UNM IRB PROTOCOL

TITLE:	Lorcaserin Effects on Alcohol Responses
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BACKGROUND/SCIENTIFIC RATIONALE

Pharmacotherapy development is a critical objective for reducing health and societal burdens associated with alcohol use disorder (AUD) [1-3]. Despite advances in this area, medication development remains a slow- moving endeavor with a protracted path from drug discovery to market, reflecting numerous scientific, regulatory and financial challenges [2-4]. Given the high degree of heterogeneity in AUD clinical presentation and treatment response, it is recognized that no single medication will be effective for all patients [5]. Therefore, the NIAAA medication development strategy specifies the long-term objective of establishing a repertoire of therapies to facilitate targeted interventions for specific AUD subgroups [3, 5, 6]. Importantly, strategies for expediting the study of novel treatments are central to these aims [3, 5, 6].

Epidemiological and clinical evidence shows that cigarette smokers comprise a sizable AUD subgroup with disproportionately high health burdens [7, 8]. Alcohol and cigarette use are two of the three leading causes of preventable mortality worldwide, jointly accounting for an estimated seven million deaths per year [9]. Population-based research shows that cigarette consumption increases as a function of alcohol use severity [7]. In one large epidemiological study, nearly half (44.6% of men, 47.3% of women) of those with alcohol dependence also met criteria for nicotine dependence [7]. Co-use of alcohol and cigarettes predicts synergistic increases in risk for numerous disease conditions [8, 10, 11], including esophageal and laryngeal cancers [12, 13]. Given these health burdens, increasing effort has been allocated to developing targeted interventions for smokers with AUD [8, 11, 14, 15].

In the absence of FDA-approved medications for concurrent alcohol and nicotine addiction, identifying candidate drugs for this indication is a priority [11, 15, 16]. Several recent studies have examined whether FDA- approved AUD and smoking cessation drugs, either alone or in combination, can facilitate joint reductions in alcohol and cigarette use [11]. For instance, naltrexone reduces alcohol consumption in heavy-drinking smokers [17, 18], and in some cases reduces cigarette consumption [17, 19]. Recent findings further suggest that naltrexone's efficacy for reducing drinking is stronger in AUD participants who smoke relative to non-smokers [20, 21]. However, a Cochrane review [22] and a large, prospective AUD trial [23] concluded that naltrexone does not appear to reduce cigarette smoking [11, 23].

Varenicline has also been tested as a candidate therapy for smokers with heavy drinking or AUD. Informed by early findings that varenicline reduced alcohol self-administration in a human laboratory trial [16], large-scale clinical trials supported efficacy of varenicline for reducing alcohol consumption in heavy-drinking smokers [24, 25] and those with AUD [26]. Recent laboratory-based studies have also examined the combination of varenicline and naltrexone as a novel treatment [27, 28]. Because those with concurrent alcohol and nicotine addiction reflect a high-priority subgroup, further efforts are needed to

screen candidate treatments for this population [8, 11, 28]. As reflected in these recent trials, and as noted explicitly under the NIAAA medication development framework [1-3], *drug repurposing* strategies can significantly expedite new treatment approaches by capitalizing on therapies that have already passed the extensive regulatory steps required for FDA approval.

Targeted serotonin (5-HT) agents as a novel therapeutic option for substance use disorders

The serotonin (5-HT) system is broadly implicated in the regulation of reward-related behavior, including drug seeking [29, 30], in part reflecting the role of 5-HT in regulating dopamine (DA) function [30, 31]. Historically, the diversity of 5-HT receptors (comprising 7 distinct families and 14 receptor subtypes) has posed challenges to characterizing the 5-HT system in relation to reward-related behavior [32]. In particular, some 5-HT receptor subtypes show opposing effects on reward-related behavior, perhaps accounting for inconsistent findings [32]. Notably, selective serotonin reuptake inhibitors (SSRIs) have not proven efficacious for addiction [29, 33]. However, given that SSRIs target multiple 5-HT receptors (and different 5-HT subtypes may have opposing effects on behavior), the lack of efficacy for SSRIs does not rule out the potential relevance 5-HT medications for addiction [29]. The more recent development of highly selective 5-HT receptor ligands has allowed for targeted investigations of 5-HT receptor subtypes in preclinical models of addiction [29]. Of relevance to this application, a substantial body of preclinical work implicates the 5-HT_{2C} receptor in addiction phenotypes - including drug-related motivation, reward, cue reactivity, and reinstatement - suggesting the potential therapeutic value of 5-HT_{2C} drugs for substance use disorders [29, 30, 34, 35].

