Author’s response to reviews

Title: Nicotine dependence in Croatian male inpatients with schizophrenia

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Version: 1 Date: 17 Oct 2017

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Date: 17 Oct 2017

To: "BMC Psychiatry - Editorial Office" Carlo.RyeChua@springer.com
From: "Marina Sagud" marinasagud@mail.com
Subject: Submission to BMC Psychiatry - BPSY-D-17-00582

Dear Editor,

Thank you very much for sending us the review of the manuscript "Nicotine dependence in Croatian male inpatients with schizophrenia" (BPSY-D-17-00582).
We have now carefully addressed all issues raised by reviewers. First of all, we wish to thank the reviewers for their comments, which have expanded our knowledge and very much improved the quality of our article.

We provide below a point-by-point response letter with a detailed response to each reviewer point raised, and where these changes/additions can be viewed. All changes in the manuscript are indicated by track changes.

We have made minor language corrections throughout the text and we hope this will improve the overall quality of the paper. However, if you believe a complete language revision needs to be performed, we will organize a more thorough and professional language editing.

In addition, one of the authors (Tea Prgic) has recently changed her e-mail address from: tea.merkas@gmail.com, to: tea.prgic1985@mal.com, which was also replaced in the text.

Thank you very much once again for considering our article for the publication in your eminent journal,

Best wishes,
Marina Šagud

Responses to reviewer comments:

Chinyere Aguocha (Reviewer 1): Assessment

General impression: The concept of the study is good. A lot of work needs to be done to improve the general quality of this study. The language, method and result need to be extensively reviewed.

Introduction -

* describe what you mean by smoking behavior. Introduction section, line 47, page 3: Instead of smoking behavior, the following was mentioned: the level of nicotine dependence Introduction section, line 48, page 3: after „differs in smokers with schizophrenia”, compared to healthy individuals was added. What are the different parameters, which studies have done on it, which aspects did they measure, what were there fings, what were the differences between the patients with schizophrenia and general population in terms of smoking behavior. Introduction section,
line 49-50, page 3. Instead of: It was reported that patients smoked more intensely [8, 9], and had higher peak and faster rise of nicotine levels [9], those studies were described in more detail. It was added: For example, among smokers who smoked at least 20 cigarettes per day, and had similar levels of nicotine dependence, those with schizophrenia or schizoaffective disorder had higher number of puffs smoked per cigarette, larger cigarette total puff volume, shorter inter-puff interval duration as well as higher carbon monoxide boosts, compared to participants who had no major mental illness (8). Similarly, smokers with schizophrenia had higher four-minute nicotine boost and a higher dose of nicotine per cigarette than persons without mental illness in the previous year (9). Moreover, male patients with schizophrenia had higher proportion of smoking more than 10 cigarettes daily, and lower proportion of individuals who stopped smoking (10) compared to males with negative history for psychiatric disorders. New reference (Jiang J, See YM, Subramaniam M, Lee J. Investigation of cigarette smoking among male schizophrenia patients. PLoS One. 2013;8(8):e71343) (10) was added in order to extend findings on smoking behavior between patients and general population. Consequently, all future references have numbers in parenthesis increased by 1.

* Line 47-53 Line of thinking is difficult to grasp. I suggest that the researchers do more literature search on this. The finds are mixed and they would do well to clearly point out different schools of thought on the effect of smoking on the outcome of schizophrenia, effect on positive and negative symptoms, total PANSS Score etc Introduction section, Lines 49-53, page 3: Some authors have reported worse symptoms in smokers in first-episode patients [10] and patients with schizophrenia [11, 12] while there are negative findings as well [5]. There is also evidence of higher doses of antipsychotics in smokers [12]; was replaced by much wider section which now includes more investigation on the relationship between psychopathology in schizophrenia and smoking, and includes 7 new literature citations as provided below:


