general population [1,2**]. In addition, patients with schizophrenia tend to smoke more heavily than smokers in the general population. This is particularly striking in light of the frequently strained financial situation of patients with schizophrenia. For instance, it has been pointed out that patients with schizophrenia may spend up to 30% of their monthly budget on tobacco products [3]. To make things worse, smoking is considered as the major cause of the two-fold higher risk for coronary heart disease of patients with schizophrenia, which contributes significantly to their 20% shorter life expectancy [4,5]. Accordingly, it is obvious that smoking has a devastating impact on most patients' lives. The question therefore is why do patients with schizophrenia smoke? Having an answer to this question may eventually help to optimize treatment schemes and to adapt smoking cessation programs to the specific needs of this patient population. In addition, understanding the reasons may also lead to a better understanding of schizo-

phrenia and – by extension – to the future development of novel drugs for treatment.

Nicotine is highly addictive in most people and patients with schizophrenia are no exception to this rule. On the contrary, this does not explain the extremely high prevalence of smokers among patients with schizophrenia. There is some evidence that smokers with a history of psychiatric disorders generally have a higher likelihood of experiencing severe withdrawal symptoms [6]. There are, however, other possible reasons that may be more closely associated with schizophrenia *per se*. For many years, two explanatory approaches have been favored among clinicians. The social explanation is that, for illness-related reasons, patients with schizophrenia have too much time with little else to do than smoking. Whereas clinical experience suggests that there is some truth in this view, this aspect has, however, attracted little attention by clinical researchers, with only preliminary data being available to date [7]. This is despite a better knowledge of the relationship between smoking habits and the daily life of patients with schizophrenia having a considerable practical value for the implementation of specific smoking

cessation programs. The pharmacotherapeutic explanation is that the basis of this explanation rests on the pharmacodynamic and pharmacokinetic properties of antipsychotic drugs [8–13]. Accordingly, antipsychotic drugs block postsynaptic dopamine D2 receptors and patients with schizophrenia may smoke to restore – through the central action of nicotine on dopaminergic neurons – the blocked dopamine effects. In this way, they may reduce common side effects, including extrapyramidal symptoms and pharmacogenic depression. In an analogous way, patients with schizophrenia may achieve this attenuation of side effects through the well known enzyme induction effect of polycyclic aromatic carbohydrates which are produced when tobacco is burnt. Enzyme induction of the cytochrome P450 1A2 isoform (CYP1A2) and UDP-glucuronosyltransferase (UGT) is caused by enzyme synthesis and is fully present 2 weeks after initiation of smoking. It is reversed within 2–4 weeks after stopping smoking. This means that smoking decreases plasma levels of many typical and atypical antipsychotics (e.g. haloperidol, chlorpromazine, olanzapine and clozapine) by approximately one-third. This effect can be counteracted to some extent by coffee consumption because coffee is a CYP1A2 inhibitor. Overall, patients with schizophrenia who smoke heavily may thus be easily undertreated with antipsychotic drugs, which may in part explain the observation that heavy smokers have higher numbers of hospitalizations and more positive symptoms during acute episodes [14]. Whereas adapting the dosage of drug treatment can be one option to deal with this situation, an alternative strategy is to switch medication. For instance, risperidone or aripiprazole are metabolized through CYP2D6 and CYP3A, and quetiapine and ziprasidone through CYP3A. Thus, plasma levels of these drugs are not affected by tobacco smoking. Knowing the relationship between smoking and drug treatment can therefore be critical for a clinician's treatment management of patients with schizophrenia. Beyond optimizing dosages schemes, selecting the most appropriate drug may also help to enhance the rate of smoking cessation. In those with schizophrenia who smoke, cessation rates are lower than in the general population. George *et al.* [15] have shown that, compared with typical antipsychotic agents, atypical antipsychotic agents (in combination with the nicotine transdermal patch) significantly improve the outcome in smoking cessation programs. An important point in this context, however, is that the introduction of atypical antipsychotic drugs led to the realization that the high smoking prevalence in patients with schizophrenia may not be entirely explained by the pharmacokinetic effect of smoking on hepatic drug clearance which has been the predominant view for decades. This gave way to the recently developed notion that nicotine consumption in patients with schizophrenia may serve to some considerable extent the purpose of self-medication of cognitive deficits and – perhaps – negative symptoms.

