Reviewer's report

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

Version: 3 Date: 6 May 2013

Reviewer: Ryan Vandrey

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Overall, this manuscript is improved from the first submission. The rationale for assessing withdrawal in the population of poly-substance users is more clearly provided, and several other areas of concern were addressed. However, several concerns remain, mostly related to the presentation of the data and confusion surrounding DSM.

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.

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.

I understand that recruiting non-cannabis users and less frequent users was attractive as a means for reducing response bias in this study (now well communicated), but data from non-users or infrequent users should not be included in the data presented. Including them in the patient characteristics or
mean withdrawal scores hampers the ability to interpret the relevant withdrawal outcomes. I recommend selecting and presenting data on only the relevant patients and having the same patient group represented in all analyses.

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.

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.

Minor Essential Revisions:
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).

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...

3) Please add a y-axis label to Figure 1 and describe in the text how the withdrawal score was calculated. Was it the sum score of the DSM-V symptoms or all items from the questionnaire?

4) The text in section 1.3.1 states that for insomnia, neither the linear or quadratic coefficients were statistically significant, yet the linear coefficient is bolded in Table 4, indicated significance. Please again check the correct designation and make this consistent.

5) Section 1.4.2 is not reflective of the current science. There have now been published 2 clinical trials demonstrating positive effects of medications (n-acetylcysteine by Gray et al., 2012; gabapentin by Mason et al., 2012). Further, there are multiple studies demonstrating efficacy of psychosocial treatments (MI, CBT, CM) for cannabis dependence (see Roffman, Budney, Carroll, Stanger, Stephens etc). This section should be expanded or removed.

Discretionary Revisions:
1) In the second sentence of section 1.1, consider changing "... does not typically cause significant medical or psychiatric problems" to something a little more
specific like "... does not typically cause life-threatening medical or psychiatric problems". The idea of inclusion in the DSM is that these withdrawal syndromes are clinically significant.

2) In the last sentence of section 1.3.1, "identically" should be "identical"

3) Why not include increased appetite, fatigue and yawning in tables and figures as done for vivid dreams?

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests