SMOKING IN SCHIZOPHRENIA: AN UPDATED REVIEW

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SUMMARY

Patients with schizophrenia continue to have the highest rate of both smoking and heavy nicotine dependence. The interaction between smoking and schizophrenia is complex. There is evidence of the shared genetic background. Recent preclinical and clinical research has further investigated self-medication hypothesis, given that nicotine might alleviate cortical dysfunction. While prior research indicated some favorable effects of smoking on cognitive performance, particulatly on attention/vigilance, recent studies did not confirm those findings. Lower severity of negative symptoms in smokers was not confirmed across studies. Cigarette smoking decreases clozapine and olanzapine concentrations. There is no consistent evidence of favorable effects of nicotine on symptoms in schizophrenia, but the evidence of detrimental effects of smoking on general health is highly consistent. Smoking cessation should be a priority in patients with schizophrenia.

Key words: *cigarette smoking - nicotine dependence – schizophrenia - negative symptoms - cognitive dysfunction - antipsychotic concentration*

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INTRODUCTION

In our previous review we have summarized the data regarding smoking prevalence, and biological effects of smoking in schizophrenia (Šagud et al. 2009). Cigarette smoking continues to be one of the hot topics in schizophrenia, given than more than 50% (Bobes et al. 2010, Van Haren et al. 2010, Fond et al. 2017, Mallet et al. 2018) or 60% of patients are smokers (Mohamed et al. 2016, Nedic Erjavec et al. 2017, Dickerson et al. 2018, Vlatković et al. 2018), which is consistent across geographic areas. Similarly, the smoking rates in first episode psychosis (FEP) (Oluwoye et al. 2018) and in patients with treatment-resistant schizophrenia (Iasevoli et al. 2013, Vlatković et al. 2018) was about 50%. Moreover, smokers with schizophrenia had higher rates of severe nicotine dependence (Zhang et al. 2012, Jiang et al. 2013, Šagud et al. 2018) and different smoking behavior (Šagud et al. 2018) compared to healthy smokers. Many studies addressed the involvement of cigarette smoking in the etiology, clinical presentation and treatment response of schizophrenia. The aim of this mini review was to summarize recent findings regarding smoking in patients with schizophrenia.

THE EFFECTS ON SMOKING ON GENERAL HEALTH

It was recently reported that smoking more than doubled the risk of natural cause mortality in patients with schizophrenia and bipolar disorder (Dickerson et al. 2018). A recent meta-analysis has confirmed that smoking, even being light, presents a large part of the risk of coronary heart disease and stroke (Hackshaw et al. 2018). Those harmful effects on cardiovascular system could be explained by biological and behavioral effects of smoking. Biological effects include, among others, metabolic and proinflammatory effects. Metabolic syndrome (MetS) is characterized by hypertension, dyslipidemia, insulin resistance, and obesity. There is accumulating evidence that smoking is a risk factor for the development of MetS in general population (Tsai et al. 2015, Kang & Song 2015). Smokers were also found to have elevated levels of plasma Zinc α2-glycoprotein, which was also found to be involved in MetS (Tsai et al. 2015), while smoking cessation elevated plasma level of adiponectin in males (Won et al. 2015). Preclinical studies reported that cigarette smoke induced damage of cellular organelles, which could also contribute to the development of MetS (Sanhghwa Kim et al. 2017). While each smoking is harmful (Hackshaw et al. 2018), heavy smoking might exert distinct, more detrimental health effects. For example, in contrast to low or moderate smoking, heavy nicotine dependence was associated with chronic peripheral inflammation, defined as a highly sensitive C-reactive protein concentration $\geq$3 mg/L, in patients with schizophrenia (Fond et al. 2017). Another link between smoking and increased somatic morbidity in schizophrenia might be related to behavioral factors, such as worse lifestyle. For example, smokers were more likely to consume alcohol regularly and less likely to avoid daily consumption of salt, saturated fat, high fiber diet, or to follow a low-caloric diet and exercise regularly, compared to nonsmokers with schizophrenia (Bobes et al. 2010).

