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**Smoking in schizophrenia: recent findings about the old problem**

**Introduction**

The association between smoking and schizophrenia was established several decades ago [1,2]. Despite worldwide reductions in cigarette consumption, smoking bans, efficacious cessation strategies, and the decrease of smoking prevalence [3], schizophrenia patients continue to smoke frequently and heavily [4]. Their smoking prevalence does not change, as shown in the literature data covering 25 years’ period in Japan [5] and 17 years in the United States [3]. Recent studies reported that 50-70% of those patients smoked cigarettes [6-12], and were more than three times as likely to smoke than subjects without psychiatric disorders [3]. Similar findings were reported in the first-episode patients (FEP) [4,13,14] and treatment-resistant patients [15], suggesting high smoking rates across disease stages. Similar to general population, men smoked more frequently than women [8,16]. Smokers with schizophrenia also consumed greater number of cigarettes [5,13,17,18], had higher severity of nicotine dependence [17] and greater expired carbon monoxide levels, despite similar nicotine dependence [19] as non-psychiatric smoking controls.

**Scope of the problem**

Such smoking behavior continues to produce devastating consequences in those patients. Tobacco smoking increased their risk of cardiovascular mortality by 86% over a 20-year period [20]. Likewise, being a smoker at baseline more than doubled the mortality risk during a 17 years period schizophrenia or bipolar disorder patients [11]. Smoking had synergistic effects on mortality from respiratory or cardiologic diseases [11]. Smoking was associated with increased high sensitivity CRP levels in schizophrenia [7], elevated levels of factor H-related protein and reduced terminal complement complex in FEP patients [4]. Despite well-known harmful (but preventable) smoking consequences, patients with schizophrenia are less likely to be screened for tobacco use, at least in primary care [6], and to receive cessation support from health professionals [21] than smokers without schizophrenia. A meta-analysis detected the association between schizophrenia and lower probability of smoking habit recorded [22].

**A complex link between smoking and schizophrenia**

Smoking in schizophrenia is beyond a bad habit [23, 24]. Nicotine activates nicotinic acetylcholine receptors (nAChRs) [25-27] which play an important modulatory role in both schizophrenia and addiction. Their stimulation on ventral tegmental area (VTA) neurons induces rapid and strong activation of midbrain dopaminergic neurons [27]. Nicotine binds to all nAChRs subtypes, but has the highest affinity for α4β2 receptors [25], with dose-dependent effects [25-27].

Novel findings provided further evidence that smoking might 1) increase the risk of developing schizophrenia; 2) share the same biological background with schizophrenia; and 3) patients might consume cigarettes in an attempt to alleviate some symptoms („self-medication “hypothesis).

*Smoking increases the risk for schizophrenia*

Smoking preceded the onset of schizophrenia for several years [9,13]. Smoking was independent risk factors for the development of schizophrenia: young smokers had almost double the risk for being diagnosed with schizophrenia in later life; prenatal exposure to maternal smoking was related to 29% higher risk of schizophrenia and heavier smoking was associated with greater risks [28]. Preclinical data offered potential explanations: perinatal nicotine exposure in rats altered both dopaminergic and non-dopaminergic neurons in VTA by modulating regulatory genes involved in the neurodevelopment [29]. These reports [28,29] strongly advice against smoking during pregnancy. Current smokers from general population had higher proportion and greater number of psychotic symptoms [30], but the cross-sectional design precludes causal assessment. Conversely, smoking status was not associated the with the higher risk of conversion to psychosis [31].

*Shared genetic background between smoking and schizophrenia*

Molecular genetic studies revealed the shared genetic roots for schizophrenia and smoking [32]. They used polygenic risk scores (PGSs) from Genome-wide association studies meta-analytic findings, which identified PGSs for complex conditions, such as schizophrenia [33] and smoking phenotypes [34]. A strong evidence of shared polygenic risk between schizophrenia and substance use was found [35]. Because of high comorbidity between substance use disorders, it was unclear if the association was driven by tobacco dependence or a general substance use disorder liability [35]. In a large Icelandic sample of individuals without psychotic disorders, PGSs for schizophrenia were higher in ever- than never-smokers, and associated with the number of cigarettes smoked daily [24]. PGSs for schizophrenia were nominally associated with all severity levels of nicotine use among non-Hispanic European-American participants [36]. The *CHRNA5*–*CHRNA3*–*CHRNB4* locus contains three genes encoding nAChR subunits, associated with both nicotine dependence and schizophrenia [32]. Recently, 22 variants on this locus were associated with smoking quantity and schizophrenia at the genome-wide significance level [32]. They might contribute to different *CHRNA5* expression in multiple brain regions [32]. Regarding individual gene variants in schizophrenia, carriers of G allele of mu opioid receptor A118G polymorphism, smoked more cigarettes, compared to the AA genotype [8]. The G allele resulted in lower sensitivity to nicotine and consequently greater cigarette consumption [8]. However, nicotine appears to produce similar epigenetic changes in schizophrenia patients and healthy individuals [37].

