Suvorexant to reduce symptoms of nicotine use: A double-blind, placebo-controlled study

NCT04234997

Version Date: 10/12/2023

Title: Suvorexant to reduce symptoms of nicotine use: A double-blind, placebo-controlled study

Principal Investigator: Robert Suchting
Co-Investigators: Scott D. Lane, Joy M. Schmitz, Michael F. Weaver, Luba Yammine, Jin H. Yoon

ABSTRACT

Background Cigarette smoking is the number one preventable cause of death and morbidity in the US[1,2]. A number of FDA-approved pharmacotherapies for smoking are available, however the vast majority of smokers do not respond to these medications and relapse is highly common[3]. Risk of relapse is particularly high immediately after the initial quit attempt when nicotine withdrawal symptoms are the strongest[4]. These findings highlight the need to continue developing novel therapies that can address smoking relapse, particularly during the initial quit attempt when relapse risk is greatest. Within the hypothalamus, the orexin (aka hypocretin) system is involved in maintaining homeostatic processes (i.e., sleep/wakefulness, food intake, etc.) through negative-feedback mechanisms. However, the orexin system also has extra-hypothalamic projections into multiple brain areas pertinent to substance use disorders (SUDs). These areas map on well to factors known to precipitate smoking relapse such as 1) disrupted sleep, 2) dysregulated stress and anxiety, 3) reaction to drug-related stimuli, and 4) drug reward. Results from both pre-clinical and recent human studies support the orexin system as a promising target to address smoking relapse. However, important human translational studies are needed carefully assessing how orexin engages each target of relapse risk.
Proposed Study A randomized, double-blind, parallel group, placebo-controlled design will assess an orexin receptor antagonist (suvorexant 0 vs. 20 mg) on relapse risk following overnight smoking abstinence among cigarette smokers. The ultimate goal will be to assess the impact of the orexin system on smoking relapse in a human laboratory model. Primary measures of interest will include (1) a two-component smoking relapse model (latency to smoking; reward magnitude) in which participants will have the opportunity to smoke their own cigarettes, (2) self-reported nicotine craving and withdrawal, (3) sleep metrics using self-report and actigraphy, and (4) self-reported changes in stress, anxiety, and stress reactivity using a modified cold-pressor task with a social component demonstrated to increase stress response. The current proposal seeks to obtain critical pilot data to support a future NIH grant application. To that end, the present study will demonstrate our ability to evaluate laboratory-based measures of smoking relapse risk and objective measures of sleep obtained using sleep-watch actigraphy.

PRIMARY HYPOTHESES AND SPECIFIC AIMS

Specific Aim 1: Assess the impact of suvorexant on established measures of smoking relapse risk (craving, withdrawal, stress reactivity, latency to self-administration).
Hypothesis 1: Participants receiving suvorexant (vs. placebo) will demonstrate lower craving, stress reactivity, and longer latency to self-administration of cigarettes in a human laboratory experiment.
Specific Aim 2: Validate the somnolent effect of suvorexant on sleep metrics in a sample of individuals with tobacco use disorder.
Hypothesis 2: Participants receiving suvorexant (vs. placebo) will demonstrate superior sleep metrics, including higher perceived sleep quality, longer duration of sleep, lower restless sleep).
Exploratory Aim: Examine the potential moderating effect of suvorexant on the relationship between sleep metrics and established measures of smoking relapse (noted in Aim 1).
Exploratory Hypothesis The relationship between superior sleep metrics (quality, duration, restlessness) and measures of smoking relapse risk (lower craving, withdrawal, stress reactivity, and latency) will be magnified in participants receiving suvorexant (vs. placebo).

1. BACKGROUND AND RATIONALE

Public Health Impact of Smoking and Treatment Challenges Smoking is the leading cause of death and morbidity in the U.S., responsible for nearly half a million deaths annually[1,5]. FDA-approved pharmacotherapies for smoking cessation (i.e., nicotine replacement therapy, bupropion, varenicline) significantly increase the likelihood of smoking abstinence, but relapse continues to be a significant challenge[3]. Among the millions of smokers that attempt to quit each year, most relapse within a few days of attempt[4]. This finding is

unfortunate as remaining abstinent during the initial two weeks of the quit attempt is a robust and reliable predictor of longer-term abstinence, even when abstinence is promoted with pharmacotherapy or intensive behavioral intervention[6–9]. These results highlight the importance of identifying interventions that can address relapse risk early in the quit attempt.

Potential Targets to Address Early Smoking Relapse Withdrawal from cigarette smoking is associated with a number of dysphoric symptoms that can precipitate smoking relapse. Below, we describe a number of key risk factors that have the potential to be addressed by targeting the orexin system.

Dysregulated Sleep Smokers have poorer sleep compared to non-smokers across virtually every measure of sleep quality (i.e., latency to sleep, quality of sleep, duration of sleep, time spent in deep sleep, rates of insomnia, daytime sleepiness, etc.) in studies using polysomnography as well as self-report[10]. Smoking cessation can exacerbate poor sleep[11] and insomnia is a clinically verified symptom of nicotine withdrawal reported by up to 42% of abstinent smokers[12–14]. Studies using polysomnography and sleep diaries report reduced sleep quality shortly after smoking cessation, which normalizes 3 to 12 months later[12,15–19]. A recent review assessed 10 studies that explicitly examined sleep metrics in relation to smoking cessation outcomes[10]. Of 10 studies, 8 noted that sleep metrics measured before and/or during cessation predicted smoking relapse. Only one study assessed a sleep intervention (cognitive-behavioral therapy for insomnia) and observed better reported sleep quality and greater latency to smoking relapse[20]. Interestingly, although current of FDA-approved pharmacotherapies for smoking (i.e., NRT, bupropion, varenicline) can alleviate nicotine withdrawal and craving, they all have side effects that negatively affect sleep quality (e.g., vivid dreams, insomnia, etc.). Taken together, these findings mark sleep as an important clinical target that can be impacted through clinical interventions that subsequently improve smoking outcomes.