Effects of selective 5-HT_{2C} agonists on drug-related phenotypes

Preclinical studies have established that targeted modulation of the 5-HT2C receptor alters reward-related responding, including food seeking and drug seeking [29, 34-36]. Importantly, 5-HT2C receptors (expressed primarily in the CNS) are implicated in 5-HT-related inhibition of DA function, and 5-HT2C agonists are shown to blunt DA release in the nucleus accumbens (NAc) [31, 37]. Preclinical findings generally show that 5-HT_{2C} agonists reduce motivation for addictive drugs, whereas 5-HT_{2C} antagonism can increase drug seeking [29, 32, 35]. For instance, preclinical studies found that 5-HT_{2C} receptor agonists reduced cocaine-induced stimulation [38], cocaine self-administration, and cocaine-induced increases in DA levels in the NAc [39]. Notably, these findings appear to generalize to other addictive drugs. Rodent studies show that 5-HT_{2C} receptor agonists reduce motivation for alcohol intake [40-42] and also reduce nicotine discrimination and self-administration (reviewed in [29, 34, 35]). Moreover, 5-HT_{2C} receptor agonists reduce cue-induced reinstatement of nicotine [36], cocaine [43], and oxycodone [44]. A non-human primate study showed that *acute* (single-dose) administration of a 5-HT_{2C} receptor antagonist significantly reduced nicotine self-administration [45]. Fletcher (collaborator on this proposal) and colleagues conducted much of the initial work on 5-HT_{2C} drugs in preclinical models of addiction, in particular nicotine (e.g., [29, 36, 46, 47]).

Selective 5-HT_{2C} agonists were developed largely in pursuit of novel treatments for obesity. **Lorcaserin (Belviq®)** was the first selective 5-HT_{2C} drug to receive FDA approval for weight management, based on findings from three large, Phase III trials totaling nearly 7,800 subjects [48-50]. In these trials, lorcaserin led to significant weight reduction (3-4kg, on average) relative to placebo, with a favorable safety profile. As the only 5-HT_{2C} drug with extensive Phase III evaluation and FDA approval, lorcaserin has near-term potential for repurposing as a novel treatment for substance use disorders [29].

Based on preclinical work with nicotine, the first Phase II trial of lorcaserin for smoking cessation was conducted recently [51]. In this trial involving 600 smokers, treatment with lorcaserin at the FDA-approved dose of 10mg BID (twice daily) increased the likelihood of continuous abstinence at study endpoint (OR = 3.02, 95% CI = 1.47-6.22) [51]. Consistent with obesity trials, lorcaserin had a favorable safety profile in smokers. This study is the only published randomized trial of lorcaserin for substance

use disorder, but ongoing trials are examining lorcaserin as a treatment for cocaine addiction and smoking cessation [35]. The combination of lorcaserin and varenicline has also been proposed as a novel treatment option [52]. Importantly, despite preclinical findings that 5-HT_{2C} receptor agonists reduce alcohol self-administration [40-42], no human trials have examined effects of 5-HT_{2C} receptor agonists on alcohol consumption or related outcomes.

Preclinical evidence that selective 5-HT_{2C} receptor agonists reduce the intake of food and multiple addictive substances has also raised the prospect of common underlying mechanisms. While the efficacy of 5-HT_{2C} agonists for weight reduction was initially attributed to drug effects on satiety, the evidence that 5-HT_{2C} agonists reduce operant responding for drugs suggested that motivational and/or appetitive mechanisms could be involved [35]. Consistent with this possibility, 5-HT_{2C} agonists are shown to reduce *impulsive responding* in animal models, with these effects appearing most robust for measures of impulsive action [35]. Given the central role of impulsivity in the etiology and maintenance of addiction, it has been noted that therapies targeting both impulsivity and drug consumption would have high appeal [53]. To date, the effects of 5-HT_{2C} agonists on human impulsivity outcomes have not been reported.