*The "Self-medication hypothesis"*

New preclinical and clinical data provided pro and contra arguments to popular hypothesis that nicotine ameliorates several symptom domains and some biological abnormalities in schizophrenia. Rats with quinpirole-induced dopamine D2 receptor supersensitivity, resembling increased D2 receptor activation in schizophrenia, had enhanced rewarding associative properties of nicotine compared to control rats [38]. Neurotoxic lesion in rats, mimicking core biological features of schizophrenia, facilitated nicotine self-administration [39]. While these results suggested that neurobiological abnormalities might enhance nicotine use, either amphetamine-induced hyperdopaminergic state or phencyclidine-induced glutamate dysfunction had no effects on nicotine self-administration [40]. Chronic nicotine administration in mice with genetic α5 nAChR subunit deletion, which resembles hypofrontality, had normalized neuronal activity deficits [41]. In a prenatal maternal immune activation model, nicotine, unlike saline, ameliorated cognitive deficits [42]. In a transgenic mouse model of schizophrenia, chronic nicotine administration reversed the increased oxytocin receptor binding in cingulate cortex and central amygdala [43].

Clinical research focused mainly on cognitive dysfunction, yielding inconsistent findings. Moderate to heavy smokers with schizophrenia, tested during early and prolonged abstinence and after smoking resumption, showed no changes in cognition [44]. Overnight smoking abstinence resulted in impaired visuospatial working and verbal memory in smokers with or without schizophrenia, which were reversed by smoking [45]. In patients with psychosis, smokers had reduced processing speed and lower working memory than nonsmokers [46]. Smokers with schizophrenia had delayed memory performance, while healthy smokers performed worse in immediate memory, visuospatial/constructional functions and global cognition, compared to non-smokers from both groups [47]. In respondents with schizophrenia, more mistakes on the 1 out of 7 items on constructional apraxia tests correlated with the severity of nicotine dependence [48]. In FEPs, there were no differences in multiple cognitive domains between smokers and nonsmokers [13]. Those recent reports and meta-analysis [49] challenged the perspective that smoking improves cognitive dysfunction in schizophrenia, based on previous findings of its favorable effects on acute performance, mostly attention/vigilance [16].

Patients might smoke to reduce negative symptoms, particularly anhedonia. In drug free patients, an inverse correlation was reported between CHRFAM7A gene (the partially duplicated chimeric gene of α7 nAChR gene) expression in lymphocytes and negative symptoms, including anhedonia [50]. Due to the low percentage of smokers [50], it was unknown if nicotine might change those findings. In smokers, anticipatory anhedonia increased during nicotine withdrawal [51]. While in schizophrenia, unlike in non-psychiatric population, anhedonia might be related to heavier nicotine dependence [18], more data is needed on different aspects of anhedonia in this population. Smokers with schizophrenia had decreased smoking and neutral cue brain activation in bilateral frontal midline regions than control smokers, which was more pronounced in those with greater negative symptoms [19]. In schizophrenia patients, smoking had preservation effects on the dynamics of influences from the salience network to the default mode network [52] and reversed abnormalities in intrinsic brain activity in right striatal and prefrontal cortices [53]. These reports proposed biological background for „self-medication“ hypothesis [52,53] with potential beneficial effects of smoking on negative symptoms [52].