15. Iasevoli F, Balletta R, Gilardi V, Giordano S, de Bartolomeis A. Tobacco smoking in treatment-resistant schizophrenia patients is associated with impaired cognitive functioning, more severe negative symptoms, and poorer social adjustment. Neuropsychiatr Dis Treat. 2013;9:1113-20;


Previous studies have reported mixed results on the association between smoking and the intensity of symptoms. While majority of studies suggested that smokers with schizophrenia had more severe symptoms [10-15], one study reported similar overall symptomatology [15], while a series of studies reported milder symptoms in smokers than in nonsmokers [16-18]. In patients with first-episode schizophrenia, smokers had higher positive and negative syndrome scale (PANSS) total score and PANSS positive subscale scores and similar PANSS negative and PANSS general scores, in comparison to patients who were nonsmokers [10]. Among patients with several psychiatric disorders, including schizophrenia, smokers were more likely than nonsmokers to report hallucination, delusions and subjective thought disorder and had worse negative symptoms [11]. In patients with schizophrenia, smokers with severe nicotine dependence had greater PANSS positive, while smokers with mild nicotine dependence had higher PANSS negative scores, respectively, compared to patients who did not smoke [12]. In another study on patients with schizophrenia, smokers had higher PANSS positive score than nonsmokers, while both groups had similar PANSS total, negative and general scores [13]. Moreover, PANSS total scores and the PANSS general psychopathology scores were higher in non-smokers compared to smokers while PANSS positive and negative scores were similar between smokers and non-smokers with schizophrenia [14]. In patients with treatment-resistant schizophrenia (TRS), smokers had higher PANSS total score and PANSS negative score than nonsmokers, while there were no differences in two groups in PANSS positive and general
scores [15]. Smoking status was not associated with PANSS total score in a sample consisted of patients with schizophrenia and bipolar disorder, although no data on PANSS subscales were presented [5]. On the opposite, in male inpatients with schizophrenia, smokers had lower PANSS positive scores, with no differences in the PANSS total score or the negative and general psychopathology subscales compared with non-smokers [16]. Notably, in this study, smokers who smoked more cigarettes had lower intensity of negative symptoms [16]. In the two studies on male patients with schizophrenia, current smokers had lower PANSS negative scores than never smokers [17] and never smokers and former smokers [18]. The discrepancies across those studies might arise from many methodological issues, such as different measures of psychopathology, sample sizes, age and sex differences, study settings (outpatients versus inpatients) and the presence of comorbid substance abuse. For example, psychopathology was estimated by The Diagnostic Interview for Psychosis [11] and PANSS total score and its subscales [10] as well as only PANSS total score [5]. Of note, smokers with schizophrenia have also received higher daily doses of antipsychotics [12, 13, 14] than nonsmokers. While larger doses are logically related to higher severity of symptoms, they could also result from smoking-induced hepatic metabolism of some antipsychotics, such as clozapine and olanzapine [19]. Interestingly, in the sample of patients with TRS, smokers and nonsmokers did not differ in terms of mean daily antipsychotic dose [15]. Majority of those studies analyzed the association of smoking versus non-smoking status with psychopathology [5, 10; 11; 14, 15; 13], while few have investigated the influence of severity of nicotine dependence on psychopathology [16].

* Line 56 There are theories on this. you need to mention them--two new references are included:


The following theory was introduced: So far, dopamine appears to play a major role in this relationship. It is well-known that schizophrenia is linked to elevated dopamine levels in dorsal striatum and reduced cortical dopamine release [reviewed in 22]. Nicotine increases dopamine levels in striatum by stimulating its release via nicotinic receptors, and decreasing its degradation by inhibiting monoamine oxidase type A and B. [reviewed in 20]. Clinical consequences include behavioral stimulation, antidepressant effects and decrease of drug-induced extrapyramidal adverse events [reviewed in 20]. More recently, it has been reported that smoking also induced cortical dopamine release, at least in subjects who smoked ≥ 10 cigarettes daily and had no current psychiatric disorder [23].
* Line 58: Who are the healthy individuals? The term „healthy individuals“ are changed to „control sample“, as described in original article. The US sample included volunteers who were not being treated for a psychiatric disorder. The Spanish control sample was recruited after a systematic and representative sampling from the population over 16 years old in the cities and towns of Spain. While, unlike in US, there was no screening for psychiatric disorders in Spain, the term „control samples“ better fits in the text. The same term „healthy individuals“ from the same reference, was also changed to „control sample“ in Introduction section, line 65, page 3.