Human laboratory methods for Phase II medication screening

As emphasized in the "Rosetta stone" approach to drug development [1] and the NIAAA medication development strategy [1, 4, 54], human laboratory trials play a pivotal role in drug development by providing a bridge from preclinical studies and full-scale Phase II/III trials [55-59]. Importantly, laboratory studies can expedite drug development by providing an efficient, cost-effective, and rigorous option for “early-Phase II” medication screening, thereby informing priorities for larger and more costly randomized trials. We recently published meta-analytic evidence that laboratory studies of naltrexone, when examined in aggregate, yield conclusions highly comparable to the aggregate data from large-scale randomized trials, reinforcing the notion that laboratory trials offer a valid approach for estimating medication effects [56]. Other advantages of laboratory trials include the ability to study putative treatment mechanisms under controlled conditions, and the ability to quickly generate initial data on drug tolerability in the clinical population of interest [1, 60].

Limitations of human laboratory trials should also be considered. One noted concern is the tendency to focus solely on self-reported craving as a proxy for consumption, an approach that has limited translational value [61, 62]. Given that craving is not always necessary or sufficient for drug intake, it has been argued that medication screening trials should prioritize direct assays of drug intake as criterion outcomes [63]. However, *self-administration* paradigms are generally under-utilized in human laboratory AUD research [64]. Modern laboratory and intervention trials have also moved toward an emphasis on behavioral economic indices of drug motivation as intervention targets and markers of therapeutic response. For instance, *alcohol demand* indexes the *relative reinforcing value of alcohol* at a particular point in time [65]. Measures of drug demand, such as the alcohol purchase task (APT) and cigarette purchase task (CPT), are considered objective and sensitive experimental assays of drug motivation [65]. For example, the APT predicts frequency of heavy drinking days after treatment [65], and is sensitive to temporal changes in alcohol’s relative reinforcing efficacy during drug administration [66]. Notably, initial evidence suggests that these measures are sensitive to the effects of pharmacological treatments, including naltrexone and varenicline [67, 68].

Another limitation of many laboratory-based pharmacotherapy trials is the tendency to focus on heavy drinkers *without* AUD, rather than participants with the disorder [63, 69]. A recent systematic review found evidence that recruiting non-clinical samples for laboratory trials can potentially limit the ability of laboratory findings to generalize to larger clinical trials, perhaps undermining translational research efforts [70]. While ethical considerations normally preclude laboratory alcohol administration methods with *treatment-seeking* AUD participants [69], studies of *non-treatment-seeking* AUD participants are

ethically acceptable, and can provide important data on medication effects and safety in the target clinical population [71].

OBJECTIVES/AIMS

The aim of this proposal is to translate preclinical findings on 5-HT_{2C} receptor medications by conducting an early-Phase II human laboratory investigation of lorcaserin's effects on alcohol consumption and related outcomes in participants with AUD. Given emergent evidence for lorcaserin's efficacy as a smoking cessation therapy, and the need for treatments targeting both alcohol and nicotine addiction, this proposal focuses on smokers with AUD. Specifically, we propose a double-blind, within-subjects, crossover trial to investigate the effects of lorcaserin vs. placebo on alcohol self-administration in the context of a validated laboratory medication screening procedure. We also aim to investigate lorcaserin's effects on secondary alcohol- and nicotine-related outcomes and behavioral measures of impulsivity.

Aim 1. To examine effects of lorcaserin vs. placebo on alcohol self-administration.

Aim 2. To examine effects of lorcaserin vs. placebo on secondary indicators of alcohol and nicotine responses and motivation.

PROJECT DESIGN

I. *Target Population and Inclusion/Exclusion Criteria*

A final sample of 42 smokers with AUD (balanced by sex) will be recruited from the community.

Inclusion Criteria

a) Age 21-65
b) Meeting DSM-5 criteria for current (past year) mild or moderate AUD, as well as NIAAA criteria for current at-risk drinking (i.e., ≥14/21 drinks per week for women/men, on average, with at least four episodes of 4+/5+ drinks in the past 30 days)
c) Daily smoker, defined as reporting smoking 1+ cigarettes per day, on average, over the past 12 months and daily smoking in the past month
d) Willingness to take study pills and complete study procedures
e) Willingness to complete lab sessions involving alcohol administration

