

## SMOKING AND SCHIZOPHRENIA

Marina Šagud<sup>1</sup>, Alma Mihaljević-Peješ<sup>1</sup>, Dorotea Mück-Šeler<sup>2</sup>, Nela Pivac<sup>2</sup>,  
Bjanka Vuksan-Ćusa<sup>1</sup>, Tomo Brataljenović<sup>1</sup> & Miro Jakovljević<sup>1</sup>

<sup>1</sup>University Department, Clinical Hospital Zagreb, Kišpatičeva 12, 10000 Zagreb, Croatia

<sup>2</sup>Ruđer Bošković Institute, Zagreb, Croatia

### SUMMARY

*Smoking prevalence for schizophrenic patients is higher than this for general population. More than 60% of schizophrenic patients are current smokers, which contributes to excessive mortality in these patients.*

*The reasons for high frequency of both smoking prevalence and heavy smoking in schizophrenic patients is thought to be at least partially related to enhancement of brain dopaminergic activity, which, in turn, results in behavioral reinforcement due to stimulant effects. Smoking stimulates dopaminergic activity in the brain by inducing its release and inhibiting its degradation. There is also evidence that cigarette smoking can reduce deficits relative to dopamine hypofunction in prefrontal cortex. Recent neuroimaging studies have further contributed the evidence of complex influences of cigarette smoking on brain dopaminergic function. It has been suggested that smoking may be an attempt by schizophrenic patients to alleviate cognitive deficits and to reduce extrapyramidal side-effects induced by antipsychotic medication. Cigarette smoke also increases the activity of CYP 1A2 enzymes, thus decreasing the concentration of many drugs, including clozapine and olanzapine. There is also evidence that smoking is associated with increased clearance of tiotixene, fluphenazine and haloperidol. Given the high frequency of smoking in schizophrenic patients, clinicians need to check smoking status in each patient.*

*Schizophrenic patients who smoke may require higher dosages of antipsychotics than nonsmokers. Conversely, upon smoking cessation, smokers may require a reduction in the dosage of antipsychotics.*

**Key words:** schizophrenia – smoking

\* \* \* \* \*

### INTRODUCTION

Cigarette smoking is a major health problem in general population. Smoking is the most important preventable cause of cardiovascular disease. Smoking acts synergistically with other cardiovascular risk factors to increase the risks of myocardial infarction, sudden cardiac death, stroke, peripheral vascular disease and aortic aneurysm (Bullen 2008). The likelihood current smoking in general population was similar between men and women (18% versus 16%) (Shiels et al. 2008).

### SMOKING IN SCHIZOPHRENIC PATIENTS

Smoking prevalence for schizophrenic patients is higher than in general population. More than

60% of schizophrenic patients are current smokers (De Leon and Diaz 2005, Salokangas et al. 2006), while 35.5% smoke 20 cigarettes or more per day (Salokangas et al. 2006). Heavy smoking is supposed to contribute to excessive mortality in schizophrenic patients.

A meta analysis has determined that the weighted ORs comparing smoking prevalence for schizophrenia patients versus the general population was 5.3, suggesting that the odds for schizophrenic patients to be current smokers are 5.3 times higher than the odds for general population (De Leon & Diaz 2005). Smokers with schizophrenia are also more likely to have an earlier age of onset of schizophrenia, a greater number of hospitalizations, higher severity of schizophrenia, expressed as higher PANSS total score (Schwartz et al. 2005), to be treated with higher doses of antipsychotics (Salokangas et al.

2006), as well as to have poorer premorbid adjustment (Kelly & McCreddie 1999) and lower school performance, compared with non-smoking schizophrenic patients (Riala et al. 2005). During adolescence, even before experiencing prodromal symptoms, subjects that will develop schizophrenia have a higher hazard of starting smoking than normal controls (Diaz et al. 2008).

## BIOLOGICAL EFFECTS OF SMOKING

The reasons for the high frequency of both smoking prevalence and heavy smoking dependence in schizophrenic patients are still unclear. Cigarette smoking results in behavioral reinforcement due to stimulant effects. Smoking stimulates dopaminergic activity in the brain at least by two distinct mechanisms. First, central nicotinic cholinergic receptors are stimulated by nicotine, resulting in the release of dopamine and serotonin (Levin and Rezvani 2007). Second, cigarette smoke decreases MAO activity (Fowler et al. 2003), thus further increasing brain dopamine concentration, which in turn could contribute to its antidepressant effects. Therefore, smoking increases dopamine concentration by inducing its release and inhibiting its degradation. Recent neuroimaging studies have further contributed to the evidence of a complex influence of cigarette smoking on brain dopaminergic function. A PET study has demonstrated a dopamine release in ventral striatum in response to cigarette smoking (Brody et al. 2004), and activation of dopamine D2 neurotransmission in the ventral basal ganglia (Scott et al. 2007). Another study revealed a low availability of dorsal striatal D(2)/D(3) receptors in heavy-smoking nicotine-dependent subjects (Fehr et al. 2008), which was not confirmed in another study (Young et al. 2008). However, the same smoking subjects had decreased dopamine transporter (DAT) availability in the striatum compared to non-smokers (Young et al. 2008). These findings suggest a compensatory down regulation of dopaminergic system, as a response to dopamine increase induced by smoking. Therefore, genes influencing dopaminergic and cholinergic systems are candidates for investigating nicotine addiction, with catechol-O-methyltransferase (COMT) Val158Met being the most commonly investigated polymorphism. Namely, variations in COMT Val158Met polymorphism result in a three to fourfold