Stress and Anxiety Stress and anxiety contribute to all phases of in the development of SUDs and are intimately connected with cigarette smoking[21]. Exposure to stressors in a human laboratory setting increases craving to smoke[22–24]. Smoking rates are significantly higher among populations with stress and anxiety disorders compared to the general population[25–29], and stress relief and relaxation are commonly cited as reasons for smoking[30–33]. Smoking dose-dependently activates the HPA-axis[34–39], and smoking cessation results in HPA-axis hypoactivity, which is associated with more severe withdrawal and craving as well as predictive increased risk of smoking relapse[11,40,41].

The Orexin System The orexins are a class of recently discovered amino acid peptides concentrated in the hypothalamus with projections widely distributed throughout the brain including the mesolimbic reward pathway[42,43]. The orexin system is neuromodulatory, increasing neural action potentials via the regulation of glutamate and GABA. A primary role appears to be in energy homeostasis, which affects systems associated with sleep, stress/anxiety, arousal, vigilance, and reward modulation[44–48]. In regards to nicotine, blocking orexin transmission reduces nicotine self-administration and seeking in rats[43]. In humans, a recent study observed that decreased orexin levels during the initial 24 hours of abstinence independently predicted time to smoking relapse[49]. Suvorexant is an FDA-approved, schedule IV compound indicated for the treatment of insomnia. Suvorexant is an antagonist for the two currently identified orexin receptors, OX1R/OX2R, and the only compound available in the US with specificity for the orexin receptor system. We recently completed a clinical trial assessing the effects of two weeks of suvorexant on inhibitory control, drug-cue reactivity, anxiety/stress, and sleep among non-treatment seeking individuals with cocaine use disorder[50]. This study was the first human laboratory-based experiment to examine the orexin system in human psychostimulant users, and the current proposal represents a natural extension of that study to cigarette smoking.

METHODS

Study Design To accomplish the project aims, we will utilize a randomized, double-blind, parallel group, placebo-controlled design, whereby consenting participants will be block-randomized to receive suvorexant 0 mg or 20 mg. Randomization will be stratified on tobacco use disorder severity (lower vs. higher defined by Fagerström Test for Nicotine Dependence (FTND) scores < 5 vs. ≥ 5, respectively). **Table 1** (below) provides an outline of study-related procedures and assessments.

Table 1. Outline of procedures and assessments

	BL	Day 1	Day 8
Baseline Screening Physical Exam, Medical History, Labs, ECG, Urine Pregnancy Test, SCID, ASI, KMSK, TLFB	X		
Smoking Related Measures FTND QSU, MNWQ, Self-Report, Breath CO	 X X	 X	 X
Stress/Anxiety Related Measures HAM-A, PSS, DASS-21, VAS	X	X	X
Sleep Related Measures PROMIS Sleep Disturbance Short Form, Epworth, PSQI Actigraphy Sleep Monitoring (Garmin Vívosmart® 3)	X	 X	X
Receive 7 days of suvorexant (0 or 20 mg)		X	
Relapse Risk Assessment Stress Reactivity Assessment (HR, BP, salivary cortisol, VAS) Dual-Component Smoking Relapse Assessment		 X X	 X X

SCID - Structured Clinical Interview for DSM-5**, ASI** - Addiction Severity Index; **KMSK** - Kreek-McHugh-Schluger-Kellogg scale; **TLFB** - Timeline Followback; **FTND** – Fagerstrom Test for Nicotine Dependence; **QSU** – Questionnaire on Smoking Urges-brief; **MNWQ** – Minnesota Nicotine Withdrawal Questionnaire; **CO** – Carbon Monoxide; **HAM-A** – Hamilton Anxiety Rating Scale; **PSS** – Perceived Stress Scale**; DASS-21** – Depression Anxiety Stress Scales; **VAS** – Visual Analog Scale; PSQI – Pittsburgh Sleep Quality Index; **HR** – Heart Rate; **BP** – Blood Pressure

Participant Recruitment and Setting (***N* = 20, n = 10/group**) will consist of otherwise healthy, cigarette smokers that report smoking at least 10 cigarettes/day, are between 18 and 65 years old and fluent in English, without greater than mild substance use disorder on drugs other than nicotine. Because suvorexant is a sedative-hypnotic contraindicated with alcohol use, participants will be excluded if they: meet DSM-5 criteria for an alcohol use disorder; report recent problem drinking (5/4 drinks for males/females in < 2.5 hours or > 10 alcoholic drinks per week); report being unwilling to stop using alcohol in the evening for the two weeks of the study; are pregnant, nursing, or planning on becoming pregnant during the course of the study; or if they have any other illness, condition, or use of medications which in the opinion of the PI and/or admitting physician would preclude safe and/or successful completion of the study. Recruitment strategies will include local advertising in print media, public service announcements on radio, and referrals to Center for Neurobehavioral Research on Addiction (CNRA) in the Houston metropolitan area. We will also recruit from the Department of Psychiatry Recruitment Registry: HSC-MS-23-0768.

Research Team **PI: Robert Suchting, Ph.D.** Dr. Suchting is an Assistant Professor in the Department of Psychiatry & Behavioral Sciences, with a primary research program involving novel applications of biostatistics and data science to health outcomes. However, his recent endeavors have expanded to first-hand research in substance use disorders and psychopharmacology, resulting in two pertinent first-author publications investigating (1) the effects of suvorexant on relapse-related factors in cocaine use disorder[50] and (2) the strongest predictors of the first smoking lapse during a quit attempt[51]. The present study will be supported by the infrastructure and research team at the CNRA, including **Jin Yoon, Ph.D.**, a frequent collaborator of the PI that will assist in the implementation of the current experimental design, and mentorship from **Scott Lane, Ph.D.**, with expertise in psychopharmacology and the neurological bases for addiction.

Study Medication & Medication Compliance Participants will be randomized to receive either suvorexant 0 or 20 mg for 7 days. 20 mg is currently the highest FDA-approved dose. The bioavailability of suvorexant is > 80% and it is highly protein-bound, with a half-life of approximately 12 hours and plasma steady-state is reached within three days [52]. Because suvorexant is a hypnotic with a moderate half-life, participants will be informed to take the medication at 10:00 PM. Compliance will be assessed using both Medication Event Monitoring Systems (MEMS) pill bottles that record the time/frequency of bottle openings as well as riboflavin.