The self-medication hypothesis

In addition to the obvious symptoms of hallucinations and delusions (i.e. positive symptoms), patients with schizophrenia frequently suffer from negative symptoms (e.g. avolition, social withdrawal, anhedonia) and cognitive deficits such as the inability to focus attention or impaired working memory [16,17*]. Negative symptoms and particularly cognitive deficits are important predictive factors in determining a patient's ability to cope successfully with everyday activities [18]. In addition, cognitive deficits, which overlap considerably with negative symptoms [19,20], possess trait-like characteristics and appear to be closer to the genetic cause of schizophrenia. In contrast, positive symptoms in particular may represent compensatory mechanisms in the brain and accordingly they vary over the course of the illness and treatment [21].

There are now several lines of evidence suggesting that patients with schizophrenia may consume nicotine to self-medicate negative symptoms and – perhaps even more so – cognitive deficits as well as associated neurophysiological abnormalities. In this regard, groundbreaking research has been conducted by the group led by Freedman in Denver, Colorado, over the last two decades. In a series of preclinical and clinical studies, they described that nicotine and smoking normalizes auditory sensory gating (P50) deficits which are frequently observed in patients with schizophrenia and their first-degree relatives [22–24]. In addition, increasing evidence was obtained that a variation of the $\alpha 7$ subunit gene, which codes for low-affinity nicotinic $\alpha 7$ receptors (see below), is linked with the P50 gating deficit and schizophrenia illness [25,26] – a finding which has been repeatedly replicated since then [27]. Extending these observations, it has become obvious that smoking or nicotine application also normalizes a number of additional sensory processing deficits which are associated with the genetic risk for schizophrenia including prepulse-inhibition (PPI) abnormalities [28] and eye-tracking deficits [29–32]. In addition, it was reported that PPI is impaired by smoking abstinence in schizophrenia and improved by acute smoking reinstatement, mediated by stimulation of nicotinic receptors [33]. It has also been recently shown in a functional magnetic resonance imaging (fMRI) study that eye-tracking performance is improved through cholinergic stimulation of the hippocampus and cingulate gyrus [34]. Mostly, the authors who conducted these studies argued that nicotine may primarily affect early sensory processing components in these paradigms through an improvement of inhibitory mechanisms although PPI and eye-tracking also involve a motor response.

The theoretical notion that nicotine primarily affects early sensory processing is, however, not easily reconciled

with numerous preclinical and clinical experiments showing that nicotine strongly enhances vigilance and attention as well as related neurophysiological surrogate measures [35[•]]. In fact, among the best described effects of nicotine on cognition is its positive impact on vigilance and attention both in animal models and in smoking and nonsmoking humans [36–50]. An interesting observation in this context is that attentional performance in nicotine-dependent rats deteriorates when deprived of nicotine [51], and that, after the cessation of nicotine consumption, nicotine-dependent patients show an only slowly resolving decline of alertness, that is, of electrophysiologically measured arousal during cognitive tasks [52]. More recently, several functional neuroimaging experiments have essentially confirmed the behavioral studies. Stein *et al.* [53] described widespread dose-dependent effects of intravenously administered nicotine on cortical and subcortical brain function (during the resting state) with the strong effects observed in the cingulate and several frontal lobe divisions, including the dorsolateral, orbital, and medial frontal cortex. Interpreting their results, the authors point out that the activated areas closely agree with the distribution of nicotine receptors in the human brain, as assessed with PET [54]. Of particular interest are neuroimaging studies that have shown nicotine effects during task conditions that require a patient to maintain attention [55–65]. For instance, using fMRI during a sustained visual attention task, Lawrence *et al.* [62] described that transdermal nicotine replacement leads to a task-independent signal enhancement in the attentional fronto-parieto-thalamic network of smokers. They also reported less task-induced brain activation during mild nicotine abstinence, which is in line with behavioral studies showing decreased performance on attention-requiring tasks during abstinence [59,66]. During recent years, these nicotine effects have also been demonstrated in patients with schizophrenia and there is some evidence that nicotine effects on attention (and working memory) might be even stronger in patients with schizophrenia than in healthy controls. For instance, Barr *et al.* [67] could demonstrate in a cross-over placebo-controlled trial with nicotine patches that in a continuous performance task (CPT) – a common measure for attention performance – the number of errors was more strongly decreased in patients with schizophrenia than in controls. Analogous results have been obtained by Jacobsen *et al.* [60] with a similar experimental design, except that fMRI was used to assess brain function during an auditory n-back task. Brain function related to both the attentional and the working memory components was more strongly improved in patients with schizophrenia than in controls. On the contrary, Hong *et al.* [68] conducted another fMRI study using similar task conditions but did not find such a diagnosis \times nicotine effect. Even so, nicotine improved sustained attention in both patients with schizophrenia and controls.

