Author’s response to reviews

Title: Nicotine dependence in Croatian male inpatients with schizophrenia

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Author’s response to reviews:

Date: December 28th, 2018.

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 the issues raised by reviewers. First of all, we wish to thank the reviewers for their informative comments, which improved the quality of our article.
Please see below responses to two comments of the reviewer, and where these changes/additions can be viewed in the text. Those changes in the manuscript are indicated by track changes.

Page 4, lines 72-73; “while both groups had similar PANSS total, negative and general scores” was deleted, and “tobacco smoking was associated with more positive symptomatology, and less negative symptoms,” were added instead.

Page 5, line 92-reference no 13 (Mallet et al, 2017), was deleted, and only references no 12 and 14 are left.

Major comments

1) I kindly ask authors to overhaul the English of the manuscript. Corrections in English are marked in track changes, in purple.

2) Table 1. and lines 197-199 ("Independent samples t-test and chi-square test were used to examine the potential differences in age and tobacco dependence parameters between schizophrenia patients and healthy control subjects."); Since the number of answer possibilities is very limited for the majority of FTND items (4 out of 6 items are in fact "yes-no" questions, so the answers for these 4 items are dummy-variables) t-test is absolutely inappropriate for their comparison. Furthermore, I would be much surprised if the distributions of the answers for the remaining 2 FTND items (both of them have 4 answer possibilities) would be normal (it is well-known that t-test requires normal distribution of the data). To sum up, I think t-test is inappropriate for the comparison of scores of individual FTND items, since these are categorical and not continuous variables. We thank you for this relevant remark; the statistical analyses were remade, and based on the types of variables and non-normal distributions (Kolmogorov Smirnoff test), we decided to use Mann Whitney U test for FTND total score, items 1 and 4, and the Chi square test for items 2, 3, 5, and 6. The necessary modifications were made in the Statistical analysis section, Results and Table 1.

3) The lost row of Table 1. ("FTND categories") contains the results of a chi-square statistics which in fact was calculated using the very data presented in Table 2. I highly suggest to delete the row in question from Table 1 and present the results of the chi-square calculation (i.e. exact values for chi-square, df and p) under Table 2 as a footnote. (Accordingly, in line 226, please change "Table 1" to "Table 2" and also delete from the footnotes of Table 1. that "FTND categories = low tobacco dependence, moderate tobacco dependence and severe tobacco dependence; * Chi square test"). Thank you for
this valuable observation. Accordingly, we have carried out all the corrections you suggested.

4) line 231: "Finally, there was no significant correlation between age and smoking status in both groups". I would be wondering what statistics was used in this calculation, since the three methods mentioned in the Methods section (i.e., chi-square; t-test; Pearson correlation) are inappropriate here (I suppose ANOVA would be a good choice for this end). We have changed ‘‘smoking status’’ into ‘‘FTND total score’’ to make this sentence more clear (it was an error on our part), and Pearson correlation was used to examine this association (as well as the correlation between other parameters).

Minor comments

1) line 28-29: ".... Test for Nicotine Dependence (FTND), and patients were also evaluated by the Positive and Negative Syndrome Scale (PANSS)." please correct as follows ".... Test for Nicotine Dependence (FTND). Patients were also evaluated by the Positive and Negative Syndrome Scale (PANSS)."-corrected in the text

2) line 27-28: "This cross-sectional study included 182 recently hospitalized male inpatients and 280 healthy males,....." I suggest to complete this sentence with the information that patients (and also healthy controls?? -- see also remark#8) were daily smokers. The sentence was completed with the following: This cross-sectional study included 182 recently hospitalized male inpatients and 280 healthy males who were daily smokers“. The next sentence: „who fulfilled the Fagerstrom Test for Nicotine Dependence (FTND)“, was replaced with: All participants have fulfilled the Fagerstrom Test for Nicotine Dependence (FTND)

3) line 30: please correct "FNTD" to "FTND"-corrected

4) I am unable to find the mention of Table 3 in the text. Line 219, page 10-the following was added: However, negative correlations between item 2 on FTND scale and PANSS total score, as well as PANSS positive and general subscores, were observed, as presented in table 3.
5) line 59: "...stopped smoking (10) compared..". Please specify what is "(10)" here. Is it a reference? Then it should be in square brackets. Thank you for this comment. This is a reference no 10, and by mistake it was not put in square brackets. Now, it has changed in the text.

6) line 116: "In addition, there are differences across countries in both smoking prevalence and smoking..." I suggest to delete "In addition". Thank you for this suggestion, „In addition“ was deleted.

7 ) line 155-156: "Exclusion criteria were: current nonsmoking status (including ex-smokers), mental retardation and other conditions.... " It is tautologic to describe that non-smokers were excluded, since it has been already clarified previously in the discussion of inclusion criteria that only daily smokers were included. Thank you for this comment, „current nonsmoking status (including ex-smokers)“ was deleted.