Measures

Baseline Screening As part of the CNRA general evaluation protocol (HSC-MS-05-0322), to determine eligibility, participants will receive a comprehensive medical and psychiatric evaluation including: a medical-history questionnaire, physical examination, laboratory chemistries (e.g., blood chemistry screen, complete blood count, urinalysis and urine pregnancy test), and ECG. Clinicians will conduct the **SCID**, the **ASI**[53], the **KMSK**[54] assessment of lifetime substance use interview, and **TLFB**[55].

Smoking-Related Measures Nicotine dependence will be assessed using the **FTND**[56].Self-report will be used to collect self-reported number of cigarettes used in the past 7 days. Nicotine craving will be assessed using a brief, 10-item version of the **Questionnaire of Smoking Urges (QSU-brief)**[57]. Nicotine withdrawal will be assessed using the 8-item **MNWQ**[58]. **Breath CO** will be used to measure severity of smoking and overnight smoking abstinence.

Sleep-Related Measures Quality of sleep in the past week will be primarily assessed using the **PROMIS Sleep Disturbance Short Form**[59], a well validated and reliable subjective measure of sleep quality. Secondary measures will include the **Epworth Sleepiness Scale**[60], and **PSQI**[61]**.** Sleep actigraphy (total hours, levels, and movement) will be measured via the Garmin Vívosmart® 3 device as validated by recent research[62].

Stress and Anxiety Measures Stress and anxiety will be assessed using standard, validated questionnaires using the **HAM-A**[63]**, PSS**[64]**,** and **DASS-21**[65]. Additionally, a single-item **VAS** measure will be used to assess self-reported stress.

Human Laboratory Measures Experimental measures will be conducted on study days 1 and 8. Participants will be instructed to stop smoking by 10 pm the day before, in order to ensure they meet the breath CO criterion (CO ≤ 4 ppm) indicating overnight abstinence. In addition to measuring nicotine craving and withdrawal using the QSU and MNWQ, respectively, we will conduct two additional assessments.

Stress Reactivity Stress reactivity will be assessed using a modified version of the CPT on study days 1 and 8. The CPT involves participants submerging their dominant arm in an ice-water bath for up to 2 min. The CPT is widely used to induce stress in human laboratory studies and activates major stress systems in the body[66–69]. Stress activation can be significantly increased by incorporating a social evaluative component[68], which will be done by having a study member present wearing a white lab coat and holding a clipboard. Participants will also be videotaped and informed that their facial expressions will be assessed. Stress levels will be assessed using both subjective and physiological measures, including HR, BP, and salivary cortisol, consistent with previous studies from our group[70,71].

Smoking Relapse Assessment A dual-component smoking relapse assessment will be conducted in which participants will have the opportunity to self-administer their preferred brand of cigarettes[72]. Participants will earn $1 for every 5 min they do not smoke for the first 50 minutes (for a total of $10). At 50 minutes or once participants indicate they want to smoke, they will be given $7 to either purchase their preferred brand of cigarettes ($1 per cigarette) or keep. The two dependent variables will be latency to smoke the first cigarette and total number of cigarettes smoked.

Study Compensation Participants will be provided $40 for completing the baseline screening. They will receive $50 for attending each study visit and a $50 bonus for completing the study/returning study equipment. Additionally, participants will receive $5 compensation per visit for parking and/or bus fare. As noted above, participants may earn up to $34 across visits during the smoking relapse assessment (if achieving maximum latency and zero cigarette purchase), bringing total possible compensation to $234/participant. Upon study completion, participants may be given the opportunity to earn an additional $20 for referring new participants to the study that successfully enroll and also complete all study procedures.

DATA ANALYSIS PLAN

Confounding Variables Preliminary data analyses will inspect relationships between baseline/demographic variables, experimental group, and specified outcome variables via traditional statistical tests (e.g., chi-square, Mann-Whitney-Wilcoxon, Kruskal-Wallis, and *t*-tests). Baseline covariates that demonstrate a relationship with both assigned group and outcome variables meet criteria for being potential confounders[73,74] and will be included as a covariate in any statistical models for hypothesis testing. All analyses will statistically control for the stratification variables (detailed above in the Study Design section).

Inferential Paradigm Following recommendations for clinical trials in the literature[75–77] analyses will proceed using parallel frequentist and Bayesian statistical inference. Frequentist results yield the probability of the data (or data more extreme), given the null hypothesis, while Bayesian results yield the probability of an

alternative hypothesis[78]. If possible, Bayesian analyses will incorporate informative priors as they develop in the literature; otherwise, weakly informative priors will be incorporated as a default (e.g., for regression coefficients: ~N[μ=0,σ2=100]; for non-linear outcomes this prior applies to the coefficient within the link-function). Sensitivity analyses using optimistic and pessimistic, skeptical priors will evaluate prior assumptions[79]. Assessing the convergence of Bayesian analyses on the posterior distributions via Monte-Carlo Markov chain (MCMC) will use graphical (Trace Plot, Autocorrelation Plot) and quantitative (Geweke Diagnostics, Gelman-Rubin Diagnostics, and Heidelberger-Welsh Diagnostics) evidence. Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Statistical analyses will use SAS v. 9.4 and the most up-to-date stable release version of the R statistical computing environment[80] using packages rstan[80] and brms[81].

Statistical Modeling Analyses will primarily use generalized linear modeling (GLM) with multilevel components (GLMM) for correlated observations. Specifically, for each hypothesis, GLMM will model each outcome measure of interest as a function of group, potential confounding variables (as described above), and random effects to account for correlated observations where necessary. Continuous, count, and dichotomous outcomes will utilize normal, Poisson/negative binomial, and binomial distribution families respectively, with identity, log, and logit link functions as appropriate. Evaluation of distributional assumptions will use residual plots, formal statistical tests, and posterior predictive checking. Violations of assumptions will be addressed via transformation, robust estimation, stratification, and/or coefficient scaling where appropriate.