Until recently a nicotine-induced activation of the prefrontal cortex seemed to be the most likely mechanism by which cognition is improved. However, an electrophysiological study published recently points to another explanation.

Couey *et al.* [69] provided evidence that the key effect of nicotine on prefrontal functioning may not be activation but improvement of the signal-to-noise ratio in prefrontal microcircuits. In this study nicotine increased the activity of GABAergic interneurons, which leads to an elevated threshold for the occurrence of a specific type of synaptic plasticity, spike-timing dependent-potential. β 2-containing as well as α 7-nicotinic acetylcholine receptors on GABAergic interneurons in the prefrontal cortex seemed to be involved in this phenomenon [69]. These findings are intriguing because there is accumulating evidence that schizophrenia may have a diminished signal-to-noise ratio in prefrontal microcircuits [16,17[•]].

Whereas the effects of nicotine on neurophysiological and cognitive parameters have been extensively studied within the framework of the self-medication hypothesis, it is somewhat amazing that only a very few studies have addressed nicotine effects on schizophrenia psychopathology [70,71]. It is therefore difficult to make a strong statement on whether nicotine has any effect, and, if yes, on what specific clinical symptom domain. Nevertheless, it appears from these studies that nicotine may particularly improve negative symptoms, which would not be entirely unexpected given the overlap of cognitive deficits and negative symptoms in schizophrenia. In this context, it is noteworthy that a recent phase 2 trial of a nicotinic agonist in schizophrenia conducted by the Freedman group revealed a favorable effect of the nicotinic agonist on negative symptoms, whereas no effect was found on the MATRICS cognitive measures [72] (see below). Interpretation of this finding certainly would have been somewhat easier if the differential effects of nicotine on negative symptoms and cognitive deficits were better known from earlier work.

Little attention has also been paid to the question of whether acute compared with chronic nicotine consumption or smoking exerts different effects in schizophrenia. For instance, it is conceivable that the self-medication hypothesis may apply only to acute nicotine effects, whereas long-term chronic nicotine exposure may have the opposite effect. Evidence for the latter notion comes from both relatively recent animal experiments and human studies (for review see [73[•],74]). These findings strongly suggest that there might be a detrimental interaction between (prefrontal) brain maturation and chronic nicotine exposure. Thus, whereas the acute nicotine effect is experienced as beneficial with regard to cognitive

functioning and negative symptoms, chronic nicotine use – particularly in young schizophrenic patients with brain maturation not yet completed – may actually go along with a deterioration of these symptom domains.

Nicotinic signaling in schizophrenia: molecular aspects

In the brain, nicotine effects are mediated by nicotinic acetylcholine receptors (nAChRs). nAChRs are membrane-bound pentameric protein complexes with a central cation channel. Multiple genes code for the receptor subunits $\alpha 2$ – $\alpha 10$ and $\beta 2$ – $\beta 4$. The pentameric receptors are either homomeric (containing only one type of α -receptor subunit) or heteromeric (containing α as well as β -subunits). The most abundant receptors in the central nervous system are the homomeric $\alpha 7$ receptors and the heteromeric $\alpha 4\beta 2$ receptors [75]. Three functional states of nAChRs can be differentiated: rest, activated and desensitized. Upon stimulation of nAChRs the central channel opens for the cations sodium, potassium and calcium. nAChRs are found presynaptically and postsynaptically on various neurons such as GABAergic, glutamatergic, dopaminergic and cholinergic neurons. Stimulation of presynaptic receptors induces Ca^{2+} -influx and thereby increases the release of neurotransmitters. Stimulation of somatic or dendritic receptors induces a depolarizing sodium current, thereby increasing the neuron's excitability and firing rate [76]. Through these mechanisms nAChRs modulate numerous systems and processes such as the reward system, the attentional network, learning and memory, brain development and neuroprotection [75]. The physiological stimulation of nAChRs with acetylcholine is characterized by rapid exposure to the ligand, high peak concentrations and termination of the stimulation within milliseconds as acetylcholine is rapidly inactivated by the enzyme cholinesterase. Under these physiological conditions nAChRs are in either their resting or their activated state. Stimulation of nAChRs by nicotine shows quite different kinetics. Smoking of one cigarette causes a longer exposure of the receptor to lower doses of the ligand compared with physiological stimulation with acetylcholine because the receptors are exposed to nicotine for several minutes and nicotine is not inactivated by cholinesterase. This nonphysiological, continuous, low-dose stimulation of nAChRs facilitates the inactivated/desensitized conformation of the receptor which mediates tolerance to nicotine [77].

