Author's response to reviews

Title: Pilot Randomized Trial on Mindfulness Training for Smokers in Young Adult Binge Drinkers

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Author's response to reviews: see over
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BMC Journal of Complementary and Alternative Medicine

Dear members of the review board,

Thank you for considering our manuscript entitled “Pilot Randomized Trial on Mindfulness Training for Smokers in Young Adult Binge Drinkers” for publication in the BMC Journal of Complementary and Alternative Medicine for peer review.

We have responded to both sets of peer reviewer comments and have provided our respective responses below.

Again, thank you for considering this manuscript. If you have any questions, I may be reached at jjamesdavis@hotmail.com or you may call me at 608-217-9405.

Sincerely,

James M. Davis, M.D.

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Letter of Response

Response to Reviewer 1, ZEV Shuman-Olivier:

Dear Dr. Davis,

Considering the depth of the problem of young adult binge drinking and co-morbid smoking, and the challenge of treatment retention, you should be commended on your bold attempt to engage this population and develop behavioral treatments. Additionally, the use of mindfulness for this population is particularly promising, so reporting the methods used in this trial is important. The sample size and retention difficulties are substantial limitations that every behavioral therapy researcher understands and the authors appropriately note several of the limitations of this trial related to small sample size and high attrition, but unfortunately the paper draws conclusions that are not fully substantiated by statistical analysis methods and then repeats them several times in ways that I am concerned could be misleading. See comments below:

Dear Dr. Shuman-Olivier,

Thank you for your careful review of this paper. We have made substantial revisions to the manuscript based on your comments. We have modified or removed statements that were not substantiated by our statistical analysis. We now report all “trend” level results as “non-significant” and have changed language in the discussion to reflect that. Regarding attrition and missing data, new analyses were performed and language was changed in an attempt to provide a more transparent and nuanced understanding of our study results. All outcomes are now reported in intent-to-treat analyses. Secondary analyses are identified as such. Figure 1 (showing non-significant findings) has been removed and Table 4 (comparing completers to non-completers) has been added. A short discussion has been added to discuss the significant association between alcohol use and smoking relapse. We have modified our language in places to emphasize that this is pilot study and our main goals are to assess feasibility and estimate effect sizes between groups. Another reviewer asked us to shorten the paper, so some content has been removed or rewritten making the manuscript about one page shorter. Specific comments are addressed below:

1) abstract, pg 2. refer to number of drinks per week as secondary analysis—see comments below

   1. This sentence in the abstract has been modified and now reads:
   “Secondary analysis showed number of drinks per week in the first 2 weeks post-quit correlated with smoking relapse at 2 weeks post-quit (p = .02).”

2) page 3. change 7 FDA med to “seven”

   2. We have changed the text to “seven.” The text now reads: “There has been considerable progress in tobacco dependence treatment through development of seven FDA-approved cessation medications…”

3) page 5. MBRP....evidence of effectiveness in the treatment…--do you mean efficacy?
3. We have changed effectiveness to “efficacy.” The text now reads: “Research on the Mindfulness Based Relapse Prevention (MBRP) has demonstrated preliminary evidence for efficacy in the treatment of alcohol dependence [60, 61].”

4) Page 6. Sentence with ref 45 is confusing to read.
4. We have modified this sentence to make it clearer. The text now reads: “Nonetheless, a recent literature review using PubMed and PsycINFO revealed only one published study on the treatment of smoking cessation and binge drinking in young adults. In this study 41 smoking binge drinkers age 18-30 years were randomized to receive either medications and semi-structured smoking cessation counseling, or the same but with an integrated brief alcohol intervention. This study showed promising effect sizes between groups favoring the dual treatment arm, but was not powered to reach statistical significance [45].”