Exclusion Criteria

a) Recent (30 day) illicit drug use (with the exception of cannabis) based on self-report or toxicology screen
b) Meeting DSM-5 criteria for a past-year substance use disorder other than alcohol use disorder, tobacco use disorder, or mild cannabis use disorder
c) Significant alcohol withdrawal, based on a Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWA-Ar) score of 8+ at baseline medical visit, or any reported history of severe withdrawal symptoms (e.g., seizures, DTs).
d) Past 30-day use of nicotine replacement
e) Past 30-day use of SSRIs, other psychiatric medications, or weight control medications
f) Lifetime diagnosis of severe mental illness (e.g., psychotic or bipolar I disorder)
g) Significant medical or neurological illness based on medical staff (i.e., physician or nurse practitioner) evaluation including severe hepatic impairment or cirrhosis, insulin dependent diabetes
h) Current alcohol or smoking cessation treatment or efforts to cut down on drinking/smoking
i) Medications which are contraindicated for use with lorcaserin (e.g., bromocriptine, cabergoline, dapoxetine, dihydroergotamine, ergoloid mesylates, ergonovine, ergotamine, methylene blue, methylergonovine, nicergoline, pergolide, thiorizadine) or which have a

significant interaction with lorcaserin (e.g., bupropion, doxorubicin, eliglustat, linezolid, perhexiline, rasagiline, safinamide, selegiline, tamoxifen) [51]
j) Body mass index (BMI) under normal range (<18kg/m2) [51]
k) History of significant cardiovascular conditions including history of arrhythmias or heart block, heart failure, valvular heart disease, heat attack, stroke, unstable angina
l) Abnormal electrocardiogram (ECG) results
m) Currently nursing, pregnant, or anticipating pregnancy
n) history of suicide attempt or recent suicidal ideation (i.e., Suicidal thoughts (intent or plan) in the last month)

o) Plans to travel outside of the Albuquerque area during the study period, or inability to commit to entire duration of study (6 weeks of potential availability)

II. *Participant Enrollment*

We anticipate phone screening up to 1000 individuals and may enroll up to 100 participants in order to obtain a final sample of 42 eligible participants who complete all study visits.

III. *Recruitment and Screening Procedures*

Participants will be recruited from the community through advertisements placed in local newspapers, radio stations/TV ads, movie theaters, community flyers, word of mouth, social media, and email communications directed towards community support groups, news paper ads, business cards, and online postings (e.g. Craigslist, Google Adwords, Facebook, Instagram, clinicaltrials.gov) within the Albuquerque metro area. Approved study recruitment text and flyers will be used in digital recruitment mediums, such as university list-servs, online advertising mediums, or digital presentation slides. Word of mouth from current and past participants, employees and collaborators, as well as other individuals will also be used and may include sharing approved information and/or recruitment materials. Finally, participants from other studies who have expressed an interest in being contacted for future studies, including from the MRN Participant Recruitment Registry, may be contacted to determine eligibility and interest in this study.

Potential subjects will be self-selected and must contact the study to express initial interest in the study. Once initial contact is made, research staff will explain the study and conduct a brief phone screen interview.

Recruitment materials are included with the application (attachments are listed below).

IV. *Informed Consent Process*

Upon initial contact, the study will be briefly introduced to the participant by a member of the research team. Participants will then complete a preliminary screen over the phone. Identifiable information will be retained for those participants who do not meet inclusion criteria only for the duration of the study to ensure that the same participant does not attempt to enroll a second time. If the participant meets inclusion criteria, the study visit will be scheduled and a copy of the consent document will be sent to them in advance if requested. Participants requesting the consent ahead of their visit will be allowed as much time as they need to decide whether or not to participate, and the PI or study staff will be available to answer questions about the consent/study procedures while the participant is making their decision. When the participant arrives for their appointment, they will be seated in a private room and given time to read the consent form with a study team member present. After the participant has finished reading the consent form, the study is described more fully by the research team and the participant is asked whether they have any questions regarding the described procedures and risks/benefits. Participants must elect to participate and can choose to discontinue their participation in the study at any time. Additionally, participants can be withdrawn from the study by the PIs for any reason (e.g., not paying attention to tasks, failure to attend

scheduled appointments, not following directions, safety concerns) throughout the course of the study.

If there are no further questions, the consent form is signed and stored in a locked cabinet in a locked office at MRN. A copy of the consent will be given to the participant.

V. *Data Collection Procedures*

In total, participation in this study will take roughly 20-25 hours over a period of approximately 5 weeks. This includes a screening visit (up to 3 hours), a baseline visit (up to 3 hours), a medication refill visit (1 hour), and two follow-up laboratory visits (6-8 hours each). Participants will receive calls twice from staff during each of the medication phases to check in on side effects (<15 minutes per call).