While in general population, smokers were 11 times more likely than nonsmokers to develop lung cancer (Jayes et al. 2016), the incidence of lung cancer among patients with schizophrenia was even more than four times higher compared to general population of the United States (McGinty et al. 2012). In another large prospective epidemiological study, men with schizophrenia had double mortality risk from lung cancer compared to French general population and duration of smoking has predicted the death of lung cancer (Tran et al. 2009).

SMOKING AND THE ETIOLOGY OF SCHIZOPHRENIA

Smoking might be involved in the development of schizophrenia very early in the life of the individual, starting from prenatal period. Notably, fetal exposure to nicotine, via maternal smoking during gestation, was related to increased odds of schizophrenia in offspring (Niemelä et al. 2016). More specifically, a greater maternal serum cotinine level was associated with increased risk of schizophrenia later in life (Niemelä et al. 2016). Those findings suggest that smoking, particularly when being heavy, affects fetal brain development in a way that might make the brain more vulnerable.

There is evidence that smoking intensity might be an important determinant of certain aspects of the illness. For example, in a prospective study, adolescents who smoked more than 10 cigarettes daily were at increased risk to develop psychosis compared to nonsmokers, while no such risk was observed for those who smoked up to 9 cigarettes per day (Mustonen et al. 2018). In addition, individuals who started smoking before age of 13 had greater risk of subsequent psychosis than those who became daily smokers after the age of 14 (Mustonen et al. 2018). While smoking heavily in the adolescence and becoming smoker early in life was related to increased risk of psychosis (Mustonen et al. 2018), it was also shown that the commencement of smoking has preceded the onset of schizophrenia for several years (Mallet et al. 2018).

SMOKING AND THE BRAIN

Recent preclinical and clinical research added new evidence to support the self-medication hypothesis (Yamazaki & Sumikawa 2017, Koukoli et al. 2017, Liu et al. 2018). A growing number of functional magnetic resonance imaging (fMRI) studies have examined the differences between smokers with schizophrenia and healthy smokers. For example, smoking normalized the right striatal and prefrontal cortical dysfunction in patients with schizophrenia, measured as intrinsic brain activity using task-free fMRI (Liu et al. 2018). Similar findings were noted in animal studies. In a mice model which resembles the hypofrontality, chronic nicotine exposure reversed the decreased cortical activity (Koukoli et al. 2017). In rats, chronic nicotine administration prevented the suppressive effect of neuregulin 1 on the N-Methyl-D-aspartate receptor (NMDAR) function, while, in turn, NMDAR hypofunction was related to cognitive dysfunction in schizophrenia (Yamazaki & Sumikawa 2017). Moreover, impaired fronto-limbic connectivity was found in schizophrenia smokers, relative to control smokers, during the exposure to anti-smoking images (Potvin et al. 2017). Those findings suggest different neural response to anti-smoking images between smokers with schizophrenia and healthy smokers, which may underlie the indifference of patients toward the negative value of tobacco smoking (Potvin et al. 2017). Likewise, lower proportion of smokers with schizophrenia completely recognizes the health risks of smoking compared to smokers without schizophrenia (Kowalczyk et al. 2017). On the contrary, smokers with schizophrenia had increased activations in the bilateral ventromedial prefrontal cortex (vmPFC) when shown appetitive smoking images, compared to smokers without schizophrenia (Potvin et al. 2016). Therefore, nicotine effects might be more reinforcing in smokers with schizophrenia (Potvin et al. 2016). It was demonstrated that smoking induces dopamine release in cortical areas, particularly in cyngular and prefrontal cortex, but also in amygdala (Wing et al. 2015). The potentially higher pleasurable effects of cigarette consumption (Potvin et al. 2016) as well as indifference to its harmful consequences (Kowalczyk et al. 2017, Potvin et al. 2017) might underlie both high smoking prevalence and lower smoking cessation rate (Jiang et al. 2013) in patients with schizophrenia. There is also some evidence that heavy smoking has harmful effects not only on somatic health, but to the brain health as well. Smoking was not related to excessive brain tissue loss in entire sample of patients with schizophrenia, but heavy smoking of more than 25 cigarettes per day, was related to excessive grey brain volume loss over five years (Van Haren et al. 2010).