Long-term exposure of a receptor to its physiological ligand or a pharmacological agonist usually leads to endocytosis and downregulation of the receptor. The effect of long-term nicotine exposure on nAChRs is a remarkable exception to this rule. Post-mortem and imaging studies consistently indicated that nAChRs are

upregulated upon chronic nicotine exposure [78–83,84^{*}], which may support a potentiation of the effects of nicotine on the cellular, network and behavioral level dependent on the receptor's conformation and readiness to be activated. Regarding specific nAChR subtypes, upregulation is clearly present for heteromeric $\alpha 4\beta 2$ receptors. Upregulation may not be present for other receptor subtypes such as for the homomeric $\alpha 7$ receptor, as indicated by a study by Cormier *et al.* [85], who demonstrated a much higher $\alpha 4\beta 2$ moiety and an equal $\alpha 7$ moiety in lymphocytes of mice administered nicotine and of healthy smokers compared with nonsmokers. The precise mechanisms of why $\alpha 4\beta 2$ upregulation is present upon chronic nicotine exposure are not yet fully understood; however, most data point towards post-transcriptional mechanisms, that is, stabilization of nAChR protein complexes, as mRNA levels of nAChR subunits remain unchanged [86,87]. In addition, neuronal Ca^{2+} -sensor protein VILIP-1, known to affect clathrin-dependent receptor trafficking, has been shown to interact with the cytoplasmic loop of the $\alpha 4$ -subunit of the $\alpha 4\beta 2$ nAChR. Zhao *et al.* [88] recently reported that overexpression of VILIP-1 enhances ACh responsiveness, whereas siRNA against VILIP-1 reduces $\alpha 4\beta 2$ nAChR currents of hippocampal neurons. The underlying molecular mechanism likely involves enhanced constitutive exocytosis of $\alpha 4\beta 2$ nAChRs mediated by VILIP-1. The two interaction partners co-localize in a Ca^{2+} -dependent manner with syntaxin-6, a Golgi-SNARE protein involved in trans-Golgi membrane trafficking. Thus, regulation of VILIP-1 expression might modulate surface expression of ligand-gated ion channels, such as the $\alpha 4\beta 2$ nAChRs, possibly constituting a novel form of physiological upregulation of ligand-gated ion channels. In this scenario, an increased number of nAChRs may cause cholinergic hyperexcitability which may be associated with withdrawal symptoms whereby a decrease of nAChRs is observed within weeks after smoking cessation [82,84^{*},89].

In patients with schizophrenia who are mostly smokers, up-regulation of nAChRs, however, appears to be considerably diminished when compared with normal controls or normal smokers. Thus, a lower number of both $\alpha 4\beta 2$ and $\alpha 7$ receptors or lower amounts of mRNA has been reported for post-mortem brains in hippocampus and cortex [80,90–92] as well as for lymphocytes and lymphoblasts [93] (Luckhaus *et al.*, submitted for publication). Furthermore, we recently demonstrated a negative correlation between negative symptoms and [³H]-nicotine binding to nAChRs in the lymphoblast model (Luckhaus *et al.*, submitted for publication) leaving open the question of whether this relates to diminished $\alpha 4\beta 2$ or $\alpha 7$ receptor binding. In any case, this finding is in good accordance with the notion of a nAChR deficit being involved in the cause of negative

and cognitive symptoms in schizophrenia, with smoking being a possible symptom remediator in this psychiatric condition [94].

