Author’s response to reviews

Title: "Decision-making capacity for research participation among addicted people: a cross-sectional study"

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Author’s response to reviews:

We would like to first thank the editor and the reviewers for their efforts and for identifying both the strong and weak points of our manuscript. Undoubtedly it has been improved as a result.

We trust that our responses to the reviewers’ suggestions will render the manuscript suitable for publication in BMC medical ethics.

Reviewer(s)’ Comments to Author:

Reviewer #1:

1. Background: It would be helpful if the authors could provide information about the ethical and legal regulations related to participation to research of patients with psychiatric disorders in Spain so readers are able to contextualize the study and especially the findings. It is stated that all subject was legally competent in method section. Who are considered legally competent in Spain? What is the position of Spain in respect of United Nations conventions surrounding the care, treatment and participation to research of people with people with Substance Use Disorders?

We have added a paragraph in the background section providing the information the reviewer 1 suggests to better contextualizing the study.

(Included in Background section, pages 4-6)

In Spain, there are no defined guidelines as to who should assess patient decision-making competence and how such assessments should be accomplished. Spanish laws about CI in
biomedical research touch upon subjects decision-making capacity and indicate those situations where the capacity is limited without define it or specify how to asses it. Laws emphasise the necessity of justifying the inclusion of “vulnerable population” in research, without specifying who vulnerable population are. There are no specific regulations related to research participation of patients with psychiatric or addictive disorders. Proxy consent in research will be necessary if (a) persons are younger than 18 years of age (except for emancipated minors which are regarded as capable of making decisions); (b) the physician responsible ascertains that the patient ability to take part in the decision-making process is impaired; or (c) the patient is legally incompetent. A person is considered legally incompetent if he is unable to understand or communicate information to meet essential requirements of physical health, safety or property management. Courts are responsible in Spain for determining the legal competence of an individual basing their judgement in two medical reports.

Given the enormous health, economic and social burdens arising from SUD, there is strong public interest in preventing drug use. The Demand Reduction Section of the United Nations International Drug Control Programme covers actions focusing in treatment and prevention, demand and supply reduction, international cooperation, training and improvement of scientific knowledge about SUD. The Spanish National Drug Strategy 2009-2016 is closely linked to the actions arising from the European Union and the United Nations (UN). The Spanish government has long cooperated in the policy and decision making bodies within the UN system, by providing technical assistance and funding for projects executed by bodies specializing in drugs. Research in this field will lead to develop more effective treatments that will reduce the harm caused to the individual and society.

2. Demographic, clinical, and decisional capacity characteristics of patient groups (% and n) should be fairly written in text.

We have better written the characteristics of patient groups as the reviewer suggests.

3. Study results are difficult to understand by the reader as given in a mixed. After the demographic characteristics of the two groups given, the statistical results among demographic characteristics of two patient groups should be given. Then, clinical characteristics of the two groups and statistical results should be written

We have rewritten the results section as the reviewers suggests.

We have added two more subheadings in results section (page 12-13): (a) Demographical and clinical characteristics and (b) decisional capacity characteristics. In the first one we describe first baselines difference between the two groups given (NPCs and SUD) and we have also added information about comorbidity of each SUD group (Table 1) as the other reviewer suggests. Later on, in the decisional capacity characteristics, we have explained
information about decisional capacity assessments in SUD and NPC group (Table 2) and within each SUD group (Figure 2).

In the subheadings Ratings and factors linked with incapacity we have first explained the baseline characteristics of people with and without mental capacity to consent to research (Table 3) and afterwards written in the text we explained the relationship between the independent variables and the dependent variables (lack of capacity). In this way we think results are easier to understand.

4. Discussion: Please do not repeat the exact data (numbers and percent such as 67.3%, OR= 2.5 (IC95%:11 0.98- 6.61) and others).

We have removed the exact data from the discussion section as the reviewer suggests.

5. Authors stated that mental capacity is also associated in our study with gender and living status (page 15, line 44). How do you interpret this result?

(Included in Discussion section, page 15)

Mental capacity is also associated in our study with living status. People who live with their parents or in an institution were more likely to lack capacity than those who live alone or with their families. To the best of our knowledge, there are no studies in the literature about why living status may be linked to lack of capacity. We interpret living status as an indicator of psychosocial deterioration: the chronic use of drugs can cause significant cognitive deficits that may impair addicted people’s capacity to take care of themselves or to live by their own so is more difficult for people with SUD to achieve emancipation.

(Included in Discussion section, page 15-16)

Our findings indicate that men were more likely to lack capacity than female patients. Although gender generally has little demonstrable influence on cognitive tasks, we don’t know specific studies about the influence of gender in research- decision-making capacity. One study examined the level of performance of women with major depression on the decision-making abilities assessed by the MacCAT-CR but they didn’t include male participants to compare the scores with. In our study when the other variables associated with lack of capacity on the multivariate analysis are considered, gender has a slightly non-significant impact on the probability of consenting. Our results will have to be explored in further research.