GENETICS OF SMOKING IN SCHIZOPHRENIA

Heritability of smoking in schizophrenia is estimated to be as high as 65% compared to only 20% in the general population (Chen et al. 2016). While schizophrenia is associated with multiple risk genes, numerous genes are associated with nicotine addiction in schizophrenia. The reason why patients with schizophrenia smoke so frequently and heavily compared to healthy subjects probably might lay in the shared genetic background (i.e. biological pleiotropy) of nicotine addiction (i.e. smoking) and schizophrenia (Chen et al. 2016, Hu et al. 2018). As both disorders are polygenic and multifactorial, patients with schizophrenia smoke since they want to reduce cognitive decline and psychotic symptoms in schizophrenia (i.e. a ''self-medication'' hypothesis), or they smoke since both smoking and schizo-

phrenia have similar genetic background, or smoking proceeds development of schizophrenia and therefore smoking is a risk factor for schizophrenia (i.e. mediated pleiotropy, Chen et al. 2016). A recent study (Hu et al. 2018) performed a systematic search and evaluation to identify genes and their corresponding pathways that were related to both smoking and schizophrenia. They compared shared genes that were associated both with schizophrenia and smoking and found out 52 shared genes out of 276 genes that were related to nicotine addiction and 331 genes that were related to schizophrenia (Hu et al. 2018). With the help of enrichment analysis, network analysis, and network and pathway analysis, the authors grouped these common genes for both smoking and schizophrenia into several groups (Hu et al. 2018). These 52 genes were grouped into genes that code the components of the neurotransmitter systems, such as genes for dopaminergic system (e.g., genes coding dopaminergic receptors types 1,2,3,4 and 5: DRD1, DRD2, DRD3, DRD4 and DRD5), serotonergic system (e.g., genes coding serotonin receptors type 2 and 6 /HTR2A, HTR6/ and genes coding enzymes tryptophan hydroxylase type 1 /TPH1/ and tyrosine hydroxylase /TH/), genes of the glutamatergic system (related to its NMDA, AMPA and kainate receptors /GRIK2, GRIN1, GRIN2A, GRIN2B, GNAS, GRM7/ and excitatory amino acid transporter 2 or solute carrier family 1 member 2 /SLC1A2/), cholinergic system (genes associated to nicotinic and muscarinic cholinergic receptors /CHRNA7, CHRNB2 and CHRM5/), and solute carrier family genes involved in the cellular transport system /SLC1A2, SLC6A3, SLC6A4 and SLC18A2/. In addition, genes coding alcohol dehydrogenase 1B (ADH1B), cytochrome P450 family 2, subfamily D, member 6 (CYP2D6), glutathione S-transferase theta1 and mu1 (GSTT1 and GSTM1), and gene for monoamine oxidase type A (MAOA), were also detected in smoking and schizophrenia (Hu et al. 2018). When looking at the possible functional relevance and biological processes related to these genes, the authors performed function enrichment analysis and found that these candidate genes were associated with 113 biological processes that could be subdivided into those of the neural processes, transmission, communication between cells, and dopamine metabolism (Hu et al. 2018). After performing pathway enrichment analysis, Hu et al. (2018) identified 12 shared significantly enriched pathways associated with both diseases, that were related to nicotine, alcohol, cocaine and amphetamine addiction, neuroactive ligand receptor interaction, dopaminergic, serotonergic, and glutamatergic synapse, estrogen signaling and cAMP signaling pathway (Hu et al. 2018). The other study, evaluating the entire genome using large GWAS datasets and plasma cotinine concentration and Fagerström test for nicotine dependence in schizophrenia, found pathways shared by schizophrenia and nicotine addiction associated with neurotransmitter transduction

and neural communication, with calcium signaling, long-term potentiation and neuroactive ligand-receptor interaction pathways, that are related to cognitive function (Chen et al. 2016). These results suggested that nicotine addiction and schizophrenia share some genetic liability, or that patients with schizophrenia smoke to alleviate their cognitive symptoms or that nicotine addiction is a risk factor of schizophrenia (Chen et al. 2016). Both studies concluded that a system level approach to evaluate genes related to both polygenic disorders such as schizophrenia and nicotine addiction (i.e. smoking) might help in identification of the shared genetic liability for both disorders and could improve understanding of the association between these two disorders and offer novel insights into pathogenetic association between smoking and schizophrenia (Chen et al. 2016, Hu et al. 2018).