Missingness & Multiple Comparisons While the short nature of the proposed trial should reduce the prospect of missing data, for the frequentist analyses, missing data will be addressed via maximum likelihood, explicit modeling of missingness, and/or imputation. Bayesian analyses will use joint modeling of outcomes and missingness to handle missing data[82]. Each approach is robust to ignorable missingness (i.e. MCAR and MAR). Analyses will address non-ignorable missingness using pattern-mixture modeling[83]. Sensitivity analyses will permit evaluation of the robustness of findings to missing data assumptions. While Bayesian analyses are not influenced by traditional concerns of multiplicity, frequentist analyses will utilize false discovery rate (FDR) to control for Type I error across multiple tests for secondary outcomes where delineated.

Exploratory Data Analyses Where not otherwise specified, to maximize the utility of the present data, exploratory analyses will evaluate relationships between variables captured as part of the study. For example, while not represented in specific hypotheses, changes in self-reported smoking behavior as functions of other variables in the present study will be explored.

Specific Analyses

Hypothesis 1: GLMM will model each primary relapse risk outcome (craving (QSU), stress reactivity (heart rate and salivary cortisol), and latency to self-administration) as a function of the main effects and interaction between time (pre vs. post) and treatment group, including any necessary control variables (as defined above in the confounding variables section) and a random intercept for participant. Secondary measures of craving and stress reactivity will be assessed in similar fashion with Type I error correction for the frequentist analyses.

Hypothesis 2: GLMM will model each sleep metric (quality, duration, and restlessness) as a function of the main effects and interaction between time (pre vs. post) and treatment group, including control variables and a random intercept for participant. Secondary measures for sleep will be assessed in similar fashion with Type I error correction for the frequentist analyses.

Exploratory Hypothesis GLMM will model each relapse risk outcome (craving, stress reactivity, and latency to self-administration) as a function of the main effects and all higher-order interactions between time (pre vs. post), given sleep metrics (in unique models: quality, duration, and restlessness), and treatment group, including control variables and a random intercept for participant.

Sample Size and Power Considerations

Frequentist Analyses With regard to sample size, the current proposal is limited to a maximum credible sample of N = 20 (n = 10/group) that may be accrued in the given time window and the budget of the funding mechanism. While the specific analyses proposed above will be thoroughly evaluated, ultimately the research proposed here will be exploratory and hypothesis-generating for the purpose of a larger-scale trial. Given these limitations, frequentist power calculations are presented as due diligence for the current proposal (conducted via G*Power 3.1.9.4) and focus on the broadest analytic goal presented by Hypothesis 1 (change over time for each treatment group for a given relapse risk outcome). Assuming alpha = 0.05, a maximum credible sample size N = 20 (10/group) provides 80% power to detect a large effect size Cohen's f = 0.66.

Bayesian Analyses An advantage of the dual frequentist/Bayesian approach in the current proposal is the ability of Bayesian inference to provide probabilistic estimates of effects for all hypotheses even in the context

of lower power to detect small effect sizes. Given the exploratory nature of the present research, Bayesian analyses will focus on posterior probabilities ≥ 0.75 (equivalent to a Bayes factor = 0.33 or 3.0) to emphasize the value in discerning a signal for model effects across analyses.

DATA SAFETY MONITORING PLAN

E1. Human Subjects Involvement and Participant Characteristics

The study will test 20 current cigarette smokers, 18 to 65 years old that report smoking at least 10 cigarettes/day (half pack). Notably, because the study medication (suvorexant) is contraindicated with alcohol use, we will exclude subjects with alcohol use disorders (via screening at intake). We will also exclude those individuals meet DSM-5 criteria for an alcohol use disorder or report recent problem drinking (5/4 drinks for males/females in < 2.5 hours or > 10 alcoholic drinks per week) or those who report being unwilling to stop using alcohol in the evening for the two weeks of the study. Additional exclusion criteria include individuals that are pregnant, nursing, or planning on becoming pregnant during the course of the study; or if they have any other illness, condition, or use of medications which in the opinion of the PI and/or admitting physician would preclude safe and/or successful completion of the study. This will be accomplished via full medical evaluation at intake by Dr. Michael Weaver, M.D., CNRA Medical Director. The study will be conducted at the Neurobehavioral Research Laboratory at the CNRA. Recruitment strategies will include local advertising in print media, public service announcements on radio, and referrals to CNRA in the Houston metropolitan area. We expect to enroll a minimum of 2 participants per month to meet recruitment goals; however, we will be able to accommodate four simultaneous participants. Participants will be required to participate for 3 days (intake/screening, baseline observations, and one follow-up observation one week later). Research data will be collected at each scheduled time point.

Men and women of all ethnic backgrounds will be recruited to participate. It is anticipated that the subject demographic profile will closely mirror the larger population from which they are recruited, however, because we are recruiting cigarette smokers, we expect to a broader range of subjects from which to select. URN randomization will stratify participants by sex (male/female), tobacco use disorder severity (lower vs. higher defined by Fagerström Test for Nicotine Dependence (FTND) scores < 5 vs. ≥ 5, respectively), and craving (lower vs. higher, defined by Questionnaire of Smoking Urges-brief (QSU-brief) scores < 50 vs. ≥ 50, respectively). Concomitant use of e-cigarette or vaping products is permitted if participants otherwise satisfy inclusion/exclusion criteria.

Children (defined here per NIH guidelines as 19-21 years old) will be included in this research. From a safety perspective, risks of exposure to the proposed study medication in cigarette smoking children have not been established. The safety and efficacy of the proposed study medication should be established in adults first, before conducting this type of treatment research in children.

Exclusion criteria will include: (1) meeting criteria for diagnosis with a substance use disorder on drugs other than nicotine or cannabis; (2) greater than moderate cannabis use; (3) have a DSM-IV axis I psychiatric disorder or neurological disease or disorder requiring ongoing treatment and/or making study participation unsafe; (4) significant current suicidal or homicidal ideation; (5) medical conditions contraindicating administration of suvorexant (e.g., severe pulmonary disease, severe cardiovascular disease or clinically abnormal EEG, severe liver or kidney disease, seizure disorder, or sleep disorder – particularly narcolepsy); (6) taking medications known to have significant drug interactions with the study medication(s) (e.g., MAO inhibitors, anticonvulsants, haloperidol, phenothiazines, anesthetics, and all sedatives); (7) currently or recently (last 3 months) treated for substance use [other than nicotine] or another psychiatric condition; (8) conditions of probation or parole requiring reports of drug use to officers of the court; (9) impending incarceration; (10) pregnant or nursing for female patients; (11) inability to read, write, or speak English [required for lab tasks and psychometric scales]; (12) unwillingness to sign a written informed consent form; (13) subjects with alcohol use disorders or report recent problem drinking (5/4 drinks for males/females in < 2.5 hours or > 10 alcoholic drinks per week). All subjects who are excluded will be given referral informatic local treatment programs.

