Author's response to reviews

Title: Time-course of cannabis withdrawal symptoms in poly-substance abusers

Authors:

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Author's response to reviews:

To the reviewers,

We thank you for your time and effort, and for the very useful comments for improving the paper. We have responded to all, and hope that these responses will suffice and qualify the paper for publication.

Kind regards,

Morten Hesse and Birgitte Thylstrup

Referee 1: David Penetar

Some minor essential revisions should be addressed before acceptance.

1. Should the caption for Table 1 read "1, 2, and 4 weeks"?
   • Following the advice of the statistical reviewer, this data has been changed into a figure.

2. There is not footnote #1 for Table 5.
   • Thank you, this is now corrected.

3. The figures would be more understandable if they contained legends briefly explaining what the figures show (especially Figure 3).
   • We have described this now in the ‘Figure legends’, but have now also added it to each graph in figure 3.
Referee 2: Ryan Vandrey

Major Compulsory Revisions:

1) In Section 1.1.4, the authors continue to suggest that prior research on cannabis withdrawal failed to address demand characteristics, which simply isn't true. The published papers described in section 1.1.2 explicitly state that withdrawal questionnaires were not labeled as such (labeled as Behavior Checklists, Health Checklists, or the like), included “filler” items to mask the intent of the study, and certainly included all of the 7 symptoms proposed for DSM-V, in contrast to the statement made in the second paragraph. I suggest that if the authors choose to retain the discussion of demand characteristics, they focus on how prior studies selectively recruited only cannabis users, and how participation of non-cannabis users in the present study may better mask demand characteristics.

- We have added some examples of ways that previous studies that have attempted to control for demand characteristics. Our focus on the demand characteristics aspect remains on the type of sample used.

- Concerning the question of the specific syndrome as described in the DSM-V, we have failed to identify any study that uses these seven symptoms without any additional criteria. The DSM-V criteria are suggested as a single syndrome, and thus it makes sense to study the construct as a whole. Certainly, some studies have included all of these criteria (e.g., Allsop and colleagues, Cannabis Withdrawal Scale), but that scale includes a number of items that are not in the DSM-V (e.g., nightmares, imagining being stoned, thinking about smoking). Without references to the particular studies that the reviewer is referring to, we do not see any reason to change this statement from the following: “No study has so far used the seven symptoms listed in the DSM-IV together as the indicator of withdrawal. Studies have either used some of these symptoms or included other symptoms such as craving.”

2) It is difficult to follow which study participants are included in the data presented, and when or how frequently cannabis was used. The paper indicates that 90 patients were interviewed. Among those, 74% (N=67) reported using cannabis, 22 of whom had not used in the prior 30 days. This results in an sample of 45 patients (half the sample) for whom cannabis withdrawal might be expected. Only 6 reported use the day prior to the first interview, but it is unclear if that was because others were daily cannabis users interviewed a few days after treatment admission, or if they smoked cannabis less frequently. Section 1.3 states the 22 who had not used cannabis in the prior 30 days were not included in regression analysis or time course analysis. Were the non-cannabis users included in these? Were all 90 users included in Tables 1 and 2? It is not clear whether the mean 14.4 days since last use includes those who haven't
used in the past month or not.

• The 22 was a typo, and should be 23, constituting the 26% who did not use cannabis in the past 30 days. The N used for all analyses were 67. We have changed the results description to clarify this issue: We have moved the statement that subjects were only included if they had consumed cannabis up to the previous section to clear up this confusion.

3) There should be more detailed description of the procedures used in investigating the impact of medications (section 1.3.2) in the data analyses section.

• We have now expanded on this section to clarify that the analysis was repeated for each type of psychotropic medication.

4) The second paragraph of the discussion is incomplete, and the portion there is inaccurate. The symptoms being assessed here are not in DSM-IV (no specific symptoms for cannabis withdrawal are provided), but are those that will be included in the DSM-5, to be published within the month. Further, the proposed DSM-V language also includes text stating that disturbing/strange dreams, fatigue, yawning, difficulty concentrating, and increased appetite following decreased appetite during the early stages of withdrawal may also occur. This distinction between DSM-IV versus DSM-V and the inclusion of other symptoms (dreams, fatigue, etc) should be corrected throughout.

• This is quite true. We were misled by the DSM-5 homepage from which we derived the criteria, as the webpage stated that the DSM-5 criteria represented no change. We have rephrased throughout and referred to the (now published) DSM-5. We have however stated that we took the items from the webpage, so that it is clear to readers that we did not have the details of the final text when constructing the instrument.

1) Table 1 and Table 2 should be reversed in order. The results start with the description of the participant demographics (currently Table 2), and later describe withdrawal outcomes (currently Table 1).

• The first reference to Table 1 is in the methods section to provide readers with an overview of the withdrawal items at that point.

2) The text in section 1.3 indicates 20% female participation, but Table 2 indicates 21%. Also, section 1.3 states that 74% of participants reported
cannabis use (90 * 0.74 = 67), but later says that there were 68 participants (75% of 90) who used cannabis AND completed more than one booklet (suggesting there were others who completed only one booklet. Please re-examine the numbers reported and provide correct and consistent data...

• We have cleared up the numbers.

Referee 3: Nicholas Horton

The authors report on a cohort of subjects withdrawing from cannabis during detoxification, and provide some credence to the existence of withdrawal symptoms. This paper has a number of minor limitations that detract from the current presentation. It would be relatively straightforward the suggestions made below. A revised manuscript would be of widespread interest to those in the cannabis abuse field.