5) The use of “Mindfulness Training for Smokers” reminds me of Brewer 2011 DAD paper which uses the same title for the mindfulness intervention. There should be a sentence to differentiate that this is a very different intervention in logistical format than the MTS previously published (though based on similar underlying theory—perhaps). Consider a different name since that one already refers to Brewer intervention??
5. At the time that Brewer’s paper came out using the name “Mindfulness Training for Smoking Cessation”, our intervention, under the name “Mindfulness Training for Smokers” was already in use at a local hospital, in several studies, with a manual, DVD, meditation CD. After the Brewer publication, we considered changing the name of our intervention to something that would be less confusing. In the end, we, however, we decided that the change would cause considerable logistical difficulties so we opted to keep it. To clarify these two names within this manuscript, we have added the following text: “To avoid confusion, it is worth noting that a similar name “Mindfulness Training for Smoking Cessation” has been used to describe another smoking cessation intervention (63), and that we opted to use the name “Mindfulness Training for Smokers” because materials with this name were already in use at the time of Brewer’s publication.”

6) Page 7. It is not clear how long treatment phase is. What study week was 2wks post-quit date? It would have been good to have some kind of post-tx follow-up phase at least for alcohol and cigs/d. This would likely have allowed for the study to have more power than just using pt prev for smoking at treatment end. Even if you couldn’t get CO, this still would have been helpful.
6. In the Procedure section, we have modified the text to read: “MTS and ILS interventions lasted six weeks with identical schedules consisting of six 2-hour weekly classes plus a 7-hour Quit Day Retreat on the weekend between classes four and five.” In addition, in the Study Assessment Visit section we have modified the text to read: “The study assessment visit was performed at the end of treatment, two weeks after the Quit Day Retreat, during the week following last class.”

7) Page 7. you talk about 16-25 as young adults throughout introduction, and then include 18-29 in study.. please comment on reason for the change.
7. The decision to change the age range from 16-25 to 18-29 was made for several reasons. The 18-year-old cut off was used to avoid IRB consent issues involved with recruitment of minors. The 30-year-old cut off was used because study recruitment was conducted primarily at local community colleges with a large number of students in their late twenties. Because the study was run on a small budget we needed to maximize recruitment, and using a wider recruitment base allowed us to meet our number needed to treat within budget. It should be noted also that the only other study on this population (Ames, 2010) used a similar age range (18-30).

8) In review of clinicaltrials.gov. The outcome that is reported numbers of days smoked in first 2 weeks is not listed as primary outcome, therefore it seems like this was a secondary analysis, allowing for greater power to have a finding in an overall negative trial. It may be better to acknowledge that outright, then keep mentioning that the trials show a large, but non-significant, effect.

8. We have modified the text to read: “Primary outcomes were defined as smoking abstinence confirmed via carbon monoxide (CO) breath testing with daily smoking assessed via time-line follow-back (TLFB) at two weeks post-quit.”

9) Page 10. The methods section headings are very non-traditional, as I am used to things like (sample selection, randomization, intervention, data analysis, etc.) The title missing data management seems odd. Missing data is just one aspect of data management and data analysis.

9. We have omitted non-essential section headings and applied more traditional headings to the manuscript. We have omitted the “Missing Data” heading and now simply use “Data Analysis.”

10) Which statistical program was used—SPSS, SAS, Stata, R?

10. We have added to the text under “Data Analysis” that “Analyses were performed using SPSS.”

11) Page 10. The major problem with the study is the use of completers analysis. You stated that imputation of data was not deemed necessary, because of a low rate of missing data, and yet more than 50% of the sample is not included in the analysis. The ANOVA repeated measures will result in a completers-only analysis, unless there is imputation in as an intent to treat. The cig dates in first 2wks excludes more than half the sample. Could this be repeated with GEE over 14 days post-quit, looking for days abstinent as dependent variable? Or using mixed models with MLE, just using cigs per day in last 14 days, getting a least squared means estimate for avg cigs per day during 14 days post-quit? These would have missing data methods to estimate standard error. Missing data techniques will account for the variability and calculate a real standard error, giving a more accurate significance test. If you just include completers then you are removing a large amount of standard error and biasing the study towards significance. For instance...what if the half of the mindfulness group that does not quit ends up smoking more than the ILS group b/c of the intensity of the meditation experience? At least conduct the full sample analysis and then you can report both if they are different.

