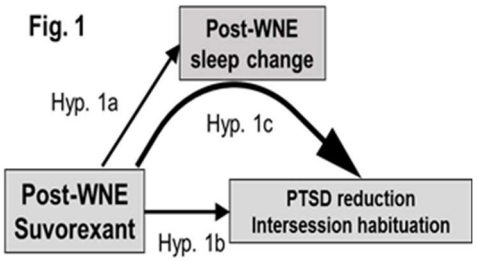
Statistical Analysis Plan

Official Title: Can Blocking the Orexin System Enhance Sleep's Benefits to Therapeutic Exposure for PTSD?

NCT number: NCT02849548

Date of the Document: July 7,2016

Data Analysis Plan: Initially, data will be pre-screened for errors, outliers, normality of distributions, and any necessary modifications such as transformation will then be conducted. The suvorexant and placebo groups will be compared on demographics and baseline measures using *t*-tests or chi-squared tests to examine group comparability. Fig. 1 describes each hypothesis. **Hypothesis 1a**: The primary comparison will be between the 2 groups (suvorexant vs. placebo) and sleep parameters measured at 3 time points (baseline, post-Session 1, and post-Session 3). A repeated-measures ANOVA will be performed to examine whether there is a Group x Time interaction effect on each sleep parameter of interest (i.e., N3, WASO, and REM sleep). If a significant interaction effect is found, group comparisons will be performed at each time point. **Hypothesis 1b:** A repeated-measures ANOVA will be performed to examine whether there is a Group x Time interaction effect on CAPS scores. In addition, 2(Group) x 2(Time) ANOVAs will be performed to examine if there is an interaction effect on intersession habituation between Session 1 & 2 and between Session 3 & 4, using a baseline-corrected highest average pulse rate as a dependent variable. **Hypothesis 1c**: To examine indirect effects of suvorexant on PTSD through the mediator, post-WNE sleep change, a path analysis using bootstrapping procedures will be performed for each sleep parameter of interest using SPSS macros developed by Preacher & Hayes.[70] Baseline CAPS scores will be included as a covariate. The same method will be used to examine indirect effects of suvorexant on intersession habituation.



Power considerations. G*Power[71] was used to perform power analysis. α = .05 was applied in all analyses. We estimate that 54 participants (27 in each group) will complete protocol (see the Feasibility section). **Hypothesis 1a:** The primary outcomes for power evaluation are WASO and REM sleep. The prior studies suggest small effects of suvorexant on N3; therefore, it was not considered for power evaluation. Herring et al's clinical trials[48,50] showed that effect sizes of one night of 20/15mg suvorexant on WASO and REM sleep (minutes and %) were *f* = -0.37, 0.32, and 0.22, respectively. A total of 16, 22, and 50 participants are needed to detect a Group x Time effect on WASO and REM sleep in minutes and percentage, respectively, with 80% power. Since no studies have examined effects of suvorexant on PTSD, power analysis for **Hypothesis 1b** is based on effect sizes found in Taylor et al's'[44] clinical trial of prazosin in civilian outpatients with PTSD. 12 participants are needed to detect the effect size found in this trial (*f* = 0.40). **Hypothesis 1c**: Sizes of the indirect effects of suvorexant on PTSD and intersession habituation through post-WNE sleep change are unknown. We selected the bootstrapping procedure as it is more powerful than Sobel test.[72]

The proposed study also includes comparisons of several other variables. The relative sample size required for multiple comparisons of variables (between 10-20) allowing for Bonferroni-adjusted test to achieve 80% power relative to the sample size required for a nominal is only 3.[73] The proposed sample size of 54 will, therefore, have adequate power to detect medium to large effects in our planned analyses. Statistical significance of effects and their clinical importance will be carefully considered in data interpretation to inform the development of subsequent grant applications.