A Preliminary Investigation of Pre-Frontal Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Cannabis Use Disorder

Statistical Analysis Plan

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We calculated descriptive statistics such as means and standard deviations (SD) for all continuous variables and proportions for categorical variables. We compared demographic, screening, blinding, and adverse event variables (compiled using MEDra criteria) across condition and site using t-tests or the Wilcoxon Rank Sum test for continuous variables and the Chi-Square or Fisher's Exact test for categorical variables.

For Aim-1, we utilized a generalized linear mixed-effects model (GLMM) to perform the analyses, with the full ITT sample (N=72) and the total MCQ-SF score as the dependent measure. We used two types of a priori models for each analysis: 1) a three-way interaction model which included an interaction between treatment, site, and time, as well as the main effects of treatment, site, time, and all pairwise interactions between the main terms, and 2) a two-way interaction model which included treatment, time, an interaction between treatment and time, and site. We considered pre- and post- variables with a strong clinical rationale for inclusion in covariate adjustment including the amount of time since the last cannabis use, CWS score, the days-per-week of cannabis use, the grams of cannabis used per day, and the number of cannabis use sessions per day.

To assess group differences in the number of weeks of abstinence in the follow-up period (Aim-2a), a Poisson regression model was fit with the total number of weeks of self-reported abstinence in the four-week follow-up period as the dependent variable and treatment, site, and treatment by site interaction as independent variables. We conservatively imputed missing values as non-abstinent, thereby including the total ITT sample. We additionally performed a sensitivity analysis for weeks of abstinence by including the weeks preceding the 9th rTMS-treatment visit and immediate post-visit since these two weeks represent the time following the delivery of a total of 16-sessions of rTMS (a similar dose to early rTMS for depression studies). We calculated the relative risk of having a week of abstinence as a measure of the effect size, along with 95% confidence intervals. We used creatinine-corrected urine cannabinoids to verify self-reported abstinence at follow-up weeks 2 and 4, and calculated the proportion that these two methods were concordant.

To evaluate group differences in the number of days of cannabis use (Aim-2b), we utilized a GLMM with the number of days-per-week of cannabis use as the dependent measure. We included participants in the model who had follow-up data (the completer sample; N=51) and given the apparent divergence in days-per-week of cannabis use in the final two-weeks of the follow-up period, we chose to focus our analysis on that period.

Residual normality was assessed for each of the above models using QQ-plots. We included sex in all models to detect a potential effect, but when no significant effects were found, we excluded sex from the subsequent final models. Apart from craving, this was a pilot trial and not powered a priori to detect statistically significant differences; however, statistically significant *p*-values are noted when observed. When reported, a level of $\alpha = 0.05$ was used (two-tailed), and no adjustments for multiple comparisons were made for this preliminary investigation. Effect sizes at each time point were estimated as Cohens d using means and pooled standard deviations. Statistical analyses were conducted using R software (version 4.2.1, GNU project) and SAS version 9.4 (Cary, NC).