E2. Sources of Materials

We will obtain information about subjects from structured interview evaluations, physical examinations, self-report measures, and computerized behavioral tasks. This information will be collected at specified time points during the study phases of intake, baseline assessment, experimental testing, and end-of-study. The biological specimens obtained from all subjects will include urine and breath samples for alcohol detection. Individuals who volunteer to participate will be assigned a subject number (e.g., 10500), under which all information collected will be filed. All materials will be obtained for the specific purposes of this research.

E3. Potential Risks

Suvorexant (BELSOMRA) is an orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and sleep maintenance. Recommended dose is 10 mg, 1x per night taken within 30 minutes of going to bed, with at least 7 hours of planned time before awakening. If the 10 mg dose is well tolerated but not optimally effective, it can be increased but not to exceed 20 mg once daily. Medication is taken PO, with dosage in tablets of 5, 10, 15, and 20 mg. Contraindicated in patients with narcolepsy. Precautions include daytime somnolence; dose-related risk of impaired alertness and motor coordination, including impaired driving; patients taking 20 mg should be cautioned against next-day driving; nighttime “sleep-driving” and other complex behaviors while out of bed and/or not fully awake; worsening of depression or suicidal thinking; compromised respiratory function; sleep paralysis, hypnagogic/hypnopompic hallucinations. Risk of the above symptoms increases with use of CNS depressants and alcohol. In obese women (BMI > 30), there is increased risk of exposure-related adverse effects. Belsomra is a schedule-IV compound with mild/modest abuse-potential in the same class as existing sleep medications and anxiolytics. The most common adverse reactions include somnolence and slowed motor coordination. Not recommended for use in patients taking strong CYP3A inhibitors, efficacy may be reduced, or for patients with severe hepatic impairment. Based on animal data, Belsomra may cause fetal harm.

Risks for Behavioral and Psychometric Testing. Items on certain psychological/psychiatric questionnaires and interviews might be perceived as personally discomforting to some subjects. Similarly, subjects may experience discomfort due to withdrawal symptoms as part of the smoking relapse assessment. With regard to the actigraphy sleep monitoring, participants may experience mild discomfort while acclimating to wearing the device during sleep. While subjects may be uncomfortable reporting these issues, the risks of serious sequelae are extremely low.

Risks for Cold Pressor Test. Individuals with cardiovascular disorders and neurological disorders should not participate. This information will be obtained during medical screening. Due to individual variation in pain and cold sensitivity, for some subjects the cold water may become too painful to sustain immersion for 120 seconds. There are no lasting effects from placing the hand and wrist in ice water (0° Celsius) for 120 seconds.

Risks for Physical Examination. The intake screening and physical exam are part of the CNRA General Evaluation protocol, and are approved under protocol HSC-MS-05-0322 and detailed therein.

E4. Adequacy of Protection Against Risks

Procedures to Minimize Drug-Related Risks

We will screen very carefully for alcohol use and depressive symptoms. It will be made explicit that participants are not to drink alcohol in evening. We will use the Alcohol Use Disorders Identification Test (AUDIT) score and our mental health counselors SCID-screeners to enroll only those with low risk for alcohol abuse. Subjects will report no current depressive symptomatology (Beck Depression Inventory, or BDI < 15), with no past depressive episodes or suicidal ideation. The Columbia Suicide Severity Rating Scale (CSSRS) will be administered at each visit (see additional details below), as per NIH/FDA s. Indication of regular

alcohol use by AUDIT score, intake self-report, or breath alcohol, or indication of increase in depressive symptomatology / suicidality as measured by the CSSRS will result in study stopping (see details below). Will exclude for any patients taking CYP3A inhibitors; patients with severe hepatic impairment; and women who are or become pregnant. Pregnancy and drug tests are administered on via urinalysis on lab testing days. Women of childbearing capacity must be taking one form of birth control. We will exclude for women with BMI > 30 to decrease risk of side effects.

In addition to the rigorous screening criteria for inclusion. At the end of each experimental day, cardiovascular measures will be taken and the subject will be evaluated for signs of impairment or side effects, first by a research assistant and then by the research nurse, medical director, or PI. The assessment battery includes subjective effects questionnaire, nystagmus, touching nose, balance, and walking a straight line). If cardiovascular measures are normal, within the range of pre-dose levels, and the subject is determined to be unimpaired, the subject will be released. If any signs of intoxication are detected, participants will be required to remain at the experimental site until such symptoms are no longer observed.

In the event of either an unexpected adverse event or a prolonged period of intoxication, we have several measures in place. First, Dr. Weaver (CNRA medical director) has clinical experience and training in emergency medicine. Thus, a physician will be in the immediate vicinity of laboratory at all times. Offices and clinical space are within 100 feet of the lab. Collaborating MDs can be paged at any time during the day. Second, Ben Taub Hospital, a level 5 emergency medical center is located just minutes away from BBSB. Finally, in the event of extended sedation, intoxication, or impairment, in which any subject does not appear clear-headed, feeling well, and in full control of his or her behavior, two steps will be taken. First, the subject will remain in the lab until such time that the primary or a co-investigator deems that it is safe for him or her to leave (e.g., passing the sobriety test described above). In the event of extended impairment, we will arrange (and pay for) a taxi service to drive the subject back to his/her home rather than having to use METRO. We will administer the Columbia Suicide Severity Rating Scale (CSSRS screening version) at each visit to assess suicidality and depressive symptoms, consistent with current FDA best practices. If the screening indicates change in suicidal ideation, we will administer the full version. If suicidality is judged to clinically significant as per CSSRS scoring criteria, we will (1) report the event to CPHS within 48 hours; (2) remove the patient from the study; (3) make a referral to either the BBSB outpatient mood disorders clinic or UT HCPC, depending on consultation from Dept of Psychiatry outpatient faculty at BBSB.