* Line 54-73: use different paragraphs for relationship between nicotine dependence and schizophrenia, prevalence of nicotine dependence in European countries (compare general populace and patients with schizophrenia) and associations between smoking and gender in the different populations—changed in the text

* Line 81: compare the pattern ……………. changed in the text

* Line 83: determine the pattern…………….. changed in the text

* Lines 102-108 should be in the results section—removed in the results section

* Line 121: only patients have been assessed by PANSS. What does this mean? Healthy group was not assessed by PANSS because they had no symptoms of psychosis. To make this clearer, the sentence: only patients have been assessed by PANSS, is removed. Instead, in line 119, Methods section, page 6- „in patients“ was added: Symptom severity in patients was evaluated…

Results

* Put more effort in the result section. More analysis needed. – Thank you for this suggestion. Accordingly, we added an entire table (see Table 3) and corresponding text in the Results section on the correlations between 6 FTND items and scores on the PANSS scale (total score and subscale scores). Corresponding text was: "However, we found negative correlations, albeit weak, of FTND item 2 with PANSS total score (r= -.18, p=0.016), PANSS positive symptoms subscale (r= -.17, p=0.021) and PANSS general psychopathology subscale (r= -.16, p=0.036) (Table 3). There is a tendency for patients with more severe pathology assessed by the PANSS scale to find it easier to refrain from smoking in places where it is forbidden.” (p. 11, line 236-240). In addition, a sentence about non-significant associations between some sociodemographic parameters and FTND scores was also introduced. ("Finally, there was no significant association between age, educational and marital status…”; p. 11, line 233-234).

* Line 155: use exact value of p– We have corrected this in the text.
* Line 157: the sentence in this line is not easily understood—Thank you for this observation. It was a mistake on our part, the sentence has been reworded into: "There was no difference in the frequencies of moderate dependence category among the groups.”

Discussion

* Are main findings 1 and 2 not alluding to the same thing? They are not the same. Main finding 1 refers to the difference in FTND total scores between smokers with schizophrenia and healthy smokers, while main finding 2 addresses differences in distribution of categories of nicotine dependences (low, moderate and severe) between schizophrenia group and healthy group

* Line 237: FTND correct-changed in the text

* Line 246: explain how you measured or determined smoking severity. Which analysis in your result section was used to determine this association? This should be in the method section—It is provided in the method section, lines 123-125, page 6: For this study, participants were divided in three groups according to the levels of tobacco dependence: (1) smokers with low dependence (FTND 0-4) (2) smokers with moderate dependence (FTND=5) and (3) smokers with severe dependence (FTND≥6). In results, it is provided in lines 155-159, pages 7-8, chi-square test was performed

* Generally difficult to follow the train of thought

Conclusion

* Lines 278-279: review language. You compared smokers with schizophrenia and healthy control. Conclusion section, line 278, page 13—“…in patients with schizophrenia—compared to healthy persons…was added

Tables

* The tables are too few—Additional table was added (Table 3)

* I suggest that the first table be on socio demographic characteristics of smokers with schizophrenia and healthy controls—We agree this would be a good idea but, unfortunately, there is a certain lack of sociodemographic data regarding the healthy control group. Therefore, we decided not to add this table and emphasized this fact as one of the limitations of our study with the following: Another limitation is that sociodemographic data for healthy control group were not collected. Limitation section, line 359, page 16.
* A table on associations between PANSS scores and FTND scores is needed—Thank you for giving us the opportunity to broaden our results. Accordingly, Table 3 was introduced, describing these correlations.