6. Additionally, I would like to see more critical discussion. The discussion was not the repeat of your study results. The discussion section needs to be more in depth rather than just analysis not addressed literature review in this section.
We have rewritten the discussion section as the reviewer suggests.

Reviewer #2:

1. Methods and Results sections need restructuring.

   Participants: please show a flow chart of eligible and included patients in the results section. The data on patient inclusion in the methods section are not consistent and at the wrong place. Procedures is far too long, please add a subheading Measures to describe the way the MacCAT-T was used.

   We have restructured methods and results sections as the reviewer suggests: we have included a flow chart of eligible and included patients in the results section (Figure 1); we have shortened procedures and we have added the subheading “measures” explaining MacCAT-CR and the others scales.

   a. Page 8: please summarize the procedure and be clear about the hypothetical research.

   We have shortened the procedure and we have explained more deeply the hypothetical research as the reviewer suggests.

   b. Please do not repeat the results presented in tables, double in the text.

   We have rewritten the results without repeating the results as the reviewer suggests.

2. Figure 2: because of selection of two different samples, they were significantly different on most of the baseline characteristics. For that reason, figure 2 makes no sense.

   Following reviewer 2 suggestions and in order to diminish the difference between the two samples, we have completed statistical analyses with a multivariate analysis in order to clarify the results adjusting the OR by the factors with more clinical and/or statistical importance. In this way, we try to exercise sufficient control over potential confounding variables that may influence the results.

   We have removed the Figure the reviewer mentioned and we have explained in the text the unadjusted OR in the univariate analyses and the definitive results controlled by the independent variables.

   (Included in Data Analysis section, page 11)

   To examine the relationship between the independent and dependent variables, we calculated the odds ratios (ORs) and 95% CIs. Multivariate analyses with logistic regression were carried out with the variables that showed a significant relation with the dependent variable in the univariate analyses and were clinically relevant. To avoid an overfit model we followed the rule which states that for every independent variable, there
should be no fewer than 10 events per covariate. Then, by direct selection, we obtained a model with the individual variables directly related to the dependent variable (lack of capacity). To assess model’s overall fit to the sample data we used the Hosmer-Lemeshow goodness-of-it test. It produced a high p-value so our model passed the test and the difference between observed and model-predicted values was small. Colinearity tests were carried out between explanatory variables, calculating the variance inflation factor (VIF) for each. This gave a value of VIF < 3 for each variable, so colinearity was rejected, meaning that the possibility of overfitting was minimal. A probability level of p ≤ 0.05 (two tailed) was considered significant.

(Included in Results section, page 13)

The relationships between participants characteristics and lack of capacity are the following: using male gender as a reference, the Odds Ratio [OR] of lack of capacity was 3.42 (IC95%: 1.23-9.5; p= 0.018) for the women of our study. Thus, in our sample, men seemed to be more likely to lack capacity than female patients. SUD diagnosis had a slightly non-significant impact on the probability of consenting OR= 2.55 (IC95%: 0.98–6.61; p=0.054). Each one-point increase in the MMSE score increases the odds of a subject consenting by approximately 5%, OR = 0.53 (IC95%: 0.36-0.76; p= 0.03).

The stepwise logistic regression model included three relevant variables that were significantly associated with lack of capacity on univariate analysis. We chose MMSE scores and SUD diagnoses by its clinical importance and gender by its apparent high OR. Only one of the three variables included in the univariate analysis was retained in the multivariate model: the MMSE scores OR= 0.55 (IC95%: 0.37– 0.81; <.001), although gender had a slightly non-significant impact on the probability of consenting OR= 3.03 (IC95%: 0.98–9.36; p=0.054). When the other variables associated with lack of capacity on our univariate analysis are considered, SUD diagnosis no longer has an impact on the probability of consenting OR=1.13 (IC95%: 0.37-3.41; p=0.83).

3. To my opinion, the key message of the article should be clarified, in a way that it expresses: Most of the people with SUD, excluding those with acute intoxication, withdrawal or cognitive deficits, possess decision-making capacity regarding research participation. In the background section, the authors might consider to add some information on possible pathological values that people with SUD may base their decision-making on (Charland), which does not only apply to healthcare decision-making.

We have tried to clarify the key message of the article in the discussion section.