For the cold pressor task, participants will be told that if the level of pain is too uncomfortable, they should remove the hand immediately and not wait to the end of the 120 sec test period. Each participant will be able to test the water temperature for 10 sec prior to beginning the procedure. These details are presented in the informed consent document. Because there are no sustained effects of cold water, if a participant cannot sustain the immersion for 120 sec at baseline, it will not preclude repeated testing on the follow-up lab test day.

Other Protections Against Risk. The following procedures will be taken to safeguard against adverse medication events: (1) careful initial intake evaluation to determine eligibility based on inclusion/exclusion criteria; (2) thorough physical evaluation prior to treatment, consisting of physical examination, standard laboratory tests, electrocardiogram, toxicology screen, pregnancy test, and vital signs; (3) repeated tests during treatment; (4) daily monitoring of pill taking using MEMS caps, returned pill counts, and self-report; (5) weekly review of adverse events and medication compliance; (6) regular evaluation by the study physician (Dr. Weaver). Specific criteria will be used to exclude potential subjects for whom any of the study medications is contraindicated. Any abnormal physiological, psychological, or behavioral event will be evaluated and, if indicated, will result in the subject's removal from the study.

For all three experiments included in this project, we will use an Adverse Event Log (AEL) based on NIDA SAFTEE procedures. The AEL will record the duration, severity, and frequency or any adverse events, signs, and symptoms. An evaluation will be made as to the event's relationship to the study drug(s), scaled as unrelated, unlikely, possible, and probable. The AEL will be included in t o DSMB.

Subjects will be monitored regularly for compliance with the study requirements, including the dosing regimen and breath alcohol testing upon arrival at the laboratory each day of testing. Written and verbal information about the medication will be given to all participants. This information will remind the subject to: (1) take food shortly after medication if needed to relieve gastric irritation; (2) inform the treatment research clinic nurse or physician of any over-the-counter and prescription medication taken, especially: cough medication, diarrhea medication, narcotic medication; (2) notify treatment research clinic nurse or physician of any side effects that persist or worsen. The study physician, nurse, and PI will review cases involving clinical deterioration of increased symptomatology or substance abuse. Appropriate actions will be taken, including study termination with proper referral.

Confidentiality will be protected in several ways. All information collected solely for research purposes will be kept in locked, restricted access files. Individual subject information will be transferred to outside sources only with the express written request of the subject. Subjects will receive a copy of their signed consent form. All personnel associated with this grant have successfully completed ethics training in the Protection and Welfare of Human Participants, and certification is on file at the Health Science Center CPHS and office of sponsored projects. All intake and experimental data that are collected will be uploaded onto a laboratory database, computers dedicated to data storage and management. These computers are protected by password. All data will be treated as confidential information. All data including urine samples, medical and psychiatric intake exams, and behavioral and drug administration data – will be obtained solely for research purposes. All individuals who elect to participate and sign the informed consent agreement will be assigned a subject number (e.g., 3200), which will serve as that subject's identifier (rather than name or SS#). A log book and electronic database that connect participants' identifying information with subject number are kept in a locked file cabinet and room and password protected, respectively.

Recruitment and Informed Consent. Participants will be self-referred in response to various study advertisements. All CNRA recruitment materials have been approved by CPHS for ongoing studies over the past 5 years. Individuals who call for information will be given a brief description of the study. Those interested will then be asked to answer questions about their current substance use. A trained research assistant will conduct this telephone-screening interview. Eligible subjects will be scheduled for an in-person intake visit at the CNRA, first floor BBSB. The first intake appointment will begin with the presentation of the informed consent form. The consent form will detail the requirements of study participation (e.g., # of visits, type of data collected, time commitment, etc.).

Subjects will be told that the purpose of the study is to evaluate the effects of medications on human behavior related to mood, sleep, and cigarette smoking. Information about the components of the experimental procedure will be explained. Details of the random assignment procedure (placebo or active dose) will be explained. Subjects will be informed of their attendance expectations. Other information on the consent form will include a full description of study requirements, reimbursement, risks, benefits, alternatives, and the role of the local IRB. All questions will be answered before written consent is requested. All research conducted in our laboratory and the CNRA has prior approval from the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center - Houston.

E5. Potential Benefits of the Proposed Research to the Subject and Others

All services provided in these studies will be free. The studies should help compliment and advise clinical research focused on stopping cigarette smoking and preventing relapse. Subjects will be told if unusual information is discovered during the study that will make a difference in treatment for this or other problems. By taking part in this research, subjects may help themselves toward recovery and others with similar problems.

Subject Payment. Participants will be provided $40 for completing the baseline screening. They will receive $50 for attending each study visit and a $50 bonus for completing the study/returning study equipment.

Additionally, participants will receive $5 compensation per visit for parking and/or bus fare. As noted above, participants may earn up to $34 across visits during the smoking relapse assessment (if achieving maximum latency and zero cigarette purchase), bringing total possible compensation to $234/participant. Upon study completion, participants may be given the opportunity to earn an additional $20 for referring new participants to the study that successfully enroll and also complete all study procedures.

E6. Importance of the Knowledge to be Gained.

Research participation may assist subjects in abstaining from cigarette smoking during study, and via study completion protocol, bring them into contact with treatment resources at our research center and in the community. Nicotine dependence is marked by repeated relapse, leading to devastating consequences on a personal and societal level. Currently there is no medication that has been shown to be broadly effective in improving withdrawal symptoms via improved sleep metrics. Suvorexant (and orexin agonists more broadly) may help reduce sleep disruptions and attenuate craving, helping to reduce risk of relapse. This experiment will compliment and provide valuable information to our ongoing and future addiction work, and contribute to the knowledge base in the treatment of tobacco use disorder. Our procedures have been designed to minimize the probability of risks. Our research center has an excellent track record in conducting human psychopharmacology experiments and clinical trials with the utmost attention to safety.