8) lines 163-164: "Healthy group consisted of male participants who and had no current or previous psychiatric disorders, and no known family history of psychiatric disorders." There are no any information about the in- and exclusion criteria applied to the control subjects. Were they also "daily smokers"? Comorbid substance abuse (other than nicotine and caffeine) as well as somatic (inclusive neurological) disorders were also exclusion criteria for controls? Please clarify these issues in the text. (Remark: the "and" between "who" / "had" seems to be superfluous). Thank you for this observation. Instead of: "Healthy group consisted of male participants who and had no current or previous psychiatric disorders, and no known family history of psychiatric disorders." The following was added: Inclusion criteria for healthy group were: males who were daily smokers, and exclusion criteria were: current or previous psychiatric disorders, comorbid substance use (other than nicotine and caffeine), as well as somatic (inclusive neurological) disorders.

9) lines 203-206: I suppose "participants" are in fact "patients" here. If yes, please change "participants" to "patients". You wrote that the degree of education for different categories (elementary school etc) are 16, 147 and 18. Unfortunately, the sum of these numbers is 181 and not 182... Please find the missing patient.... Anyway, the majority of this paragraph (i.e. the first paragraph of the Results section) may be delete, since authors did not gather/present data on either educational attainment or marital status of control subjects so it is impossible to compare the patient and control groups in these regards. Thank you for this suggestion. The following text was deleted: „Regarding educational status, 16 (9%) participants had completed elementary
school, 147 (81%) had completed high school, and 18 (10%) had a college degree, while 38 participants (21%) were employed, 55 (30%) unemployed and 89 (49%) were retired. Finally, the sample comprised of 55 (30%) married participants, 120 (66%) single participants, and 7 (4%) divorced participants”.

10) line 233: please put a dot to the end of the sentence; corrected

line 236: please put a comma to the end of the sentence containing the first main finding; corrected

line 241: please put a dot to the end of the sentence containing the third main finding.- corrected

11) line 259: "The discrepancy with 29," please change to "The discrepancy with reference [29],". However I suppose, since a lot of new references were put into the second version of the MS, 29 (Kishi et al.) is in fact 38.....Thank you for this observation, "The discrepancy with 29," was replaced with: „The discrepancy with reference [38]“, 

12) I suggest to replace "smoking dependence" and "tobacco dependence" with "nicotine dependence" in lines 24, 142, 220 and 363.-replaced in the text

13) line 373: please replace "Symptom" to "Syndrome"-replaced in the text

14) lines 213-215: I reckon that this paragraph is superfluous while the topic discussed in it is out of the scope of the study. The paragraph: „In the patient group, we found a significant negative correlation (r= -.21, p=0.01), albeit relatively weak, between age and the total PANSS score. There was a tendency for older patients to exhibit less severe symptoms of schizophrenia.” was deleted.

15) lines 216-218: "The differences between the groups (patients and healthy controls) in the total score on the FTND scale, individual items as well as the three tobacco dependence categories, are shown in Table 1." Since the "three tobacco dependence categories” are presented
in fact in Table 2. (and not in Table 1.), I suggest to write "Table 1. and 2.". In „...are shown in Table 2“., correction was made to: Table 1. and 2.

16) line 225: "No differences were observed in items 3 and 5." please change to "No significant differences were observed in items 3 and 5." Thank you for the suggestion, the word „significant“ was inserted

17) lines 232-233: "there was no correlation between the PANSS total score and positive and negative scores with FTND total score in the patient group (p>0.05)" Perhaps this result should be reported in table 3. in a new row. Thank you, these values were added in Table 3 in the last row.

18) line 228 (line 157 in the first version): "There was in the frequencies of moderate dependence category among groups." What does this sentence mean exactly? In its current form it does not make much sense. Reviewer #1 has already requested the correction of it, but in the second version of the MS. this sentence has remained exactly the same... Please fix it! Thank you for this observation. By mistake, „no difference“ was dropped out from this sentence. Now it was put back in the tekst, and the sentence is now: "There was no difference in the frequencies of moderate dependence category among groups."

19) Discussion (especially subchapters entitled "Severity of nicotine dependence in patients and healthy controls" and "Nicotine dependence and severity of symptoms") is long-winded. For instance, speculations on the causes of agreements/disagreements of results of the current study with results of others are frequently difficult to follow and are suggested to be shortened. Thank you for this suggestion. In the subchapter, the sentence: „In patients with schizophrenia, longer disease duration was associated with parkinsonian axial signs [40] and more frequent treatment with antidepressants [41]“. was deleted. (page 11., lines 241-243). After the sentence: “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” (lines 243-245), “which are related to longer disease duration [40, 41]”. was added. The following paragraph was deleted (lines 258-261, page 12): “For example, smoking was associated with chronic peripheral inflammation only in patients with severe levels of dependence [42]. Interestingly, cortical thickness of the right dorsolateral prefrontal cortex was negatively correlated with FTND in young male adult smokers [43].” After: “There is some evidence that severe nicotine dependence may have distinct biological changes” (lines 257-258, page 12), the
following was added: such as chronic peripheral inflammation [42] and decreased cortical thickness of the right dorsolateral prefrontal cortex [43]. The sentence: “While the present study did not measure biological markers, we can only speculate that increased rates of smoking severity in some patients might be related to biological dysfunction” (lines 261-263) was deleted, and: “However, the present study did not measure biological markers”. In the subchapter: "Nicotine dependence and severity of symptoms", the sentence: „Similar to 10, 9, 60, we have excluded patients with alcohol and illicit drug abuse, which was not the case in 61, 57, 59 and 30”. (lines 338-339) was deleted.

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

Best wishes,

Marina Šagud