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Study Protocol with SAP

Design overview

The study was a randomized, double-blinded, placebo-controlled treatment trial evaluating varenicline combined with nicotine patch and counseling compared with placebo plus nicotine patch and counseling on smoking cessation and drinking behavior in HDS. The study was fully approved by the University of Chicago Institutional Review Board.

Participants were enrolled between February 2018-February 2020. The majority of study visits (88%) took place at the Clinical Addictions Research Laboratory – East facility at the University of Chicago and 12% of visits were conducted at the Respiratory Health Association of Chicago. Participants were recruited via advertisements on social media, public transit and community outreach to local organizations. Candidates completed a brief phone interview and those deemed eligible were invited to an in-person screening visit. Eligibility criteria included age 18-85 years, seeking treatment for smoking cessation, smoking $\geq$5 and $\leq$ 30 cigarettes daily, English fluency, $\geq 8^{th}$ grade education, stable residence, and no history of adverse reactions to varenicline or nicotine patch. Candidates were also required to meet hazardous drinking levels consistent with the National Institute on Alcohol and Alcoholism (NIAAA) guidelines [>14/7 drinks weekly for men/women and ≥1 heavy drinking days (>5/4 drinks per occasion for men/women) per month for the past year] (National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2005). Desire to change drinking was not a requirement for enrollment. Individuals with any major medical or psychiatric contraindications, including uncontrolled hypertension, history of seizures, liver enzymes outside of the normal range, current suicidal ideation, and severe alcohol withdrawal

symptoms when stopping drinking, determined by the study physician to be at significant risk for adverse interactions with study medications or measures were deemed ineligible and were not included. Also for women, current pregnancy or breastfeeding, plans to become pregnant in the next three months, or not using effective birth control were reasons for non-inclusion.

At the screening visit, candidates completed surveys on demographics, medical history, smoking, mood, and substance use history. They also completed a Fagerström Test for Cigarette Dependence (Fagerström, 2012), the Structured Clinical Interview for DSM-IV, nonpatient version (First et al., 1995), the Columbia Suicide Severity Rating Scale (CSSRS; Posner et al., 2011), the Alcohol Use Disorder Identification Test (AUDIT; Babor et al., 2001), and a Timeline Follow-back Interview of past month (28-day) daily cigarette and alcohol use. Upon arrival, candidates were required to have a breath alcohol concentration of 0.00 g/dl, a score < 10 on the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar; Sullivan et al., 1989), and test negative for all drugs of abuse (except cannabis). Individuals deemed eligible at in-person screening were accepted into the study and worked with the research assistant to schedule their 4 study visits with their target smoking quit date on the second study visit.

Randomization and interventions

Randomization to varenicline or placebo was stratified by sex and smoking level (light, <10 cigs/day vs heavy, ≥10 cigs/day). Pfizer, Inc. supplied both the varenicline and matching placebo pills. Participants and research staff were blind to treatment assignments throughout the study. Study participation began with the randomization visit occurring one week prior to the scheduled quit date. Subsequent study visits occurred on quit day (week 0), week 2, and week 12 (end of treatment). The follow-up assessment took place at week 26. Medication was started one week before the target quit date. The titration for varenicline followed the standard dosing regimen: 0.5 mg once daily for 3 days, 0.5 twice daily for 4 days, and 1 mg twice daily for the remainder of the 12 weeks of treatment. After

Week 12, participants were given the option for a down-titration dosing schedule of 0.5 mg twice daily for 4 days and then 0.5 mg once daily for 3 days. Participants assigned to placebo received identical-appearing tablets with the same dosing instructions. Dose reductions were allowed and participants who discontinued medication could continue attending counseling and research sessions and continue receiving nicotine patches. All participants initiated nicotine patch on quit day and continued daily at dosing levels recommended by the manufacturer for 10 weeks (i.e. lighter smokers: 14 mg daily for first 6 weeks then 7 mg daily for 4 weeks; heavier smokers: 21 mg daily for the first 6 weeks, then 14 mg daily for 2 weeks, and then 7 mg daily for 2 weeks). Medication and patch compliance was monitored through a combination of pill and patch counts returned at each study visit and self-reported daily log entries of pill and patch use that participants completed at home and returned to each study visit.