There is some indirect evidence from experimental studies in rats that $\alpha 4\beta 2$ receptors may play a crucial role in mediating the effect of nicotine on certain aspects of cognitive performance, that is, attention performance and related prefrontal activity [95[•]]. Additional evidence from this work indicates that stimulation of *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors is necessary for the manifestation of nAChR-agonist-evoked cholinergic signal amplitude. Interestingly, the $\alpha 7$ antagonist methyllycaconitine did not affect choline signal amplitudes but partly attenuated the relatively slow decay rate of nicotine-evoked cholinergic signals. The authors suggest that dopaminergic mechanisms mediate the slower decay rate of nicotine-evoked cholinergic activity because there is evidence suggesting that nicotine can produce sustained release of dopamine by increasing, via stimulation of $\alpha 7$ nAChRs, the size of the releasable pool of dopamine-storing vesicles [96]. In any case, there are several experimental neuroscience studies indicating that both receptor subtypes are differentially involved on a molecular and physiological level in certain aspects of a particular cognitive operation including attention performance as well as lasting effects of nicotine on downstream neuroplastic processes which by themselves may have an impact on cognition [97[•]].

Drug development and nicotinic ligands in schizophrenia

Two drugs that are currently in clinical use may have direct effects on the $\alpha 7$ nAChRs. Thus, the anticholinesterase inhibitor galantamine is thought to have modulatory effects on $\alpha 7$ nAChRs and was reported to be beneficial in patients with schizophrenia in a case study [98]. Likewise, topisetron, a 5HT₃ antagonist marketed as an anti-nausea drug, also has efficacy as an $\alpha 7$ nAChR agonist and increases the inhibition of P50 auditory gating in schizophrenia [99].

On the basis of the nicotine self-medication hypothesis, several drug companies have recently started to develop drugs which target the nicotinic system in schizophrenia (these drug candidates are also considered to be potentially useful for the treatment of Alzheimer's disease, Parkinson's disease, epilepsy, neuropathic pain, depression, attention-deficit disorder and smoking cessation [100^{••},101^{••}]). Targeting nicotinic receptors is complicated not only by the limited availability of compounds selective for particular subtype combinations, but also by the development of rapid agonist-induced receptor

desensitization, which makes it difficult to treat over the long term with an agonist and maintain a physiological effect [102^{••}]. Thus, desensitization requires a drug to be administered very frequently, analogous to chain smoking in patients with schizophrenia unless a compound is found that stimulates the receptor without desensitization.

At present, the focus of research and development is primarily on $\alpha 7$ nAChR agonists. The alkaloid GTS-21 is a partial agonist of $\alpha 7$ nAChRs that improves memory-related behavior under various task conditions and it also normalizes auditory gating [103]. GTS-21 is a lead compound from the privately held biopharmaceutical company Athenagen, Inc. It is currently the leading clinical drug candidate in the field [100^{••}]. Initially, GTS-21 was found to significantly improve attention and memory in normal healthy volunteers. In a second phase I trial [104], GTS-21 normalized P50 auditory gating in patients with schizophrenia. Although the subsequent initial phase II trial did show an improvement in the negative symptoms of schizophrenia, there was no cognitive effect [72], which may be due to the fact that GTS-21 is also a strong $\alpha 4\beta 2$ antagonist, together with the occurrence of a significant learning bias during the trial [102^{••},105]. Further proof-of-concept studies are currently under way to support drug development of $\alpha 7$ nAChR ligands from companies such as Targacept, Envivo, Sanofi-Aventis and Johnson & Johnson. For completeness it should be mentioned that AZD3480, a selective $\alpha 4\beta 2$ nAChR partial agonist that has been used in studies for Alzheimer's disease, is currently being evaluated in a phase IIb trial in cognitive dysfunction in schizophrenia. However, the results did not meet the trial's criteria and it is therefore not expected to progress to phase III studies [101^{••}]. Overall, agonists and positive allosteric modulators of $\alpha 7$ and $\alpha 4\beta 2$ nAChRs, enhancers of nAChR function, have clearly gained considerable interest as potential therapeutics for schizophrenia.

Conclusion

Heavy smoking in schizophrenia is to some considerable extent related to self-medication of clinical symptoms. Apparently, molecular and physiological abnormalities of the central nicotinic system account at least in part for the clinically observed relationship, providing us with clues about the cause of schizophrenia. Currently, there are intensive efforts under way to develop novel drugs which target the nicotinic system in order to treat cognitive and negative symptoms.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 171–172).

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