Participants will be asked to complete the following procedures:

Telephone screen

Initial participant screening will be conducted by telephone by trained research staff and will assess participant alcohol, cigarette, and drug use, medications, and basic medical inclusion/exclusion factors. Potential participants will be given a brief description of the study. Contact information will be collected from interested callers who pass the initial screen who will then be scheduled for in-person screening, consent and medical assessment visit. Participants will be instructed to refrain from alcohol use the day of their scheduled in person screening. The initial telephone screen is estimated to take roughly 15 minutes.

Screening and Baseline Data Collection Visits

The in-person screening visit will include both a clinically-oriented screen by a medical staff member, and self-report and interview questions, conducted by the research assistant or medical staff member. The staff will administer a breathalyzer and urine drug screen (for females, the test will include a pregnancy screen), and then briefly review and verify information collected over the phone. Participants who have a BAC greater than 0.00 will be rescheduled and given snacks and water until their BAC is reduced to a safe level (BAC<.02-.04g%), in accordance with NIAAA guidelines (or to 0.00 in the event that the participant drove to the session). If participants are unable to arrange for transportation, we will provide a taxi or car ride (e.g., Uber) voucher for up to $25 per ride. In addition to BAC, we will measure potential alcohol withdrawal symptoms (CIWA) expired alveolar carbon monoxide (CO).

Additional screening criteria, including symptoms of alcohol and nicotine dependence, and aspects of medical history (see criteria listed above) will assessed. The **Structured Clinical Interview for DSM-V** [94] will be used to assess inclusionary/exclusionary diagnoses. The **Timeline Follow-Back (TLFB)** [95] will be used to assess alcohol, cigarette and other drug use in the 90 days prior to baseline and during the experimental phase. The urine sample will be used to test for the presence of several drugs (for example, marijuana, heroin, cocaine, methamphetamines, opiates). If a participant tests positive for drugs other than marijuana (or if females screen positive for pregnancy) the participant will be excluded from the study. Additionally, participants will complete a blood draw (up to 20 ml) for a complete blood count (CBC), a basic metabolic panel, baseline measure of nicotine metabolites, a hepatic function panel. The baseline blood sample will also serve as the sample for DNA analysis. Participants will also complete an ECG test. Blood draws will be performed by trained research staff. ECG results will be evaluated by qualified medical staff. During the medical history any medications that the participant is taking will be checked for interactions with lorcaserin in an established online database such as Epocrates or Lexicomp, and prescribing medical staff will be contacted for dose adjustments, if deemed necessary. Any incidental medical findings during the assessment or subsequent participation in the study will be communicated by the MD or NP directly to the participant. If indicated, the participant will be instructed to follow-up with their GP, or will be provided with a referral.

If a participant shows symptoms of acute alcohol withdrawal (e.g., based on the CIWA cutoff noted above), the study medical staff will take appropriate steps to manage the symptoms (including escorting the participant to UNM Hospital if necessary). Participants who meet all study eligibility procedures will be provided with a study overview, and informed consent, locator, and collateral contact information will be obtained.

If results of the baseline screening/medical assessment indicate that the participant is eligible, they will be scheduled for a return baseline visit. This visit will include a more comprehensive orientation to the study, a questionnaire battery, cognitive tasks, and dispensing of the first set of study pills.

Participants will complete the following questionnaires, which will be programmed in RedCap software. A **Demographic Screening Questionnaire** will assess basic demographic factors (e.g., age, education, income). A **Locator** collects contact information for three to five individuals who can be contacted if a participant is unable to be reached by study staff for follow-up visits. Other baseline measures (to be administered by computer using RedCap software) will include the **Alcohol Use Disorders Identification Test** [96], **Self-Report of the Effects of Alcohol Questionnaire** (SRE) [97, 98], **Fagerström Test of Nicotine Dependence** [91], and the **Nicotine Dependence Syndrome Scale** [99]. Baseline measures that will be repeated at subsequent visit will include the **TLFB**, the **Penn Alcohol Craving Scale (PACS)** and **Tiffany Questionnaire of Smoking Urges (TQSU)** [100], the **Yale Craving Scale**, and the **Minnesota Nicotine Withdrawal Scale** [101]. To assess potential medication effects on changes in motivation and self-efficacy for resisting alcohol/cigarettes, we will use alcohol and smoking **Contemplation Ladder** items, alcohol and cigarette **Abstinence Self-Efficacy (AASE and SEQ)** and **Inventory of Drinking Situations** scales [102, 103, 118]. Given lorcaserin's effect on food intake, changes in appetite will be assessed with the **Three Factor Eating Questionnaire** [104] and the **Reward-Based Eating Drive Scale** [105]. The **PROMIS** Depression scale and Beck Depression Inventory-II will be administered to assess potential depressive symptoms. If participants report suicidal ideation, standard MRN protocols will be followed, including further assessment of the participant by medical staff and/or the PI, offering a referral, and following up with the participant. The **Wechsler Test of Adult Reading (WTAR)** will be used to estimate intelligence. During the medication phases, side effects will be assessed with the **SAFTEE** questionnaire [106] and an **Adverse Events Checklist** [107].