difference in COMT enzyme activity. In the large sample from general population (10 059 participants), no associations were found between common single nucleotide polymorphisms (SNPs) of COMT, dopamine beta hydroxylase (DBH) and monoamine oxidase-A (MAO-A) genes (Shiels et al. 2008). In another study, in a community sample in Japanese subjects, male participants with the Val/Val genotype had a significantly higher risk of heavy smoking compared with those with other genotypes of COMT Val158Met polymorphism, while no association were found in females (Tochigi et al. 2007). In the same study, no association between smoking and the MAOA variable number tandem repeat polymorphism, the MAOA 1460 T/C polymorphism was reported (Tochigi et al. 2007). In addition, no significant association was found between MAOB intron 13 G/A polymorphism and smoking status in female (Tochigi et al. 2007) and male (Pivac et al. 2006, Pivac et al. 2007) healthy persons. In patients who attempted to quit smoking, a likelihood of abstinence on active nicotine replacement treatment was greater in the COMT Met/Met genotype group compared to the Met/Val + Val/Val group (Johnson et al. 2007). Meta-analysis found no association of the dopamine type-2 receptor (DRD2) Taq1A polymorphism with tobacco use and cigarette smoking behaviors (Munafò et al. 2009).

## BIOLOGICAL EFFECTS OF SMOKING IN SCHIZOPHRENIA

It has been suggested that smoking is an attempt to self-medicate in schizophrenic patients, in terms of reducing extrapyramidal symptoms associated with antipsychotic treatment, and alleviating cognitive deficits associated with schizophrenia. Cigarette smoking induces the metabolism of many medications, including antipsychotics, because of an increase in CYP 1A2 and CYP 3A4 enzymes. Cigarette smoking also significantly enhances CYP2E1 activity, and both CYP 1A2 and CYP 2E1 are involved in the activation of some procarcinogens (Zevin & Benowitz 1999). Since majority of schizophrenic patients smoke cigarettes, nicotinic interactions with antipsychotic drug pharmacokinetics are common. Concentration of olanzapine and clozapine is decreased in smokers compared to non-smokers (Van der Weide et al. 2003; Nozawa

et al. 2008). It is assumed that daily consumption of 5 cigarettes per day is sufficient for induction of olanzapine metabolism (Wu et al. 2008), and 7-12 cigarettes daily is sufficient for the maximum induction of clozapine and olanzapine metabolism (Haselmo et al. 2006). This is particularly important for drugs with narrow therapeutic window, such as clozapine. Clozapine intoxication was reported in patients stabilized on clozapine, who abruptly stopped smoking (Derenne & Baldessarini 2005). There is also evidence that smoking is associated with increased clearance of tiotixene, fluphenazine and haloperidol (Desai et al. 2001). On the other hand, pharmacokinetics of quetiapine do not appear to be altered by cigarette smoking (De Vane & Nemeroff 2001).

Hence, the vulnerability to schizophrenia might be associated with vulnerability to smoking initiation (Diaz et al. 2008). The key question is whether the neurobiology of schizophrenia makes the patient more vulnerable to nicotine addiction, and/or whether nicotine improves the cognitive or sensory-gating deficits (De Luca et al. 2004). The further question is if there are biological differences between schizophrenic patients who smoke and who do not smoke.

Cigarette smoking appears to induce both clinical and biological effects in schizophrenic patients. Schizophrenic patients who smoked had more gray matter in the superior temporal gyrus and lateral prefrontal cortex, compared to non-smoking patients (Tregellas et al. 2007). The authors speculated that smoking either prevents a loss of grey matter, increases grey matter, or, in turn, patients with greater grey matter volume are more inclined to smoke (Tregellas et al. 2007). Furthermore, cigarette smoking was associated with improved performance on Iowa gambling task in female, but not in male schizophrenic patients (Yip et al. 2009). Schizophrenic patients treated with olanzapine and risperidone had significantly higher percentage of striatal D2 receptor occupancy (mean 74.3%) compared to non-smoking patients (mean 49.8%) (De Haan et al. 2006), suggesting that low availability of D2 receptors may increase smoking behavior. Schizophrenic smokers were reported to have decreased platelet vesicular monoamine transporter 2 (VMAT2) density compared to schizophrenic non-smokers (Schwartz et al. 2005). While schizophrenic patients in general had increased platelet VMAT2 density (Zucker et al. 2002), it is hypothesized that

smoking induces VMAT2 downregulation (Schwartz et al. 2005), which compensates for increase in dopamine concentration induced by smoking.

