Published in final edited form as:

J Addict Med. 2019 ; 13(1): 81–82. doi:10.1097/ADM.0000000000000450.

Reply to Letter to Editor:

We appreciate the interest and thoughtful critique of our manuscript (Lammert et al, 2018). Howe (2018) raises important concerns which highlight limitations of this secondary subgroup analysis, however, these concerns should lead investigators to advocate for further exploration of the topic.

The results of this manuscript should be viewed in the context of the parent study. As detailed in the manuscript, results were from a secondary subgroup analysis of data collected prior to randomization in the parent study. The parent study recruited people who use tobacco to evaluate an intervention (exogenous progesterone vs. placebo) to help with smoking cessation. We expanded recruitment to participants who used both marijuana and tobacco to increase the size of the sample and to collect pilot data.

We offer an explanation and correction to several points raised by Howe. The inclusion criteria for this study included self-report of no hormonal contraceptive use, regular menstrual cycles for at least the past 3 months and negative pregnancy tests at each visit. Women with polycystic ovarian syndrome would not likely have regular menstrual cycles as they have chronic anovulation resulting in oligomenorrhea or amenorrhea among other symptoms (Strauss and Barbieri, 2013) and therefore would have been excluded from the parent study. This secondary subgroup analysis included all 13 female participants who co-used marijuana and tobacco in the parent study. Three of the 13 participants who co-used marijuana and tobacco were > 45 years of age but all were age matched to participants who used tobacco only, and they met the inclusion criterion for the parent study. Although we agree a better cutoff would have been 45 years of age we chose to use a method to control for age and to include all the women who co-used given our small sample size.

Identifying the start of the luteal phase was important to the parent study because our goal was to time a quit attempt in the luteal phase of the menstrual cycle. Our previous work suggests that women have better smoking cessation outcomes when they quit smoking in the luteal phase (Allen et al. 2009, 2010, 2013). We have used First Response LH testing in our previous work and have had 98% (Allen et al. 2014) accuracy in serum confirmed luteal phase identification with LH testing and back counting between cycles. The manufacturer recommends first morning urine testing. Further, such specimens are most accurate in identifying a LH surge because the LH is more concentrated; thus we chose first morning urine samples. Our team works to balance participant burden while using recommended data collection methods.

Regarding the assertion that progesterone levels were not able to be used to confirm ovulation, participants came in 0–4 days after their LH surge and completed a baseline appointment, collected baseline measures and were randomized to the parent study intervention, progesterone vs placebo. Progesterone levels were collected one week after baseline, 7–11 days following the LH surge. These samples were not available to confirm

luteal phase accurately because participants were taking exogenous progesterone or placebo and the results would be confounded. Further, this would have compromised the blind of the parent study. We concur that progesterone levels to confirm ovulation may have been a stronger methodology for this analysis. However, it is accepted that an LH surge is a reliable indication that ovulation will soon occur (Grinsted et al. 1989; Luciano et al. 1990).

While we recognize there are limitations of this secondary subgroup analysis, we reaffirm that using self-reported menstrual cycle and first morning urine LH testing is a reasonable method for identifying ovulation and luteal phase length (Allen et al. 2016). Our findings suggest that women who use marijuana and tobacco may have differences in cycle length compared to women who use tobacco only, and these findings warrant further exploration.

References

- Allen AM, McRae-Clark AL, Carlson S. et al. Determining menstrual phase in human biobehavioral research: A review with recommendations. *Experimental and Clinical Psychopharmacology* 2016 2;24(1):1–11. [PubMed: 26570992]
- Allen SS, Allen AM, Tosun N, et al. Smoking and menstrual-related symptomatology during short-term smoking abstinence by menstrual phase and depressive symptoms. *Addictive Behaviors* 2014 5;39(5):901–906. [PubMed: 24594903]
- Allen AM, al' Absi M, Lando H, et al. Menstrual phase, depressive symptoms, and allopregnanolone during short-term smoking cessation. *Experimental and Clinical Psychopharmacology* 2013;21(6): 427–433. [PubMed: 24059585]
- Allen AM, Allen SS, Lunos S, et al. Severity of withdrawal symptomatology in follicular versus luteal quitters: The combined effects of menstrual phase and withdrawal on smoking cessation outcome. *Addictive Behaviors* 2010;35(6):549–552. [PubMed: 20167436]
- Allen SS, Allen AM, Lunos S, et al. Patterns of self-selected smoking cessation attempts and relapse by menstrual phase. *Addictive Behaviors* 2009;34(11):928–931. [PubMed: 19501984]
- Grinsted J, Jacobsen JD, Grinsted L, et al. Prediction of ovulation. *Fertility and Sterility* 1989;52:388–393. [PubMed: 2776892]
- Howe RS. A flawed design produces flawed results. *J Addiction Med* 2018
- Lammert S, Harrison K, Tousin N, Allen SS. Menstrual cycle in women who co-use marijuana and tobacco. *J Addiction Med* 2018
- Luciano AA, Peluso J, Koch EI, et al. Temporal relationship and reliability of the clinical, hormonal, and ultrasonographic indices of ovulation in infertile women. *Obstetrics and Gynecology* 1990;75:412–416.
- Strauss JF, Barbieri RL. *Yen and Jaffe's Reproductive Endocrinology: 7 th Edition* Philadelphia: Elsevier/Saunders, 2013.