**Smoking and features of schizophrenia**

Smokers had less severe extrapyramidal symptoms (EPS) [54], and were less frequently prescribed anticholinergics than nonsmokers, despite higher antipsychotic doses [55]. Smoking was associated with more severe positive symptoms [54], higher levels of physical aggressiveness in schizophrenia [9] and insomnia in FEP patients [14]. These effects might be explained by nicotine stimulant and dopamine-increasing effects [25]. The history of tobacco use was associated with suicide attempts in cross-sectional studies, and predicted suicide in cohort studies [56]. These studies did not measure the levels of nicotine dependence [9,15,54-56], although nicotine effects are dose-dependent [25]. Patients with predominantly negative and/or cognitive symptoms might consume less nicotine to achieve stimulation, while those with more positive symptoms and aggressiveness might use higher doses to induce sedation [25]. Smokers in schizophrenia might not be a unique category. For example, levels of depression were similar in smokers and nonsmokers with schizophrenia [54], but severely dependent smokers showed higher rates of depression and antidepressant use than mildly dependent smokers [57]. Majority of studies were cross-sectional [9,54,55,57], and did not explore the causality. Although smoking was not associated with negative symptoms [54], meta-analysis suggested that more severe negative symptoms were alleviate by smoking. Severe nicotine dependence was also associated with the childhood trauma history [57], suggesting potential effects of stress in nicotine dependence. Interestingly, rats injected with saline had higher nicotine self-administration than non-injected rats [40]. Stress might represent the missing link between genetic vulnerability, smoking and schizophrenia. Stress might also be a confounder, as the relationship between increased risk for schizophrenia and smoking disappeared after inclusion of daily stressors [31]. However, neither smoking nor levels of nicotine dependence were associated with salivary cortisol levels in schizophrenia patients [10], suggesting possible desensitization to effects of stress in schizophrenia.

**Smoking and antipsychotics**

The relationship between smoking and antipsychotics is bidirectional [16]. While smoking influenced antipsychotic metabolism, antipsychotics affect to a variable degree nicotine-induced stimulation of reward processing [58]. Smoking was associated with the use of first-generation antipsychotics (FGA) [9], while clozapine or aripiprazole were associated with lower smoking frequencies [55]. Patients treated with FGAs, including haloperidol, tended to have lower craving scores than clozapine-treated [59]. Haloperidol also exerted stronger effects than clozapine in animal models [38,60].

Higher antipsychotic doses in smokers were observed in stabilized [55] and hospitalized patients [10]. Tobacco use was associated with prescription of 4 or more psychotropic agents in schizophrenia-spectrum disorder [61]. Higher doses of antipsychotics in smokers might result from their blunting of nicotine-induced reward, particularly in strong dopamine D2 receptor blockers such as haloperidol. They might more markedly decrease nicotine rewarding effects, causing more intense smoking to overcome such blockade (Referenca??). In addition, smokers might be treated with higher antipsychotic doses because of greater positive symptoms [54]. Another plausible explanation is that smokers, due to increased antipsychotic clearance [62], required greater doses, and being a smoker was prospectively associated with diminished olanzapine efficacy [63]. Doses of atypical antipsychotics correlated with the number of cigarettes smoked daily, although the proportion of patients on clozapine or olanzapine was not reported [5].

Smoking affects the metabolism of CYP1A2 substrates clozapine [62] and olanzapine [64]. It induces CYP1A2 activity, as reflected by higher caffeine clearance in smokers [65], and increased hepatic CYP1A activity in mice after exposure to cigarette smoke [66].

Smokers had reduced olanzapine levels by one third compared to nonsmokers, irrespective of the route of administration [64], while earlier study demonstrated less pronounced influence of long-acting injections [67]. However, smoking behavior was not reported [62,64,67], although smoking affected CYP1A2 activity dose-dependently. Heavy smokers had 2-fold higher caffeine clearance than nonsmokers [65]. Clozapine and olanzapine prescribing information mention the influence of smoking on their pharmacokinetics, but provide no dosage modifications (www.FDA.gov; www.halmed.hr). However, literature data recommended 50% higher clozapine dose in smokers, 30-40% dose reduction after smoking cessation, and 30% lower olanzapine dose in nonsmokers [16]. New antipsychotic asenapine is also a CYP1A2 substrate [68], but there is no information whether smoking alters its pharmacokinetics. The metabolism of other SGAs occurs primarily via other pathways [68] and is unlikely to be affected by smoking, as recently confirmed for quetiapine and risperidone levels [62]. Smoking might also affect CYP2C19, CYP3A4, UGT1A3, and UGT1A4 enzymes [62].

**E-cigarettes and schizophrenia**

Electronic cigarettes (e-cigarettes) were introduced 12 years ago [69], with the intent to deliver nicotine and produce similar sensations as combustible cigarettes, without releasing other tobacco constituents. Their use is on a rise [70]. It was reported that 7% of patients with schizophrenia currently consume e-cigarettes, 37% have tried, while 24% of never-users consider their use [71]. The content of polycyclic aromatic hydrocarbons, the main CYP1A2 inducers from cigarette smoke, is reduced in e-cigarettes. So far there are only two case reports on their influence on clozapine levels, which were increased after transition from combustible to e-cigarettes [72,73], and there is no data on the olanzapine concentration. Given no current recommendation regarding antipsychotic dose adjustment after switching to e-cigarettes, caution is needed when changing of smoking device in patients on CYP1A2 substrates.