At the first two study visits, participants met with a trained smoking cessation facilitator and received semistructured, individual counseling sessions adapted from Courage to Quit, an evidence-based smoking cessation intervention developed by the principal investigator (A.K.; Asvat et al., 2014). At the randomization visit, the 30-45 minute counseling session supported medication adherence and discussed preparing for quit day, which was set to occur on the same day as completing the varenicline up-titration. At the quit day visit, the 15-20 minute counseling session addressed techniques for coping with smoking urges and nicotine withdrawal symptoms.

Participants received $60 in compensation at the end of treatment and $40 for the follow-up at week 26. Individuals who indicated past-week smoking abstinence at follow-up attended an in person visit for biochemical verification and were eligible for an additional $20-$50 in compensation from a random drawing.

Assessments

At each of the four study visits, participants completed breath tests for CO and alcohol, vital sign readings, and body weight measurements, as well as the following interviews: CIWA-Ar, CSSRS, and

Timeline Follow-back for daily cigarette and alcohol use since the prior visit. Participants also returned any unused pills and patches and a completed calendar log of daily pill and patch use. The Brief Questionnaire of Smoking Urges (Cox et al., 2001) and Minnesota Nicotine Withdrawal Scale-Revised (Hughes, 2017) were also administered at each visit. In addition, participants completed a 16-item assessment of varenicline and nicotine patch adverse effects during the week prior to their visit and, if present, rated their experiences as mild, moderate, or severe.

Statistical analysis

Demographic and baseline characteristics were compared between groups using Student's *t* test, chi-square test, or Fisher's exact test of independence as appropriate. The primary outcome was continuous cigarette abstinence during weeks 9-12 of treatment as confirmed by a breath CO reading of ≤ 10 ppm at the week 12 visit. A logistic regression model adjusting for baseline cigarettes per smoking day analyzed this outcome, as well as the 7-day point prevalence of smoking abstinence at week 26. Self-reported continuous smoking abstinence throughout 12 weeks of active treatment were compared by a Cox Hazard model adjusting baseline cigarettes per smoking day. For these analyses, all randomized participants (i.e. those who received at least one medication dose as the first dose was taken under observation during the first study visit) were included, with drop-outs conservatively classified as relapsed to smoking. Due to local mandatory quarantine restrictions imposed as a result of the COVID-19 pandemic, thirteen participants (varenicline, n=9; placebo, n=4) were unable to complete their week 12 visit in-person and thus, their smoking statuses could not be biochemically verified. Of these participants, nine (varenicline, n=7; placebo, n=2) self-reported smoking abstinence during weeks 9-12 and were treated as abstinent in analyses of smoking outcomes.

For the drinking outcomes among those who did not drop out of the study, Generalized Estimating Equation models were used to compare changes from baseline in drinks per week and weekly heavy drinking days between medication condition during the 12-week treatment period. For

baseline drinks per week, 3 subjects were identified as outliers (>3 SD above the mean) and as a result, their data were normalized to 3 SD of the sample mean prior to analysis. At week 26, Changes from baseline drinks per week and weekly heavy drinking days were compared by t-tests.

Sample size calculations were based on data obtained from several studies examining varenicline on smoking and drinking outcomes and our past community-based smoking cessation intervention study (King et al., 2012). Varenicline's effect was obtained from prior research on quit rates (44%; Burke et al., 2016; Jorenby et al., 2006) and as the placebo group was receiving an active treatment, we expected slightly higher quit rates compared to those obtained in earlier varenicline clinical trials (18%). Therefore, we deemed 61 subjects per group to be sufficient to detect a significant difference between groups with 80% power and at a 0.05 level of significance.

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