SMOKING AND CLINICAL PRESENTATION

In spite of the aforementioned findings, possibly beneficial effects of smoking on schizophrenia-related brain changes (Koukoli et al. 2017, Yamazaki & Sumikawa 2017, Liu et al. 2018), smoking and/or heavy smoking was not very consistently reported to influence the severity of symptoms. The studies have compared symptom severity between smokers and nonsmokers, or investigated the association of heaviness of smoking and psychopathology among smokers. In general, those studies reported controversial findings. In patients with schizophrenia, smoking was associated with higher scores of physical aggressiveness, current alcohol dependence and FGA use (Mallet et al. 2018), but no associations were found with psychotic symptomatology or depression (Mallet et al. 2018). Another study reported higher disease severity and general symptoms in smokers compared to nonsmokers (Nedic Erjavec et al. 2017). Smokers with schizophrenia had lower intensity of negative symptoms (Zhang et al. 2012, Jiang et al. 2013) than nonsmokers. However, in FEP, smokers had higher severity of overall, positive, negative, controlled hostility and excitement symptoms, relative to nonsmokers (Oluwoye et al. 2018). In treatment-resistant schizophrenia, smokers had higher severity of overall and negative symptoms than nonsmokers (Iasevoli et al. 2013). Nonsmokers received lower doses of chlorpromazine equivalents than smokers (Nedic Erjavec et al. 2017), while other studies reported no changes (Jiang et al. 2013). Studies addressing the relationship between nicotine dependence and symptoms among smokers also yielded inconsistent findings. Some studies reported lower severity of negative symptoms in patients who had higher levels of nicotine dependence (Lee et al. 2015, Misiak et al. 2015), while, on the other hand, other studies reported the lack of association between levels of nicotine dependence and the severity of psychopathology in smokers with schizophrenia (Kishi et al. 2013, Rey et al. 2017, Šagud et al. 2018). The

differences across those studies might arise from variations in hospital smoking-ban policies, definitions of heavy smoking, age and gender differences, treatment with various antipsychotics, the presence or absence of alcohol or cannabis abuse, and in particular, overall symptom severity, since some studies included patients in remission, while others enrolled acutely psychotic subjects. Interestingly, being smoker was associated with reduced prolactin concentration in patients with schizophrenia, schizoaffective disorder or bipolar disorder treated with antipsychotics (Mackin et al. 2011).

SMOKING AND COGNITION IN SCHIZOPHRENIA

Cognitive dysfunctions represent a core feature of schizophrenia, including impairments in processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Keefe et al. 2011, Green & Harvey 2014). These deficits predate the clinical onset of first psychotic episode, become more evident in the early years of illness, and tend to reach a relatively consistent level thereafter (Lewandowski et al. 2011). Most individuals suffering from schizophrenia exhibit cognitive deterioration that ranges from moderate to severe, and those deficits are supposed to be the best predictors of functional and vocational outcomes in this population (Tsang et al. 2010).

One popular, long-standing perspective is that individuals with schizophrenia smoke cigarettes more than the general population to "self-medicate" the above-mentioned cognitive deficits. Many clinical trials have been conducted to study the effects of nicotine intake on cognitive function in schizophrenia (D'Souza & Markou 2012). However, the degree of nicotine dependence, the state of nicotine satiety, the state of nicotine withdrawal, and method of administration have differed drastically across studies. Nicotine administration studies to enhance cognition in schizophrenia have used gum, transdermal patch, nasal and orally inhaled, and subcutaneous nicotine (see Boggs et al. 2014). Boggs et al. (2014) have conducted a systematic review of studies in which nicotine is given to individuals with schizophrenia and, based on the available data, it was concluded that nicotine may acutely improve attention/vigilance. Unfortunately, the short duration of these studies does not confirm any long-term benefits to attention. Also, the studies examined several cognitive tests with several outcomes but the vast majority failed to control for multiple comparisons. It seems that available evidence suggests that nicotine does not enhance general cognitive ability, particularly that of long-term effect. In fact, two studies conducted within large populations of European and Han Chinese schizophrenia patients and healthy controls, showed that smoking is associated with significant cognitive impairment in both patients

