Enhancing Panic and Smoking Reduction Treatment with D-Cycloserine

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Data Analysis.

Overview. First, we will assess the equivalence of the treatment groups on key baseline variables (demographics, smoking characteristics, psychological variables); variables on which the groups differ will be used as a covariate in final analyses. We will then examine missing data patterns, dropout rates (see below), and distributional properties of measures and use transformations to improve distributions when necessary.

Following recommendations of the Society for Research on Nicotine and Tobacco (Hall et al., 2001), the effects of treatment on PPA will be examined using Generalized Linear Mixed Models (GLMM), employing the logistic linking function. In our GLMM analyses, the repeated measures will be nested within individuals, which will be nested within their treatment cohort, thereby appropriately accounting for correlated scores within the small cohorts. Our GLMM analysis will model outcome as a curvilinear (quadratic) or exponential function of time (based on AIC and BIC) since PPA is expected to decrease rapidly at first and then level off over time. Using this model, one can test differences between treatment groups by including treatment condition as an "individual level" predictor of rate of decrease in PPA over time. We can also examine treatment group differences in PPA at any assessment point. Multi-level models (MLMs) similar to the GLMM models will be used to test treatment differences in continuous outcomes (the psychological variables: withdrawal symptoms, negative affect, panic severity, distress intolerance, and anxiety sensitivity). All models will include relevant control variables (e.g., gender, education, nicotine dependence, etc.). We will also run a Cox proportional hazards survival analysis predicting risk of lapsing or relapsing to smoking and compare the two conditions on these outcomes.

Tests of specific aims. Aim 1a: Treatment differences in slopes will indicate different rates of decrease in PPA. To determine whether there are treatment differences in PPA at any particular time point (e.g., week 24), we will center the "Time" variable in the GLMM model at that time point (Singer & Willett, 2003). **Aim 1b:** Cox proportional hazard models will be used to test for differences between treatments in relative risk of lapse and relapse, and in time to first lapse and to relapse. ***Aim 2a:*** The same analyses in Aim 1a will be used in MLMs to test for treatment differences in the psychological outcomes (withdrawal symptoms, negative affect, panic severity, distress intolerance, anxiety sensitivity). ***Aim 3a:*** The "a" paths in our mediation model (see Figure 1 in Specific Aims) will be calculated as in Aim 2a. Because we expect the "a" paths to be moderated, separate analyses will be conducted to calculate the "a" paths for each treatment condition (Tein, Sandler, MacKinnon, & Wolchik, 2004). The "c" path will be calculated as in Aim 1a. ***Aim 3b:*** The "b" paths in our mediation model will be the regression coefficients for the mediators when all the mediators are simultaneously added to the GLMM equation predicting PPA used in Aim 1a. ***Aim 3c.*** Tests of the mediated pathways will be conducted separately for each treatment condition (due to moderated mediation [Tein et al., 2004]). Significance of mediated pathways will be determined using Bayesian bootstrap mediation analysis (Yuan & MacKinnon, 2009).

Missing Data. Following Hall et al. (2001) and Enders (2011), we will use pattern mixture modeling to assess the effect of missing data. We will rerun our analyses coding for various missing data patterns (no missing data, sporadic missing, dropouts, etc.) to determine both if missingness impacts our findings and how the differences between PSRT+DCS and PSRT+PBO depend on the missing data pattern.

Power Analysis. Because we will have a sample size of 80, this application is not powered to detect small differences between treatment conditions. However, consistent with the aims of a Stage IB study, our primary goal is determining 1) the feasibility of the new intervention and 2) whether a Stage II study is warranted. Below we estimate (for the lowest powered analyses) the effect sizes (ESs) that we will be able to detect as statistically significant with 80% power.

Aim 1a: GLMM model comparing PPA in the PSRT+DCS condition vs. the PSRT+PBO condition. We performed a Monte Carlo study to calculate the minimum PSRT+DCS PPA rate detectable by our analysis. Our assumptions were: an average of 5 assessments per participant (71% of the post quit date assessments) (Zvolensky et al., 2008) and a 27% PPA in PSRT+PBO at the last follow-up (Piper et al., 2010). We examined numerous PSRT+DCS PPA rates to determine the lowest rate detectable by our analysis, performing 1000 simulations for each PPA rate. The results indicated that we would have .80 power to detect a significant treatment effect if the PPA rate in PSRT+DCS at the follow-up was 43% or greater. This difference – i.e., 43% vs. 27% - is equivalent to a Cohen's ώ effect size (the effect size measure for proportions) of .17, between a small (.10) and medium (.30) ώ effect size (Cohen, 1988). Thus, we have sufficient power to detect a smaller than medium effect.

Aim 3: Moderated Mediation of changes in PPA. The first step in our moderated mediation power analysis was to determine the power to detect moderation of the "a" path (see Figure 1. Using the MLM power analysis program PinT 2.12 (Snijders & Bosker, 1993) to calculate our power to detect moderation of path "a", we found that we had over .95 power to detect a medium effect size (d = .50) for moderation of the "a" path. Next we calculated the power to detect longitudinal mediation for each treatment group, over time. For this analysis, path "a" was the slope of change in the mediator over time, and path "b" was the relation between the mediator and the outcome over time. We performed a Monte Carlo study to calculate the power for a bootstrap mediation analysis. We assumed that the effect sizes for the "a" paths (the change in the mediators over time) would be large (d>.80; see 3C.2a), the effect size for the "b" paths would be medium, and the PPA rates were assumed to be those found in Aim 1a (27% for PSRT+PBO and 43% for PSRT+DCS). The Monte Carlo study consisted of 400 samples, for each of which we performed a bootstrap mediation analysis each consisting of 1000 resamples. Results indicated that we would have at least .81 power to detect a mediated effect.