11. We agree that the description of this study would benefit from greater attention to intent-to-treat analyses and analysis of data on participants who dropped
out. We have made a number of changes to try to meet your recommendations, and performed the analyses that you have recommended with varying success.

a) To begin, we are providing an analysis comparing baseline data of participants who dropped out to those who did not. In summary, there were no statistically significant baseline differences between groups except for number of cigarettes smoked. The results of this analysis are shown in Table 4. This analysis now receives its own paragraph in the results section and is highlighted in the discussion section.

b) Regarding the analysis of smoking abstinence, we now provide data from an intent-to-treat analysis as well as a completer analysis (Table 3). The intent-to-treat analysis defines all dropouts as relapsed, leading to smoking cessation rates of 20% (MTS) and 4% (ILS). In addition, Table 3 provides effect sizes (odds ratios and their 95% confidence intervals) for intent-to-treat analysis and completer analysis. In the text of the paper, we have described this comparison.

c) Non-weighted GEE could not be performed because this would require data that is Missing Completely at Random. Our dropouts, at best, are likely to be “Missing at Random” which requires weighted GEE. This type of analysis is substantially complex and typically beyond the scope of a pilot study.

d) We conducted a mixed effects model (random effects model) to analyze tobacco and alcohol outcomes with missing data. Results demonstrated no change in significance levels when comparing mixed model analyses and simpler methods. After exploring mixed effects models further, it appears that a more accurate analysis to explore missing data would be obtained using “pattern mixture modeling” as described by Hedeker, D., & Gibbons, R. D. (1997) “An application of random-effects pattern-mixture models for missing data in longitudinal studies.” This type of analysis is also complex and typically beyond the scope of a pilot study. With these findings we have returned to simpler methods for managing missing data often found in pilot studies. This approach is recommended by Dr. Sunni Barnes et al. when approaching small studies with large amounts of missing data. As a reference, please see “Missing data assumptions and methods in a smoking cessation study” (2009). In order to place our findings in their proper context, we have highlighted that our goal with this study is to provide feasibility information on this population and intervention and to provide initial estimates on effect sizes between groups.

12) Page 10. I would include the IRB and Helsinki language at the beginning of methods in sample selection instead of data analysis.

12. We have moved the IRB and Helsinki statement to the beginning of the Methods, sample selection section as recommended.

13) Page 11. It is hard to conduct pilot stage 1 studies, and hard to get significant findings, but we should still do our best not to overstate our findings and just present the significant findings that are there. many people suggest that we should avoid reporting trends. Trends are not a significant finding even in low power. Additionally, given that it is a completers analysis, the standard error may be much greater, and these trends may actually be non-significant.
13. In multiple places throughout the results section and discussion section, we have changed the language from “the finding trended toward significance” to “the finding was not significant.”

14) Page 12. regarding ref to figure 2. Again DF is only 23 out of 55. that means groups have 10-13 each... Can you use mixed models with MLE that would include missing data? Good to report non-sig finding, but why bother putting in a non-sig figure anyway? 
14. We have removed Figure 2 from the manuscript.

15) Page 12. Do you want to have Heavy drinking days or days abstinent as drinking outcomes? 
15. We have omitted “number of drinks on heaviest day” from the paper and are employing “number of drinks per week” as our outcome measure.

16) Page 12. the attrition section is hard to follow. Why would attrition be defined by just missing the quit day retreat. What if they missed the 6 classes, but attended retreat, what if they missed multiple classes but attended retreat? 
16. We defined intervention attrition as missing the quit day because it provides a simple and intuitive model for understanding completion or non-completion of the intervention. For instance, attending the quit day assured us that participants had made a quit attempt, whereas not attending the quit day suggested that it was most likely that they had not. Furthermore, quit day attendance reflected overall class attendance fairly well. Review of the data shows that all participants who attended four or more classes also attended the Quit Day Retreat and that all who attended 1 or less class also did not attend the Quit Day Retreat. It seemed cumbersome to spell this out in the manuscript, but to add some clarity to the attrition results we have modified the text to read: “Intervention attrition was defined as non-attendance at the Quit Day Retreat. All participants who attended the Quit Day Retreat also attended the 2-week post quit assessment visit. Attrition for all participants from randomization to assessment visit was 55% with no significant difference between groups (MTS = 50.0%, ILS Controls = 60.0%), $\chi^2(1, N = 55) = 0.55, p = .46.$”

17) Page 12. specify 2-week post-quit study visit on third line from bottom. What is reason for listing all reasons for attrition? 
17. The list of reasons for attrition is not necessary to the manuscript and has been omitted.