and controls (Zhang et al. 2012, Nunez et al. 2015). The investigated cognitive domains included semantic fluency, visuospatial function and immediate memory indices. Interestingly, they documented beneficial effect of smoking on negative symptoms (Zhang et al. 2012), as well as protective role of caffeine intake on complex cognitive tasks (semantic fluency, cognitive speed, working memory, and visual memory) (Nunez et al. 2015). In addition, one recently published study tested the self-medication hypothesis by examining the effects of smoking abstinence and resumption on cognition in patients with schizophrenia (Boggs et al. 2018). Cognitive abilities were examined while smoking as usual (baseline), one day after smoking cessation (early abstinence), 1 week later (extended abstinence), and within 3 weeks of resuming smoking (resumption). The investigated measures comprised tests of processing speed, attention, conflict resolution, verbal memory, working memory, verbal fluency, and executive function to evaluate multiple cognitive domains affected by schizophrenia. There were no significant changes in general cognitive performance with smoking cessation, abstinence, or resumption. Therefore, the results of this research challenge the popular and long-standing "self-medication" view of smoking and schizophrenia, question the extent of pro-cognitive effects of smoking and nicotine, and support encouraging smoking cessation in schizophrenia (Boggs et al. 2018). Finally, another well-designed study on 17 patients with schizophrenia and 17 normal controls tested the cognitive self-medication hypothesis, and it was concluded that subjective or objective short-term attentional benefits (which were documented) are unlikely the primary driving force of tobacco consumption in schizophrenia (Hahn et al. 2013).

Overall, although prior research indicated limited favorable effects of smoking on acute cognitive performance, namely attention/vigilance, growing body of empirical evidence suggests insignificant or even detrimental consequences of nicotine dependence on most cognitive functions in chronic schizophrenia patients. More prospective empirical studies with larger samples are warranted.

SMOKING AND ANTIPSYCHOTICS

Investigations regarding smoking and antipsychotics focused on two issues. Firstly, smoking was found to impact the disposition of some antipsychotics, and, secondly, antipsychotics might differently affect smoking behavior.

The influence of smoking to antipsychotic levels

Cytochrome P450 1A2 (CYP1A2) is highly inducible by smoking and also the main enzyme involved in the degradation of clozapine and olanzapine (Dobrinas et al. 2011). This might lead to their decreased effectiveness in smokers and intoxication after smoking cessation.

Table 1. Recommendations regarding clozapine and olanzapine dosage according to smoking status

Antipsychotic	Effects of smoking	Recommendation
Clozapine	Smoking was associated with 45% ↑ in clearance of clozapine and 54.3% ↑ in clearance of its metabolite norclozapine (Li et al. 2012)	Nonsmokers require 50% ↓ dose than smokers (Tsuda et al. 2014) Clozapine dose ↓ by 30-40% after smoking cessation (Lowe & Ackman 2010) Therapeutic drug monitoring (TDM) is strongly recommended (Kennedy et al. 2013)
Olanzapine	Smokers had 53% ↑ in clearance of olanzapine than nonsmokers (Bigos et al. 2011)	Nonsmokers require 30% ↓ dose than smokers (Tsuda et al. 2014) TDM is strongly recommended (Kennedy et al. 2013) Doses required for minimum therapeutic levels: 5 mg 2x daily for female nonsmokers, ≥ 5 mg daily plus 10 mg in the evening for male nonsmokers, >10 mg twice daily for male smokers (Yin et al. 2016)

For example, a 1.55-fold decrease in CYP1A2 activity was reported after smoking cessation (Dobrinas et al. 2011). Therefore, smoking status should be taken into account when considering clozapine and olanzapine dose. While the influence of smoking on drug degradation is mentioned in prescribing information for clozapine and olanzapine, no official dosage modifications regarding cigarette consumption are provided (www.FDA.gov; www.halmed.hr). However, there are some literature suggestions on dosing adjustment regarding smoking status, as provided in Table 1.