Impulsivity/Learning Tasks: To examine medication effects on behavioral measures of impulsivity and reward-based learning (as reported in preclinical studies), participants will complete computerized cognitive tests of impulsive action, attention, and reward-based learning at the baseline session, lasting roughly 45 minutes in total duration. These measures will be repeated at follow-up visits. Additionally, any measures noted above that would be expected to show change across sessions (or in response to medication) will be repeated at follow-up visits 1 and 2. These measures include: Stop Signal task, CPT, Reward Responsiveness Test, Monetary Choice Questionnaire, Food Discounting Task, Alcohol Purchase Task, and Cigarette Purchase Task.

The baseline session is projected to take approximately 2-3 hours. Patients will be given breaks, snacks, and bottled water as needed.

Medication Schedule and Safety Monitoring. Participants will receive the first 7-day supply of pills (medication or placebo, randomized and counterbalanced) at the completion of the baseline visit. In the first Phase II trial of lorcaserin for smoking cessation, the FDA-approved dose of 10mg BID (twice-daily) significantly increased abstinence relative to placebo, with a larger effect size relative to a comparison low-dose condition (10mg QD / once-daily) [51]. The BID and QD conditions were equivalent on discontinuations due to adverse events (AE; 2.5% and 3.0%, respectively) [51]. Therefore, we will use the FDA-approved dose of 10mg BID. Of note, steady-state plasma concentration occurs in 3 days. All pills will include a small amount of riboflavin to facilitate urinalysis as an index of adherence, and participants will be asked to bring their pill bottles at each visit. To monitor emergent side effects, the study staff will contact participants twice during the 7 day period (e.g., days 2 and 4). Participants will complete a brief web-based assessment each morning using Redcap (link texted by research staff or automated system), including 1) prior-day number drinks consumed; 2) number of cigarettes smoked; 3) side effects; and 4) medication

adherence for the prior day. Participants will be texted a link to the survey, which can be completed via smartphone. If preferred, participants can opt to receive an email link, or a text message with these questions embedded in a SMS text.

On Day 7 participants will return to complete the alcohol administration session described below. This visit will also include a repeat medical screen/measurements (as noted above), a calendar-based assessment of interim alcohol use and cigarette use, and a pill count. Following the laboratory visit on Day 7, participants will undergo a 7-day washout phase. Next, they will repeat the same 7-day sequence in the alternate pill condition, culminating in a second, identical alcohol administration session. Depending on scheduling and participant availability, we will be flexible in accommodating slight deviations from the 7-day schedules noted above, and at the discretion of the study physician, participants may be provided with additional days of medication as needed.

Follow-up Visits 1 and 2. At each of two follow-up visits, participants will report to MRN in the morning, having received instructions to abstain from alcohol and recreational drugs for 24h, and from food for 4 hours. Upon arrival participants will provide breathalyzer and expired CO readings, as well as repeat measures of body weight and vitals (HR, BP). Participants will also repeat the CIWA assessment and will complete a blood draw (up to 20 ml) at each session which may only be used for determining the level of medication metabolites present (i.e., a measure of adherence). Blood draws will be performed by trained research staff. Participants will take that day's morning pill under observation. Next, participants will be given the first of three 15-minute smoking breaks (to ensure that participants are not nicotine-deprived during testing), which is a common approach in laboratory studies [16]. Smoking breaks will occur in a ventilated room, which has been used for prior smoking studies. Participants will also be asked to complete short questionnaires before and after the break (measuring craving and subjective effects, see measures above). After the break, participants will consume a standardized snack, followed by self-report and computerized assessments, including interim assessments of substance use and craving, side effects and adherence, and computer-based impulsivity tasks (see Measures). Next, participants will complete the medical assessment with the study medical staff, including a weight measurement and a urine screen (to detect riboflavin as a measure of adherence). Assuming no medical contraindications, participants will proceed to begin a previously validated alcohol self-administration procedure, described below.