**Decreasing smoking in schizophrenia: a realistic goal**

Nicotine effects appear more rewarding in individuals in schizophrenia [74]. Patients had also greater odds of tweeting about tobacco than control users [75]. Their most common barriers to quit smoking were cravings and addiction, followed by a perceived increased risk of negative affect during smoking cessation [21]. The clinician's concern that smoking discontinuation might worsen patient's condition is not supported by the recent research [13,76,77], which actually encourages smoking cessation at least in clinically stable patients [13,77]. Even patients with severe symptoms should be motivated to reduce or quit smoking [78].

Several treatment options exist [79]. Vareniciline is a partial agonist of α4β2, and a full agonist of α7 nAChRs, which attenuates reinforcing effects of nicotine, and demonstrated superiority over placebo in the number of cigarettes consumed daily, the expired carbon monoxide levels and higher abstinence rates in patients with schizophrenia [77]. Nicotine replacement therapy delivers nicotine in order to reduce abstinence symptoms, while bupropion decreases withdrawal symptoms via dopaminergic and noradrenergic mechanisms [79]. Importantly, all three agents were effective, none worsened symptoms of schizophrenia, but the data on prolonged abstinence in unremitted patients and individuals with polysubstance abuse are missing [79].

**Conclusion**

The reasons for consistently high rates of both smoking and heavy nicotine dependence in schizophrenia patients are still incompletely understood. Smoking in schizophrenia is a complex phenomenon and not all smokers are the same. The greatest difference might exist between heavy and light smokers. Severe dependence might represent biologically and clinically distinct category [18]. Patients with schizophrenia have numerous abnormalities, some of which are alleviated by smoking. While beneficial effects of smoking on cognition have recently been questioned, there is new evidence on the possible nicotine effects on negative symptoms. However, risks of smoking substantially outweighed any potential benefits. Effective treatment exists particularly for stable and motivated individuals, while severely symptomatic, treatment-resistant and in-cooperative patients remain a challenge. Given the important role of nAChRs in both schizophrenia and smoking, new molecules acting on specific nAChR subtypes might target nicotine dependence, cognitive deficits and negative symptoms in schizophrenia, and hopefully replace „self-medication by nicotine “ by medication with more effective and safer drugs.

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Key points

Despite the worldwide reductions in cigarette consumption, smoking rates in patients with schizophrenia remain high and continue to display detrimental effects on their health

New preclinical and clinical data emphasized the complex biological link and shared genetic roots between nicotine consumption and schizophrenia

Recent research suggested that self-medication by smoking for cognitive dysfunction is unlikely, but patients might smoke to alleviate negative symptoms and EPS

While cigarette smoking reduces clozapine and olanzapine concentrations, caution and more data are needed in patients starting to use e-cigarettes

The evidence encourages smoking cessation in schizophrenia across all phases of the disease and several effective treatment strategies exist

Purpose of review

To summarize recent findings on the epidemiology, biological and clinical findings, interference with antipsychotics and treatment strategies regarding cigarettes consumption in schizophrenia.

Recent findings

New data have shown that the prevalence of smoking in patients with schizophrenia continues to be high, despite world-wide efforts to reduce smoking rates. Recent reports did not confirm earlier findings on beneficial effects of smoking on cognitive dysfunction, and also demonstrated the association between smoking and positive symptoms and suicidal behavior. However, some patients might smoke in an attempt to alleviate EPS and negative symptoms. Molecular studies revealed shared genetic roots between smoking and schizophrenia, while smoking itself might also increase the risk for developing schizophrenia. Preclinical and clinical studies extended previous knowledge of a complex, bidirectional interplay between pathology of schizophrenia and brain effects of nicotine,

Summary

Cigarette smoking continues to produce harmful effects on health in individuals with schizophrenia. Such persistence of both smoking and heavy nicotine dependence is more than a bad habit, given the complex biological findings which initiate and facilitate smoking in schizophrenia. Nevertheless, smoking cessation is strongly advocated in schizophrenia, in terms of replacing „self-medication by nicotine “by medication with more effective and safer drugs”.

Key words: Smoking, nicotine dependence, schizophrenia, “self-medication” hypothesis, antipsychotics