* The different dimensions of FTND are they associated with socio demographic characteristics of the smokers with schizophrenia—There was no statistically significant association between FTND scores and sociodemographic variables. This was stated in the Results section (lines 230 – 231).

* In table 1, was it chi square test or t-test that was done? –We clarified this in the table; t-test is stated at the top of the table, whereas FTND categories were marked with a "*" indicating that the chi square test was used (stated in the table legend).

Jasmina Mallet (Reviewer 2): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Thank you for the opportunity to review this interesting manuscript. These results are useful and expand our knowledge on this topic. The paper has a number of strengths, including a large sample and an interesting discussion. The study is clearly presented. The main outcomes are FTND scores in healthy males and SZ males, and its correlations with psychotic symptomatology in SZ males.

There are some limitations as well. These include the FTND cut-off for severe dependence (why 6 and not 7, as in most studies and national recommendations…), and the rationale for studying only male gender is the final purpose is to describe characteristics in SZ smokers. Other comments:
1- In the abstract and all along the article, it is written "Positive and Negative Symptom Scale" while it is Syndrome Scale (Kay et al.).-changed in the text, Methods section, line 119, page 5- "Positive and Negative Symptom Scale" was deleted, because it is mentioned already in the introduction section.

2- Background, l55: do the authors mean " shared genetic vulnerability"?–changed from „viability“ to vulnerability“ in the text

3- Methods: Were all the assessment undertaken by the treating therapist? Psychiatrists? If so, the authors could comment on the potential bias. Assessments were done by 5 psychiatrists (Marina Sagud, Suzana Vlatkovic, Alma Mihaljevic Peles, Bjanka Vuksan Cusa, Maja Zivkovic) who were previously trained and very experienced in PANSS rating-now added in 121, methods section, page 6. In majority of cases, aforementioned psychiatrists have rated (and included) their own patients. Line 275, Limitation section, page 13, the following was added: given that PANSS rating was performed by 5 psychiatrists, who were in most cases also treating psychiatrists for those patients, potential bias cannot be excluded.

4- Methods: Why only male patients, if the authors want to better characterize the smoking profile of SZ patients in Croatia? The article seems to aim at a more epidemiological aspect than biological, and the rationale for such a choice should be clearer for the reader (why "confounding variable"? for instance)-Line 91, Methods section, page 5-the formulation: „Given that might be a confounding variable…” is deleted, and the following statement was inserted instead: Given the observed differences in smoking patterns observed in both healthy subjects [24,29] and individuals with schizophrenia [25,30] only males were enrolled.

Examples of studies reporting gender differences in smoking patterns are provided in the introduction section, lines 66-72, page 4, in the first (before revision) version of the article. This is also a limitation, and it was added in the limitation section (please, see comment no 14).

5- Methods: all included patients are in patients, did they have access to nicotine substitute, e-cigarettes? Are they allowed to smoke whenever they want? Nicotine substitute is (unfortunately) not provided to patients in routine care, and no patient in the present study has used e-cigarettes. According to the Croatian law, all psychiatric units are required to have smoking area, and the patients are allowed to use it round the clock.