E7. Inclusion of Women and Minorities

Women, minorities, and children will be included at minimum to the extent that they are reflected in this population. In previous clinical studies at the Treatment Research Clinic (TRC), the percentage of females and males is approximately 20% and 80% respectively; however, this imbalance reflects a historical trend of studies focusing on male-dominated drugs of abuse (e.g., cocaine). Recruitment efforts will seek to achieve a 50-50 balance and further stratify group membership on the basis of sex.

The ethnic representation has been 67% Black, 25% White, and 8% Hispanic. The medical center environment is not known to be uniquely avoided by any particular ethnic group and patients view it as favorable and neutral. Nevertheless, we are prepared to implement recruitment procedures to ensure a more diverse patient population. These procedures include: 1) Targeted advertising in newspapers which serve minority communities (e.g., Hispanic or Latino communities). 2) Distribution of flyers and notices in neighborhoods known to have a high minority population. 3) Engaging in outreach activities on an ongoing basis, e.g., contacting church and community leaders in the Hispanic communities to provide educational material about cigarette smoking and its consequences; providing contact information to aid in referrals to our clinic (see Core for additional details).

E8. Inclusion of Children

Children (age 18-21years) will be included in this research. From a safety perspective, risks of exposure to the proposed study medication in tobacco-dependent children have not been established. The safety and efficacy of the proposed study medication should be established in adults first, before conducting this type of treatment research in children.

E9. Data and Safety Monitoring Plan (NIH/NIDA specific issues)

1. The Principal Investigator will be responsible for knowing the policies of the local IRB (the UT – Houston Committee for the Protection of Human Subjects, CPHS). The PI will adhere to CPHS policies and maintain accurate documentation of CPHS correspondence and reports (e.g., annual report). The PI is responsible for documentation and handling of all possible study-related adverse events. The Treatment Research Clinic (TRC) within our Center for Neurobehavioral Research on Addictions (CNRA) has longstanding data collection and safety monitoring systems in place that will be available for the proposed study. These include staff training, weekly audit of data collection/entry, medical screening with results reviewed by on-site nurse and physician, use of standardized assessments, continued medical monitoring during the study, procedures to monitor medication compliance (MEMS caps, texts). As PI, Dr. Suchting will assure that the above systems are in place and functioning properly during the study.

2. A Monitoring Committee will provide additional, independent oversight of data related to subject safety. This committee will perform the following activities: (a) review the research protocol and plans for data and safety monitoring; (b) evaluate study progress, including data quality, participant recruitment rates, retention rates, outcome and adverse experience data, and risk versus benefit profile; (c) make recommendations to the PI for a discontinuation of study medication for an individual patient based on adverse experiences; (d) make recommendations to terminate the study because of safety concerns; and (e) protect the confidentiality of the data and the results of monitoring. The Committee will be blind to study medication, unless they believe that termination of the trial is warranted. This committee meets annually to review all CNRA studies, and this present study will be added to the DSMB review in 2020. The DSMB report is submitted annually to CPHS.
3. Adverse events (AE) will be reported to the UT-CPHS on an annual basis. Serious adverse events will be reported immediately (verbally within 24 hours) to the UT-CPHS, the Monitoring Committee, and to the NIDA. A written report will follow as soon as possible but in no more than three days. The written report will be in the format required by the local IRB and will contain information regarding the date of the AE, description of the AE, severity rating (Grade 1 to 4), assessment of cause, whether the AE indicates an increased risk for current or future subjects, and whether changes to the informed consent form are necessary.
4. We will also use an ongoing Adverse Event Log (AEL) based on NIDA SAFTEE procedures. The AEL will record the duration, severity, and frequency or any adverse events, signs, and symptoms. An evaluation will be made as to the event's relationship to the study drug(s), scaled as unrelated, unlikely, possible, and probable. The AEL will be included in the report to DSMB.

E10. Specific Issues: NIDA / NACDA Guidelines on Administration of Drugs to Human Subjects.
Risk/Benefit. These issues are described in sections **E1 through E6**. As noted above, the potential for advances in scientific and treatment domains related to addiction are considerable. Based on the qualifications and long history of work in this area by the investigative team and the careful screening and monitoring for subject safety, we feel there is a favorable balance of potential benefit against risk.
Data Safety Monitoring Board is described in **E9**.
Informed Consent is described in section **E4**.
Subject Selection is described in section **E1**.
Confidentiality is described in section **E4**.
Medical and Psychological Screening and Services are described in sections **E1, E4, and E9**, as well as sections **D1 and D2** of the application.
Administration of Drugs to Individuals Who Have Never Used Drugs. Study drugs will not be administered to subjects who have never used drugs. By definition all subjects will be cigarette smokers.

Involvement of Individuals Currently Addicted to Drugs and/or Are Frequent Drug Abusers. We have taken into consideration the need to assess the participant's ability to provide informed consent (via use of screening and the Shipley-2 aptitude assessment). At study end, subjects will receive a follow up medical examination and a session with a licensed counselor in our treatment research clinic, who will provide information about treatment options and referrals. As described thoroughly in D1, D2, E1 and E4 we have rigorous medical examination and screening procedures to assure the absence of any medical or mental condition for which further drug exposure would be contraindicated. Our procedures do not entail exposure to higher doses, rates of administration, or new route of administration than they would normally encounter by under usual circumstances. If subjects have participated in prior clinical drug intervention trials at our treatment research clinic, a complete list of drugs and dosing protocols will be reviewed and kept in his/her evaluation record. Subjects using any current CNS active medications will be excluding from testing and rescheduled (if medication use was idiosyncratic, e.g., OTC for recent cold or headache) or excluded (if medication use is regular or for a chronic condition). In particular, we will exclude subjects with alcohol use disorders or report recent problem drinking (5/4 drinks for males/females in < 2.5 hours or > 10 alcoholic drinks per week), as suvorexant is contraindicated with alcohol due to potentially dangerous interactions with regard to sedative effects.

Administration of Drugs to Incarcerated Individuals. Individuals who are currently on parole or probation with random drug testing by court officers, or who are currently incarcerated, will be excluded

Administration of Drugs to Individuals with Mental Disorders. Individuals with DSM-IV Axis - I mental disorders other than SUD will be excluded.

