BROWN
School of Public Health

Center Alcohol and Addiction Studies

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TITLE: A Pilot Study on the safety and efficacy of Mifepristone for the prevention of relapses of alcohol drinking

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Statistical analysis

Distributional characteristics of outcome measures were examined to evaluate similarity to the normal distribution, detailed descriptive analysis of demographics, substance use, and clinical characteristics were conducted. Comparisons with these characteristics, in relation to enrolled versus completer status, were performed using *t*-tests to analyze continuous variables (e.g., age) and Chi square (χ^2) for categorical variables (e.g., sex, race, smoking status). Attrition rates between the screening visit and follow-up visit were examined descriptively to assess for potential bias. In addition, a logistic regression was performed to test for possible bias due to period (A/B: placebo first, then mifepristone and B/A: mifepristone first, then placebo) or medication carryover (1: placebo and 2: mifepristone), as done in our prior cross-over trial[1].

Primary outcomes: safety and tolerability of oral administration of mifepristone was assessed after 7 days in outpatient setting, and when it was administered with yohimbine and alcohol during the laboratory paradigms. These analyses included comparing the number of adverse events (AEs) between the mifepristone and placebo condition via a χ^2 test. The results were presented using summary statistics such as number of subjects (*n*); mean (*M*); standard deviation (*SEM*) or frequency distributions (%).

Primary outcomes: safety and tolerability assessed by the number of adverse events (AEs) of oral administration of mifepristone was assessed after 7 days in an outpatient setting, and when it was administered with yohimbine and alcohol during the laboratory paradigms. Additional safety and tolerability analysis included hemodynamic response, alcohol pharmacokinetics, and subjective effects of alcohol between the mifepristone and placebo condition (χ^2 test).

Secondary outcomes: Craving measures included alcohol craving questionnaire short form-revised (ACQ-SF-R)[2]. Values of the water trials for each dependent variable were inserted as covariate in the model (allowed for the dependent variable to be specific for alcohol), time coded: t_1=alcohol trial 1 and t_2=alcohol trial 2. In the bar laboratory, alcohol consumption was measured by number of drinks consumed (*t*-test). In the outpatient setting, alcohol consumption was measured by self-report using the timeline follow back method, reported as heavy drinking days and drinks per week.

All statistical analysis was performed after participants had their follow-up visit and the study database had been locked. All the statistical procedures were performed by IBM SPSS Statistics for Windows, version 27 with Macro MEMORE extension[9] (IBM Corp., Armonk, NY, USA) and GraphPad Prism (v.5) was used to generate figures (La Jolla, CA, USA). The effect sizes were calculated as η^2 for GLM and Cohen *d* for *t*-test. All statistical tests were two-tailed, and statistical significance was accepted if an alpha value $p<.05$ was obtained.

For all outcomes, we utilized an intention-to-treat (ITT) approach, where participants were examined based on their *a priori* randomized protocol and received at least one dose of the study medication

(mifepristone or placebo)[3]. All analyses were conducted using Generalized Estimating Equations (GEE)[4] with robust standard errors, and an unstructured correlation matrix, unless noted.

Power

This was a proof-of-concept trial to demonstrate the feasibility of the combined study design, the safety and tolerability of mifepristone and yohimbine while consuming alcohol, and the potential value of testing mifepristone in an appropriately-powered larger RCT. In selecting a target sample size, we balanced power considerations and feasibility given the translational nature of this trial. Because of the within-subjects design, power to test the effects of study drug is optimized for this modest sample size (originally *N*=20 then, after additional funding, increased to *N*=32). For the safety and tolerability outcomes (primary) adverse events difference was detected based on a judgement concerning the minimal effect which has clinical relevance in the management of patients. In a noninferiority trial, the exact sample size cannot be fixed in advance because it depends upon the chosen stopping guideline[5].

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