There is also some evidence supporting the hypothesis that there might be a significant genetic difference between schizophrenic patients who smoke and those who do not smoke. For example, schizophrenic patients who smoked had the increased proportion of 113-bp allele of the D15S1360 marker in the CHRNA7 gene (De Luca et al. 2004), which encodes for the  $\alpha$ -7-nicotinic receptor. This receptor is thought to mediate nicotinic effects on cognitive processes including attention and memory.

The social and cultural contributions to smoking initiation and smoking persistence could not be neglected.

## CONCLUSION

A large number of worldwide studies describing current smoking in schizophrenia consistently suggest that schizophrenic patients from all countries share a common biological factor, that makes them more prone to smoke (De Leon & Diaz 2005). There is also evidence that cigarette smoking can reduce deficits relative to dopamine hypofunction in prefrontal cortex. All these data suggest that clinicians should consider smoking as an important factor in the disposition of these drugs. Namely, schizophrenic patients who smoke may require higher dosages of antipsychotics than nonsmokers. Conversely, upon smoking cessation, smokers may require a reduction in the dosage of antipsychotics.

## REFERENCES

1. Brody AL, Olmstead RE, London ED, Farahi J, Meyer JH, Grossman P, Lee GS, Huang J, Hahn EL, Mandelkern MA. *Am J Psychiatry* 2004; 161: 1211-1218.
2. Bullen C. *Impact of Tobacco Smoking and Smoking Cessation on Cardiovascular Risk and Disease. Expert Rev Cardiovasc Ther.* 2008; 6:883-895.
3. De Haan L, Booij J, Lavalaye J, van Amelsvoort T, Linszen D. *Occupancy of dopamine D2 receptors by antipsychotic drugs is related to nicotine addiction in young patients with schizophrenia. Psychopharmacology (Berl).* 2006; 183:500-505.
4. De Leon J, Diaz FJ. *A meta-analysis of worldwide studies demonstrates an association between*