Alcohol self-administration protocol. Medication effects on alcohol intake will be examined using a validated oral self-administration procedure, which has been established as sensitive to medication effects [16, 90]. After completing physiological readings (systolic and diastolic blood pressure, heart rate) and baseline measurements of self-report questionnaires (e.g., measures of alcohol and cigarette craving and demand, see Measures), the procedure will commence with a scheduled *priming drink*, calculated to achieve a target breath alcohol concentration (BrAC) of .03g% [16, 90]. The priming drink serves two purposes: 1) to allow investigation of within-subjects medications effects on self-report outcomes (e.g., subjective effects, craving) following a controlled, low dose, and 2) to serve as a prime for the subsequent self-administration period. The priming drink will include 1 part 80-proof liquor (of the participant's choice) to 5 parts mixer, and will be consumed as a bolus dose over 5-10 minutes, followed by an absorption period lasting approximately 30 minutes. At the completion of the priming phase, participants will complete the next set of self-report measures, including alcohol and cigarette craving, alcohol and cigarette demand, and subjective effects of alcohol, see Measures).

After the post-priming assessments, participants will complete a 2-hour *ad libitum* self-administration period, separated into two 1-hour blocks. Participants will be allowed to self-administer up to 8 additional "mini-drink" beverages (4 per block), each calculated to achieve an average BrAC increment of .015g% per drink [16, 90] . Prior research with this protocol shows that participants tend to show modest levels of alcohol ingestion (averaging 30-40g, equivalent to 2-3 standard drinks), on average[64]. This finding is consistent across studies of both non-dependent

heavy drinkers and non-treatment-seeking, dependent drinkers,[64] which is the sample in the current study. The use of two distinct 1-hr. blocks prevents participants from consuming all drinks in short succession. Additionally, the average expected rate of decline in breath alcohol level (due to ongoing metabolism) is -.015g% per hour during the session. Therefore, while it is possible that participants can exceed the legal driving limit (.08g%) during the two-hour session, the protocol is unlikely to result in unsafe levels of consumption. Breath alcohol concentration will be monitored at regular intervals.

Participant-specific doses will be calculated using established formulas [93] that includes determinants of total body water (e.g., height, weight, sex, age). Consistent with prior studies using this self-administration protocol, participants will have the choice of receiving monetary reinforcement at the end of the session for drinks not consumed (e.g., $3 per beverage), which provides a competing incentive against consumption. Participants will repeat additional rounds of self-report assessments at 30-minute intervals during the *ad libitum* phase (i.e., at 60, 90, and 120 min. after the end of the priming phase), with physiological assessments and BrAC readings taken at these intervals. After the last assessment (120 min.), participants will be provided with another smoking break, as described above. Participants will then be escorted to a private room, will receive a standardized meal, and will be monitored until being discharged when BrAC declines below .03g% (if participants did not drive to their appointment) or to .00g% if they did drive to the appointment [71].

Alcohol administration session Questionnaires. At baseline prior to alcohol ingestion and each subsequent assessment interval (30, 60, 90, 120 min), participants will complete some or all of the following (not all questionnaires will be administered at each time point): the PACS and TQSU (noted above) to assess changes in alcohol and cigarette craving, as well as the **Alcohol Purchase Task** [65] and **Cigarette Purchase Task** [108] as behavioral economic indices of drug demand. Measures of subjective alcohol effects will include the **Biphasic Alcohol Effects Scale (BAES)** [109], **the Alcohol Urge Questionnaire** (AUQ) [110] and **Drug Effects Questionnaire** [111], which will be supplemented with items to assess potential effects related to medication (e.g., “tired”, “nauseous”) [16].