18) Page 13. The conclusions in the discussion overview of findings seem to go beyond the data in number 1 re: smoking abstinence. Remember MTS had higher percent abstinent, but that was non-significant finding and odds ratio CI includes 1. 
18. 1) This text has been modified and now reads: “In our primary outcome, point prevalent smoking abstinence was higher in MTS than controls, but the difference was not significant. As a secondary outcome, MTS compared to ILS participants showed significantly greater number of days abstinent in the first two weeks.”

19) Page 14. Top of first paragraph—ILS not ITS. 
19. Thank you for catching this error! We have changed the text to “ILS.”
20) Page 14. Is it possible ILS was actually leading to worse retention than a standard control? You are not comparing MTS to a well-validated active control, but rather to a novel active control, which may actually be detrimental to retention or worsen smoking. I would discuss this as a limitation and temper the conclusions.

20. We have added this as a limitation in our discussion section. Text in the discussion now reads: “This finding might suggest that mindfulness training did not deter participants from completing the intervention. On the other hand, because ILS was a novel, previously unstudied control, it is possible that the ILS intervention may have actually led to worse retention and worse smoking outcomes.”

21) Page 14. no need to capitalize meditation/walking

21. We have changed meditation/walking to lowercase.

22) Page 15. why are the n=50 and n=40 included in the first paragraph. We usually don’t include those for other people’s studies we are referencing in a discussion.

22. We have omitted these n’s from the discussion section.

23) Page 15. isn’t this speculation?—“the change is not large enough…, but if a relationship is present, then mindfulness…. would be particularly effective…”

23. We have removed this speculative statement from the paper.

24) Page 17. Yes, treatment effect sizes were fairly large, and this would be good data for a grant application to conduct a larger study, but I worry that you may mislead reader by stating “large effect”, while it happens to be non-significant.

24. We have omitted the statement of the “effect” of MTS in our concluding paragraph. The text now reads: “Primary findings from this study suggest that MTS, compared to a closely matched control, produced non-significant increases in short-term (2-week) smoking abstinence and showed reasonable acceptability among those who completed the intervention.”

25) Page 17. Line 4. thank you for stating that participants most interested in mindfulness might be most well retained—this is an important limitation especially when you have done a completers analysis.

25. Thank you.

26) Table 2: I recommend removing number of yrs smoked and number of quit attempts—these were not taken at baseline and represent a skewed sample of just completers. It is confusing. Do you have this from baseline—if so were they different at baseline?

26. We have removed number of years smoked and number of quit attempts from the paper.

27) Were there predictors of retention or dropout in this study?

27. We found no correlations with attrition and baseline variables and we have added a table 4 to show comparison of baseline data for completers with non-completers. Text in the Results section has been modified to read: “We found no predictors for attrition, including age, gender, FTND, FMI, DTS, PSS or WISDM. When comparing those who attended the two-week post-quit assessment visit (completers) to those who did not (non-completers) on
baseline variables, we found no significant differences between intervention randomization, gender, ethnicity, age, FTND, FMI, DTS, PSS, or WISDM (Table 4), but did find that completers reported smoking fewer cigarettes per day at baseline (11.88, SD = 3.00) than non-completers (15.30, SD = 7.89), \( t(53) = 2.19, p = .04. \)

Overall, I commend the authors on conducting this important study and preparing the data for publication. Publishing negative trials are important for the field, and the sample size and retention difficulties are substantial limitations that every behavioral therapy researcher understands; however, it is still important not to overstate the findings or speculate about them in the abstract, results and the discussion. The analyses should be repeated with all subjects included, and then see which findings are still significant. Outcome variables that were not apriori specified generally represent secondary analyses and should be noted as that. The secondary analyses, such as the relationship between smoking abstinence and alcohol use reduction, which is a statistically significant finding could benefit from more discussion in the manuscript. Overall, this is an important study to be published that should be published after some additional analyses and more careful language around the interpretation of the findings. Clearly, while this manuscript is being edited for publication, a grant should be written to replicate this trial in a larger sample to see if the differences and trends found here can be substantiated, possibly with a previously studied control group or in a three-arm trial with ILS and a more traditional control.