We have added information about values that people with SUD base their decision-making in a paragraph in the background section.
As defined in psychiatric classification, addiction is a disorder in which an individual’s control over their drug use is impaired. People with an addiction continue to use drugs in the face of enormous negative consequences, and despite often expressing a wish that they could stop. This perspective is codified in the diagnostic criteria for addiction, in which a loss of control over drug use is central and becomes compulsive-something engaged in at the expense of all other goal-directed activities such as work or relationships. Concerns have been raised about the capacity and voluntariness of people with SUD to participate in research. Some ethicists and clinicians have interpreted the DSM-5 criteria that describe loss of control and compulsive behavior in absolute terms. They argued that people with SUD fail to satisfy the required standards for competent voluntary consent and that we should assume that addicts are incompetent to consent to trials unless proven otherwise.

4. Page 5: the authors might add information on procedures of proxy decision making in the case of incompetent patients.

We have added a paragraph in the background section providing the information that the reviewer 2 suggests.

Proxy consent in research will be necessary if (a) persons are younger than 18 years of age (except for emancipated minors which are regarded as capable of making decisions); (b) the physician responsible ascertains that the patient ability to take part in the decision-making process is impaired; or (c) the patient is legally incompetent. A person is considered legally incompetent if he is unable to understand or communicate information to meet essential requirements of physical health, safety or property management.

5. Page 6, participants: As it reads, participants can have comorbid psychiatric diagnoses. Can the authors clarify this?

The patients with SUD had psychotic, mood and anxiety disorders as comorbid diagnosis. We didn’t find statistically significant differences between the SUD groups in terms of psychiatric diagnosis.

We included a table (Table 1) with the demographic, clinical and cognitive characteristics of each SUD group. Within this table, information about comorbid diagnoses is included.

Page 15, discussion, refers to outcomes of GAF and CGI, which may be explained by comorbidity.

(Included in Discussion section, page 16)
Most patients in our study have also a psychiatric disorder. These patients with dual diagnosis may have dual deficits in decisional capacity—compounded by impaired response to short-term versus long-term gains and losses and those secondary to cognitive impairment associated with psychiatric disorders. Symptom Severity of SUD, as measured by GAF and CGI scores was associated with incapacity in this study. Our research suggests that the SUD dual diagnosis severity, as measured by lower social functioning may be a factor in the decisional process. The more severe the SUD, the less likely the individual is able to consent to research.

6. Page 10: information on validity and reliability of MacCAT-CR is lacking.

We have added a paragraph in measures providing information about validity and reliability of MacCAT-CR.

(Included in Measures section, pages 8-9)

Previous studies in populations with dementia or psychiatric disorders have demonstrated a high degree of reliability and indications of validity.

Also page 18: some authors (Kim, Hein) did examine cutoffs.

We apologise for not having included these two relevant studies. We have added to the bibliography the other authors who determined cut-points (references number 28 and 29).

7. Page 11: could the authors please clarify how the MacCAT interviews were reviewed? Was there a verbatim transcription?

(Included in Procedures section, pages 10-11)

After each interview, the researcher scored the four subscales according to MacCAT–CR criteria. The interviews weren’t videotaped but there was a verbatim transcription because the investigators interviewed the subjects with other co investigator present who took notes. Later on, these transcripted interviews were inde reviewed by two people (a medical ethics specialist and a psychiatrist), each of whom assigned their own scores to each patient based on the MacCAT-CR rating guidelines. A consensus meeting was held to derive a single score for each case when the judgment was felt to be difficult. In practice this amounted to seven interviews. The research team made a global judgement about the patient’s capacity to consent to research, based on information from both the MacCAT–CR and the clinical interview with the patient. The investigators met regularly with I.M.S. and M.D.P.C. to review and discuss any scoring questions

Line 11: was the binary decision based on the MacCAT-CR manual or on the MacCAT-T approach?
The binary decision based on the MacCAT-CR manual. We have removed this sentence from the draft: The judgement about capacity followed the approach outlined by Grisso & Appelbaum in order to reach a binary (yes/no) decision [21].

8. Page 14, line 9-11: new data appear on probability of consenting, which have not been mentioned in the results section.

The data the reviewer mentioned do already appear in results section (page 13, lines 21-23 of the former draft): “Using the NPC group as a reference, the OR of lack of capacity was 2.55 for those who were diagnosed of a SUD but this difference wasn’t statistically significant: OR= 2.5 (IC95%: 0.98–6.61).” In the new version, this data appear included in results section page 13 line 11.

9. Page 14, line 19-22: could the authors please clarify why they explain variability in decision-making competence by type and degree of SUD groups, while figure 1 shows no significant differences between groups.

The reviewer is right; the way is written is a bit confusing. We have rewritten this paragraph to clarify this point.

(Included in Discussion section, page 14-15)

There is much variability in addicted individuals’ response to drugs and the degree of impairment they experience. As literature suggests, impairment may differ depending on the type of drug being abused, the route of administration, the severity of the addiction, the level of tolerance, and the amount of time since last drug use. Unexpectedly, we didn’t find significant differences between SUD groups in our study in terms of lack of capacity. The limited number of patients included in each SUD group could be one explanation for these results.