Drug Doses and Routes of Administration. The proposed dose in these experiments (20 mg) have been safely given to human subjects in previous laboratory experiments and clinical trials. Standard routes of administration (PO capsules) will be used. No doses will be given outside the range of those already administered to humans in previous studies and indicated in the prescribing information in the investigator's brochure.

Prior and Current Drug Treatment Status. All subjects in the proposed experiments will receive a follow up medical examination and a session with a licensed counselor in our treatment research clinic, who will provide information about treatment options and referrals.

Prior and Current Treatment Experience. If subjects have participated in prior clinical drug intervention trials at our treatment research clinic, a complete list of drugs and dosing protocols will be reviewed and kept in his/her evaluation record. Subjects using any current CNS active medications will be excluding from testing and rescheduled (if medication use was idiosyncratic, e.g., OTC for recent cold or headache) or excluded (if medication use is regular or for a chronic condition).

Women of childbearing potential will not be excluded from these experiments.

Pregnant Women will be excluded from these experiments, and urine pregnancy testing will be performed at each visit to the research center.

Special Considerations Across the Lifespan. Individuals under the age of 19 will be excluded from this research due to risks and unknown effects of these drugs in adolescents, and ethical concerns of administering drugs of abuse to individuals this age. Additionally, individuals this age may be in school, which would preclude the normal daytime participation time. We will also exclude individuals over age 55, as elderly subjects also constitute a vulnerable population with regard to drug effects. Additionally, changes in anatomy and physiology in the elderly that may alter the metabolism and short and long-term effects of drugs, compromising both safety and scientific validity.

Study Personnel Training and Experience. All medical and psychiatric screening and interviews will be conducted by trained clinicians, who are first trained by experienced SCID interviewers using standardized training videotapes from Biometrics Research, NY. All personnel associated with this grant have successfully completed ethics training in the Protection and Welfare of Human Participants, and certification is on file at the Health Science Center CPHS and office of sponsored projects. CNRA pharmacists will carry out preparation of medication; distribution of medication by research assistants will follow after training has been conducted by the PI (Suchting).

Infection Risk Reduction Counseling and Testing. As described in sections D1, D2, E1 and E4, we recognize these risks and have included the necessary tests and precautions for disease transmission and infection risk (HIV, tuberculosis (TB), hepatitis, syphilis). HIV counseling will be made available as deemed appropriate by medical personnel in the treatment research center.

Safety of Research Participants Outside of the Research Site. These issues are addressed in section E4. They are repeated here for clarity. In addition to the screening criteria for inclusion, each visit to the laboratory will include a full side effects profile. Additionally, subjects will be evaluated for signs of impairment or side effects, first by a research assistant and then by a PI and CNRA research nurse. The assessment battery includes subjective questionnaire, nystagmus, touching nose, balance, and walking a straight line. If the subject is determined to be unimpaired, s/he will be released promptly. If any signs of sedation or other impairment are detected, participants will be required to remain at the experimental site until such symptoms are no longer observed. In the event of either an unexpected adverse event or heavy sedation, we have several measures in place. First, Dr. Weaver (CNRA medical director) is a licensed MD with clinical experience and training in emergency medicine. Thus, a physician will be in the immediate vicinity of laboratory. Offices and clinical space are contiguous to the lab. Second, Ben Taub Hospital, a level 5 emergency medical center is located less then 5 minutes away from our building. Finally, in the event of extended sedation or impairment in which any subject does not appear clear-headed, feeling well, and in full control of his or her behavior, two

steps will be taken. First, the subject will remain in the lab until such time that the PI, medical director, or research nurse deems that it is safe for him or her to leave (e.g., passing the test described above). Second, if necessary, we will arrange for a taxi service to drive the subject back to his/her home.

The following procedures will be taken to safeguard against adverse medication events: (1) careful initial intake evaluation to determine eligibility based on inclusion/exclusion criteria (including exclusion for alcohol use disorder or frequent regular use); (2) thorough physical evaluation prior to treatment, consisting of physical examination, standard laboratory tests, electrocardiogram, toxicology screen, pregnancy test and vital signs; (3) repeated tests during treatment; (4) daily monitoring of pill taking using MEMS caps, returned pill counts, and self-report; (5) weekly review of adverse events and medication compliance; (6) evaluation by the study physician (Dr. Weaver). Specific criteria will be used to exclude potential subjects for whom any of the study medications is contraindicated. Any abnormal physiological, psychological, or behavioral event will be evaluated and, if indicated, will result in the subject's removal from the study.

For this project, we will use an Adverse Event Log (AEL) based on NIDA SAFTEE procedures. The AEL will record the duration, severity, and frequency or any adverse events, signs, and symptoms. An evaluation will be made as to the event's relationship to the study drug, scaled as unrelated, unlikely, possible, and probable. The AEL will be included in the report to DSMB. Relevant information is also included in section E9.

Referral to Treatment. As noted above, at study end subjects will receive a follow up medical examination and a session with a masters-level licensed counselor or RN in our treatment research clinic, who will provide information about treatment options and referrals. If depression or suicidal ideation is measured at risk during the study, participation will be terminated and appropriate referrals made (see above).

Incomplete Disclosure. We have no elements of deception in this project, other than withholding of dose information to subjects about dose contents on days of testing (e.g., suvorexant or placebo). However, informed consent documents will contain full disclosure of the drug that may be received during the course of the experiments, along with potential side effects. No information about study risks will be withheld from subjects.

Payment for Participation in Research. Subjects will be paid daily for attendance and for performance on the behavioral tasks, and a bonus at the end of the study for completion. Participants will be provided $40 for completing the baseline screening. They will receive $50 for attending each study visit and a $50 bonus for completing the study/returning study equipment. Additionally, participants will receive $5 compensation per visit for parking and/or bus fare. As noted above, participants may earn up to $34 across visits during the smoking relapse assessment (if achieving maximum latency and zero cigarette purchase), bringing total possible compensation to $234/participant.

F. Vertebrate Animals
Not applicable.

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