As mentioned above, the findings of this paper have been re-written in all sections so that they do not overstate the results. At the request of another reviewer, the paper has been shortened where ever possible and is about 1 page shorter in length. Thank you again for your helpful recommendations.

James Davis
Response to Reviewer 2, Steven Ames:

Major Compulsory Revisions

(1) The second paragraph of the Background section contains text that is substantially similar to text found in the first paragraph of the Introduction of the following prior publication: Ames et al. (2010). Integrated smoking cessation and binge drinking intervention for young adults: A pilot investigation. Annals of Behavioral Medicine, 40, 343-349. I suggest modifying the text substantially to avoid concerns of plagiarism.

Dr. Ames, I am both disturbed and embarrassed to find that this occurred. As this is my manuscript and my research group, I take responsibility and apologize to you for this serious error. Occasionally, I will have a promising research assistant look up references and help develop background section for a manuscript. In this case, I asked such a research assistant to look at your paper and make reference to it in our background section. I did not realize that the student had used your writing almost exactly. The section provided to me was nicely written so I did not substantially modify it from the student’s draft during later edits. It is clear to me now that I did not explain the rules or seriousness of plagiarism to this research assistant. The student has been reprimanded and the paragraph has been edited. I am thankful that the manuscript was sent to you so that you might recognize this and that you might give me the opportunity to apologize and make appropriate edits. Again, I would like to apologize to you for this serious error and assure you that substantive edits have been made to our manuscript and that steps have been taken to ensure that this does not happen again in our lab. This text now reads:

“Over the last 50 years, there have been only a small number of studies published on smoking interventions targeted to young adults [20]. These include a 1972 study in which male undergraduate smokers were exposed to 24 hours of sensory deprivation as a smoking cessation therapy [21], a 1988 study that compared a brief counseling intervention vs. no intervention [22], a 1990 study that evaluated a behavioral therapy in undergraduate smokers [23], and a 2007 study that applied a brief office intervention vs. the same plus expressive writing in young adult smokers [24].”

(2) Recruitment took place over a rather lengthy period of time (i.e., 9 months) and resulted in many calls (468 callers) in order to yield 55 smokers being randomized. Given the difficulty of recruiting and engaging young adults to participate in smoking cessation clinical trials, providing more detail about recruitment efforts would be of value to readers.

Recruitment for this population was challenging for several reasons. The main reason for exclusion to the study was that callers did not drink enough alcohol (at least 5 binges per month) to meet our criteria. Another issue making recruitment challenging is the large number of dropouts we had after scheduling for an orientation. A full two thirds of callers scheduled for an orientation did not come, despite our continued efforts. Our experience was that the population – their youth and rather chaotic lifestyle was mostly the cause of this. The project took considerable time because it studied the MTS and ILS interventions- each of which were seven weeks long. These interventions were provided sequentially so it took
repeated waves of recruitment reach a desired number of participants. We have modified the Results section to more information about recruitment dropout. We have also modified the discussion section to add more discussion on this issue as well. The paragraph on recruitment attrition in Results reads as follows:

“Recruitment efforts took place over 9 months to allow for multiple sequential 7-week interventions. We assessed 468 callers for eligibility via phone screening, and after declines and exclusions, we scheduled 215 callers for orientations. The main reason for exclusion was insufficient alcohol use (less than 5 binges per month). Of scheduled callers, 74 (34%) attended an orientation, after which 55 were randomized to MTS (N=30) or ILS (N=25). Among these 55 participants, a total of 25 (45%) completed treatment and testing, including 15 MTS participants and 10 ILS participants (Figure 1).”

Minor Essential Revisions
(1) When referring to the age of participants please list units, that is years.
1. We have added “years” whenever mentioning participant age.

Discretionary Revisions
(1) The manuscript is quite lengthy, consider reducing its length.

We have made an effort to reduce the overall size of the document. We removed approximately 2 pages of writing, and at the request of another reviewer we have removed figure 2. Unfortunately another reviewer has asked us to add additional information and table 4. After all requested edits, the length is about a page less than it was.