- schizophrenia and tobacco smoking behaviors. *Schizophrenia Res* 2005; 76: 135-157.
5. De Luca V, Wong AHC, Muller DJ, Wong GWH, Tyndale RF, Kennedy JL. Evidence of association between smoking and  $\alpha 7$  nicotinic receptor subunit gene in schizophrenic patients. *Neuropsychopharmacol* 2004; 29:1522-1526.
  6. Derenne JL, Baldessarini RJ. Clozapine toxicity associated with smoking cessation: case report. *Am J Ther*. 2005; 12:469-471.
  7. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs*. 2001; 15:469-494.
  8. DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet*. 2001; 40:509-522.
  9. Diaz FJ, Velásquez DM, Susce MT, De Leon J. The association between schizophrenia and smoking: unexplained by either the illness or the prodromal period. *Schizophrenia Res* 2008; 104:214-219.
  10. Fowler JS, Logan J, Wang GJ, Volkow ND. Monoamine oxidase and cigarette smoking. *Neurotoxicology* 2003; 24:75-82.
  11. Fehr C, Yakushev I, Hohmann N, Buchholz HG, Landvogt C, Deckers H, Eberhardt A, Kläger M, Smolka MN, Scheurich A, Dielentheis T, Schmidt LG, Rösch F, Bartenstein P, Gründer G, Schreckenberger M. Association of low striatal dopamine d2 receptor availability with nicotine dependence similar to that seen with other drugs of abuse. *Am J Psychiatry*. 2008; 165:507-514.
  12. Haslemo T, Eikeseth PH, Tanum L, Molden E, Refsum H. The effect of variable cigarette consumption on the interaction with clozapine and olanzapine. *Eur J Clin Pharmacol*. 2006; 62:1049-1053.
  13. Johnstone EC, Elliot KM, David SP, Murphy MF, Walton RT, Munafo MR. Association of COMT Val108/158Met genotype with smoking cessation in a nicotine replacement therapy randomized trial. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:1065-1069.
  14. Kelly C, McCreadie RG. Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *Am J Psychiatry* 1999; 156: 1751-1757.
  15. Levin ED, Rezvani AH. Nicotinic interactions with antipsychotic drugs, models of schizophrenia and impacts on cognitive function. *Biochem Pharmacol*. 2007; 74:1182-1191.
  16. Munafo MR, Timpson NJ, David SP, Ebrahim S, Lawlor DA. Association of the DRD2 gene Taq1A polymorphism and smoking behavior: a meta-analysis and new data. *Nicotine Tob Res*. 2009; 11:64-76.
  17. Nozawa M, Ohnuma T, Matsubara Y, Sakai Y, Hatano T, Hanzawa R, Shibata N, Arai H. The relationship between the response of clinical symptoms and plasma olanzapine concentration, based on pharmacogenetics. *Ther Drug Monit* 2008; 30:35-40.
  18. Pivac N, Knezevic J, Mustapic M, Dezeljin M, Muck-Seler D, Kozaric-Kovacic D, Balija M, Matijevic T, Pavelic J. The lack of association between monoamine oxidase (MAO) intron 13 polymorphism and platelet MAO-B activity among men. *Life Sci*; 79: 45-49.
  19. Pivac N, Knezevic J, Kozaric-Kovacic D, Dezeljin M, Mustapic M, Rak D, Matijevic T, Pavelic J, Muck-Seler D. Monoamine oxidase (MAO) intron 13 polymorphism and platelet MAO-B activity in combat-related posttraumatic stress disorder. *J Affect Disord*; 103: 131-138.
  20. Riala K, Hakko H, Isohanni M, Jokelainen J, Weiser M, Räsänen P. Poor premorbid school performance is associated with later cigarette smoking in schizophrenic patients. *Psychiatry Res* 2005; 137:137-141.
  21. Salokangas RKR, Honkonen T, Stengard E, Koivisto AM, Hietala J. Cigarette smoking in long-term schizophrenia. *Eur Psychiatry* 2006; 21: 219-223.
  22. Schwartz K, Iancu I, Stryjer R, Chelben J, Kotler M, Weizman A, Rehavi M. Reduced platelet vesicular monoamine transporter density in smoking schizophrenia patients. *Eur Neuropsychopharmacol* 2005; 15: 557-561.
  23. Scott DJ, Domino EF, Heitzeg MM, Koeppe RA, Ni L, Guthrie S, Zubieta JK. Smoking modulation of mu-opioid and dopamine D2 receptor-mediated neurotransmission in humans. *Neuropsychopharmacology*. 2007; 32:450-457.
  24. Shiels MS, Huang HY, Hoffman SC, Shugart YY, Hoffman Bolton J, Platz EA, Helzlsouer KJ, Alberg AJ. A community-based study of cigarette smoking behavior in relation to variation in three genes involved in dopamine metabolism: Catechol-O-methyltransferase (COMT), dopamine beta hydroxylase (DBH) and monoamine oxidase-A (MAO-A). *Preventive Med* 2008; 47:116-122.
  25. Tochigi M, Suzuki K, Kato C, Otowa T, Hibino H, Umekage T, Kato N, Sasaki T. Association study of monoamine oxidase and catechol-O-methyltransferase genes with smoking behavior. *Pharmacogenet Genomics*. 2007 Oct;17(10):867-872.
  26. Tregellas JR, Shatti S, Tanabe JL, Martin LF, Gibson L, Wylie K, Rojas DC. Grey matter volume differences and the effects of smoking on grey matter in schizophrenia. *Schizophrenia Res* 2007; 97: 242-249.
  27. Van der Weide J, Steijns LSW, van Weelden MJM. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. *Pharmacogenetics* 2003; 13:169-172.
  28. Wu TH, Chiu CC, Shen WW, Lin FW, Wang LH, Chen HY, Lu ML. Pharmacokinetics of olanzapine in

- Chinese male schizophrenic patients with various smoking behaviors. Prog Neuropsychopharmacol Biol Psychiatry.* 2008; 12;32(8):1889-1893.
29. Yip SW, Sacco KA, George TP, Potenza MN. Risk/reward decision-making in schizophrenia: a preliminary examination of the influence of tobacco smoking and relationship to Wisconsin card sorting task performance. *Schizophrenia Res* 2009; 110:156-164.
30. Yang YK, Yao WJ, Yeh TL, Lee IH, Chen PS, Lu RB, Chiu NT. Decreased dopamine transporter availability in male smokers -- a dual isotope SPECT study. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008; 32:274-279.
31. Zevin S, Benowitz NL. Drug interactions with tobacco smoking. An update. *Clin Pharmacokinet.* 1999; 36:425-438.

*Correspondence:*

Marina Šagud

University Psychiatric Clinic Rebro, Clinical Hospital Centre Zagreb

Kišpatičeva 12, 10000 Zagreb, Croatia

E-mail: weekend@paris.hr