Similar findings were observed in olanzapine long-acting injections (OLAI) pharmacokinetic data, although the effects of smoking were somewhat less pronounced than for oral olanzapine (Heres et al. 2014). To the best of our knowledge, there is no dosing recommendation in the literature for OLAI in respect with smoking. Additionally, the aforementioned studies did not account for either heaviness of smoking or daily number of cigarettes (Lowe & Ackman 2010, Bigos et al. 2011, Li et al. 2012, Heres et al. 2014, Tsuda et al. 2014, Yin et al. 2016). However, the number of cigarettes smoked per day was related to greater CYP1A2 activity (Dobrinas et al. 2011). Importantly, major differences were observed between 10–19 and 30–39 or 40–70 daily cigarette consumption (Dobrinas et al. 2011), which suggests that those who smoke heavily, might have low clozapine and olanzapine concentration. Those recommendations are only approximate, given the 17-fold variation in CYP1A2 activity observed among smokers (Dobrinas et al. 2011) and the influence of other variables on CYP1A2 activity, such as the use of contraception (Dobrinas et al. 2011), -163C>A polymorphism (Koonrungsesomboon et al. 2017), cotreatment with fluvoxamine, carbamazepine, and numerous other substances (Kennedy et al. 2013).

These findings highlight the importance of careful observation of patient condition and the individual dosing of clozapine and olanzapine. It was recently demonstrated that smokers showed lower dose-adjusted plasma concentration for paliperidone and risperidone active moiety compared with non-smokers, and that smokers have received higher oral daily doses of risperidone (Schoretsanitis et al. 2017). However, smoking did not alter quetiapine (Handley et al. 2013) and aripi-

prazole (Suzuki et al. 2014) concentrations. Given that asenapine (Citrome 2014), and some other antipsychotics, such as ziprasidone, fluphenazine, perphenazine, haloperidol and chlorpromazine, are minor substrates for CYP1A2 enzymes (reviewed in Franchiser 2013), interaction with smoking cannot be completely ruled out. Of note, nicotine replacement products and electronic cigarettes do not induce hepatic CYP1A2 enzymes (Franchiser 2013).

The influence of antipsychotics on smoking behavior

Interestingly, administration of second-generation antipsychotics was associated with lower tobacco smoking (Mallet et al. 2018), more specifically, clozapine and aripiprazole (Mallet et al. 2017). These findings were not confirmed in other reports (Mohamed et al. 2015, Wearing et al. 2017). However, in the former study (Mohamed et al, 2015) patients did not receive clozapine or aripiprazole, while the latter trial had much smaller sample size (Wearing et al. 2017). Intriguing data come from preclinical studies, showing that clozapine and haloperidol have both suppressed nicotine seeking in rats (Abele et al. 2018).

CONCLUSION

Smoking is related to schizophrenia in many ways. Ameliorative effects of smoking in patients with schizophrenia, and the lack of insight to harmful smoking effects, might reinforce heavy smoking. In spite of some observed benefits of smoking in patients with schizophrenia, smoking has a deleterious impact on patient's psychiatric and somatic health. The ultimate goal should be complete smoking cessation, given that smoking only one cigarette daily carries a much greater risk of developing coronary heart disease and stroke compared to never smokers (Hackshaw et al. 2018). The delivery of smoking cessation treatments should be a high priority in settings that provide care to patients with schizophrenia. In theory, beneficial effects of brain functioning exerted by nicotine, might be obtained by substances mimicking those effects, which is an important area for future research.

Contribution of individual authors:

Research initiative and study design: *Marina Šagud, Bjanka Vuksan-Ćusa & Nenad Jakšić;*

Literature search: *Marina Šagud, Bjanka Vuksan-Ćusa, Nenad Jakšić, Alma Mihaljević-Peleš, Martina Rojnić Kuzman & Nela Pivac;*

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