Major compulsory revisions:

1) Would a graphical presentation of the results in Table 1 be more comprehensible? At present it is difficult to see patterns. The paper by Gelman et al (Let's practice what we preach: turning tables into graphs, 2002, The American Statistician 56:121-130) provides several similar examples.

• We have read the paper by Gelman and colleagues and prepared a graph to illustrate the course of symptoms over assessments. As recommended by Gelman et al, we produced multiple line plots for the new figure 1.

2) Minimal information is provided regarding the psychometric properties of the DSM-IV cannabis withdrawal scale. In addition, this scale should be referenced. Does this decompose into a reasonable factor structure?

• We have now clarified that the withdrawal scale was produced specifically for this study. Following the comments of reviewer 2, we now know that this was in fact DSM-V criteria. Previous studies have relied on varying conceptualizations of cannabis withdrawal, most of which have overlapped with the DSM-V criteria. After the reviewers’ comments, we conducted a factor analysis of the eight DSM-V items, and report that the factor structure led to a one-factor solution based on Hull’s method as well as parallel analysis. In addition, we report Cronbach’s # at each week.
3) The manuscript would benefit from a clearer analytic flow (in the introduction, with list of goals) and a parallel structure in the methods (how these will be assessed) and results. This will help to guide the reader through what at present is a somewhat convoluted path.

- We have clarified the goals and set them up with bullets, as well as added several comments in the analyses to specify how exactly the hypotheses were tested. In addition, we have changed the organization of the first part of the introduction.

4) How were non-responses to questions handled in the analysis process, if any?

- Non-responses were handled by two different methods: When calculating the mean cannabis withdrawal severity, missing items were replaced by the mean of the respondents’ responses to other cannabis withdrawal items at the same time point. For all other analyses, data points with any missing information were excluded. This has now been described in the analysis section. As stated in the results section, missing items were rare, affecting <1% of observations.

5) Section 1.2.2 second paragraph is the pharmacological treatment measure that the authors created? More information is needed.

- Yes, there is no standard instrument for collecting this data. This has been added to the methods section.

6) There’s some ambiguity regarding which variables included in table 3 are included in the models in table 4? Can the Notes provide additional detail regarding the "Additional substances" column?

- The same analyses were carried out for individual symptoms as for the full scale. To clarify this, we have used the exact same labels in the notes under Table 4 as are used in Table 3, and stated that “All effects controlled for three additional substances (all time-variant variables): Days since last alcohol or benzodiazepine use; Days since last opioid use; Days since last CS use.”

7) While the authors are to be commended for a clear and comprehensive discussion of limitations, it should also be added that multiplicity are a potential issue here, as the number of tests run and reported are considerably larger than the sample size.
We have added this section to the limitations section: “A further limitation is that the sample size is not very large. Interpretations concerning individual symptoms should be done in light of the existing literature, rather than based on significance testing, given that this study included multiple tests.”

Discretionary comments:

1) Section 1.1.1 second sentence consider splitting sentence after “… [2]”. 2) Section 1.1.2 second paragraph consider re-phrasing “The following discusses studies…”

We have generally reworked the introduction.

3) Section 1.1.2 third paragraph second sentence consider splitting after “… [5]”

Thank you, we have done so.

4) Section 1.1.2 fourth paragraph second sentence consider an alternative to the word “causes”

We have rephrased this paragraph as: … that nervousness associated with cannabis withdrawal is a source of significant distress

5) Section 1.1.2 fifth paragraph first sentence consider rewording to “frequently reported as a withdrawal symptom”

Thank you for this, done.

6) Section 1.1.3 third paragraph second sentence consider rewording “The time course of these dreams differs from other symptoms studied with a later onset and a longer duration”

Thank you for this, done.

7) Section 1.1.4 first paragraph fifth sentence consider changing second “believe” to “perceive”
• Thank you for this, done.

8) Section 1.1.4 third paragraph second sentence remove “per se”

• Thank you for this, done.

9) Section 1.1.5 first paragraph consider adding “The present study was part…”

• Thank you for this, done.

10) Section 1.1.5 fourth paragraph consider removing “in and by itself”

• Thank you for this, done.

11) Section 1.2.1 second paragraph second sentence run-on consider splitting sentence

• Thank you for this, done.

12) Section 1.2.1 third paragraph last sentence is a run-on. Just because you can’t think of any serious harm does not mean that there may not be any harm, might consider just adding a “greatly harmful”

• Thank you for this, done.

13) Section 1.2.2 second sentence confusing sentence consider rephrasing

• Thank you for this, done.

14) Section 1.3 second paragraph third sentence consider rewording to “Eleven people…”

• Done
15) Section 1.3 third paragraph add a SD to the 14.4 mean

• Thank you for this, done.

16) Section 1.3.1 second paragraph fifth sentence consider rewording to “into two, such that assessments…”

• Thank you for this, done.

17) Section 1.4 second paragraph the end of the sentence appears to be missing

• Thank you for this, changed.

18) Section 1.4 third paragraph last sentence consider removing the word “both”

• Thank you for this, done.

19) Section 1.4 fifth paragraph last sentence consider removing “And” and “in their study”

• Thank you for this, done.

20) Section 1.4.1 fourth paragraph second sentence consider revising to “the potential risk that the treatment providers that collected the data for this study could have influenced…”

• Thank you for this, done.

21) Label figures, consider adding the observed data points to the figures, label y-axis for figure 1

• We have described this in the file ‘Figure legends’, but have now also added it to each plot in figure 3.

22) Fix the incomplete sentence in the second sentence of the paragraph of the discussion.
• Thank you for this, done.