6- Methods: assessment, p6: in many researches and national recommendations, severe dependence is when FTND> or = 7: did the authors compare their results with this cut-off? Why did the authors choose 6 and not 7? This choice is important for the findings of the study and should be clearly explained. The cut-off value for high nicotine dependence in FTND questionnaire was chosen to ≥ 6, primarily in accordance with scoring guidelines from the FTND which defines severe nicotine dependence as ≥6 (Heatherton et al, 1991). Although majority of studies used FTND cut-off ≥ 7 to describe severe nicotine dependence, several studies have also
determined FTND cut-off ≥ 6 for high nicotine dependence, such as Wang et al, 2014; Yu et al, 2015; Krishnadas et al, 2012; Zhang et al, 2012; and de Leon et al, 2002:


de Leon J, Becoña E, Gurpegui M, Gonzalez-Pinto A, Diaz FJ. The association between high nicotine dependence and severe mental illness may be consistent across countries. J Clin Psychiatry. 2002;63(9):812-6


7- Statistical analysis: why only univariate analysis were performed? – Thank you for this observation. We opted for univariate analyses after seeing that all the sociodemographic variables were not significantly associated with FTND scores and categories. Therefore, we found no need for introducing them in the statistical analyses, e.g. multivariate regression analysis. However, based on the first reviewer's suggestion, additional analyses were performed (please see Table 3 and the corresponding text in the Results section).

8- Results: ddl should be mentioned for statistical results ( t, Chi square..) – Dimensions of freedom (df) were added in Table 1.

9- Results: the sentence L157-158 "there was …" is not clear for the reader – Thank you for this observation. It was a mistake on our part, the sentence has been reworded into: "There was no difference in the frequencies of moderate dependence category among the groups.”

10- Discussion: p8, L176: the formulation "10" is not really clear for the reader (idem L180 etc.). The formulation: between our findings and 10; is now deleted
Discussion: do the authors have an explanation for the increasing of smoking with age in SZ patients? We did literature search to explain this relationship and the following text was added (Discussion section, lines 248-256, pages 11 and 12, in the revised version of the manuscript): Smokers with schizophrenia were older than nonsmokers [17]. In patients with schizophrenia, longer disease duration was associated with parkinsonian axial signs [40] and more frequent treatment with antidepressants [41]. Given the self-medication hypothesis of smoking in schizophrenia [20], it might be speculated that older patients smoked more often in order to alleviate extrapyramidal and depressive symptoms. However, other studies on individuals with schizophrenia have reported that smokers were actually younger than nonsmokers [14, 16]. Because schizophrenia is highly heterogenous disorder, longitudinal studies are needed to investigate whether and how the pattern of smoking changes throughout its course.

In this text, two new references were added:

40. Morgante F, Barbui C, Tinazzi M; Italian DIP study group. Parkinsonian axial signs in schizophrenia. Parkinsonism Relat Disord. 2017;36:89-92


Discussion: p11, L231: as all patients are inpatients, do they really are alloed to smoke during the night at the hospital? Hospitals have smoking area in psychiatric departments, which is several steps from patient rooms, so they are free to smoke even during the night

Discussion: overall, this section is realistic and there is no speculation about findings. However, authors could give a more comprehensive and neurobiological review to try to explain their findings. What could be the link between schizophrenia physiopathology and cigarette smoking? It is added in revised article in the introduction section, lines 105-114, page 5. this is the following text: So far, dopamine appears to play a major role in this relationship. It is well-known that schizophrenia is linked to elevated dopamine levels in dorsal striatum and reduced cortical dopamine release [reviewed in 21]. Nicotine increases dopamine levels in striatum by stimulating its release via nicotinic receptors, and decreasing its degradation by inhibiting monoamine oxidase type A and B. [reviewed in 20]. Clinical consequences include behavioral stimulation, antidepressant effects and decrease of drug-induced extrapyramidal adverse events [reviewed in 20]. More recently, it has been reported that smoking also induced cortical dopamine release, at least in subjects who smoked ≥ 10 cigarettes daily and had no current psychiatric disorder [22].
14- Limits: This sample is only a men sample, with inpatients SZ, with no other substance use disorder. Thus it is not representative of SZ patient’s population, this should be mentioned in the limits of the article. The following was added in lines 347-348, limitations section, page 15, revised text-. In addition, given than only men without recent substance abuse were included, those findings might not be generalizable to women and / or patients with current substance abuse.

15- Tables : Tables are clear.