Table 1. Study Measures

VISIT	MEASURE/PROCEDURE	TIME (MINS)
Screening	Consent	30
	Breath alcohol test	2
	Urine drug screen	5
	Urine pregnancy test (females)	5
	Expired CO	2
	TLFB	30
	SCID	60
	CIWA	5
	The Wechsler Test of Adult Reading (WTAR)	10
	Blood draw	5
Medical screen (may occur on different day than screening	Physical Exam	10
	Medical History	15

VISIT	MEASURE/PROCEDURE	TIME (MINS)
depending on availability)	EKG	20
	CIWA	5
Baseline/First Dispensing Visit	Demographics form	5
	Locator form	10
	CIWA	5
	AUDIT	2
	SRE	2
	FTND	1
	NDSS	3
	TLFB	10
	PACS	1
	TQSU	1
	Yale Craving Scale	5
	Contemplation Ladder	1
	Three Factor Eating Questionnaire	3
	Simplified Nutritional Appetite Questionnaire	2
	Reward Based Eating Drive Scale	2
	PROMIS Depression/BDI-II	4
	Stop signal	10
	CPT	10
	Reward Responsiveness Test	15
	Monetary Choice Questionnaire	2
	Alcohol Purchase Task	2
	Cigarette Self-efficacy (SEQ)	1
	Alcohol self-efficacy (AASE)	1
	Cigarette Purchase Task	2
	Inventory of Drinking Situations (IDS-30)	5
	Food delay discounting task	4
	SAFTEE	10
Between Baseline & Follow up visit 1	Call participant on days 2 and 4 to assess side effects SAFTEE/Adverse Effects Checklist	10
Follow up visit 1 (including alcohol consumption session)	Expired CO/Breath Alcohol	4
	CIWA	5
	Yale Craving Scale	5
	Blood draw	5
	Take dose of medication	2
	Smoking break	15
	TQSU	1
	MNWS	1

VISIT	MEASURE/PROCEDURE	TIME (MINS)
	PACS	1
	TLFB	10
	SAFTEE/Adverse Effects Checklist	8
	Cigarette Self-efficacy (SEQ)	1
	Alcohol self-efficacy (AASE)	4
	Stop signal	10
	CPT	10
	Reward Responsiveness Test	15
	Monetary Choice Questionnaire	2
	Alcohol Purchase Task	2
	Cigarette Purchase Task	2
	Food delay discounting task	4
	Weight	1
	Three Factor Eating Questionnaire	3
	Reward-Based Eating Drive Scale	2
	PROMIS Depression/BDI-II	4
	Simplified Nutritional Appetite Questionnaire	2
	Medical check-in	5
	Urine test (pregnancy, drugs, riboflavin)	5
	Priming drink + absorption	35
	TQSU	1
	BAES	1
	AUQ	1
	DEQ	1
	Ad libitum drinking session	120
	Smoking break	15
	TQSU	1
	BAES	1
	AUQ	1
	DEQ	1
	Alcohol Purchase Task	2

VISIT	MEASURE/PROCEDURE	TIME (MINS)
	Cigarette Purchase Task	2
	Smoking break	15
Washout	7 days with no medication	
	TLFB	10
	Dispense 2nd medication	10
	Simplified Nutritional Appetite Questionnaire	2
Between Dispensing & Follow up visit 2	Call participant on days 2 and 4 to assess side effects SAFTEE/Adverse Effects Checklist	10
Follow up visit 2 (including alcohol consumption session)	Expired CO/Breath Alcohol	4
	CIWA	5
	Yale Craving Scale	5
	Blood draw	5
	Take dose of medication	2
	Smoking break	15
	TQSU	1
	MNWS	1
	PACS	1
	TLFB	10
	SAFTEE/Adverse Effects Checklist	8
	Cigarette Self-efficacy (SEQ)	1
	Alcohol self-efficacy (AASE)	4
	Stop signal	10
	CPT	10
	Reward Responsiveness Test	15
	Monetary Choice Questionnaire	2
	Alcohol Purchase Task	2
	Cigarette Purchase Task	2
	Food delay discounting task	4
	Weight	1
	Three Factor Eating Questionnaire	3

VISIT	MEASURE/PROCEDURE	TIME (MINS)
	Reward Based Eating Drive Scale	2
	PROMIS Depression/BDI-II	4
	Simplified Nutritional Appetite Questionnaire	2
	Medical check-in	5
	Urine test (pregnancy, drugs, riboflavin)	5
	Priming drink + absorption	35
	TQSU	1
	BAES	1
	AUQ	1
	DEQ	3
	Ad libitum drinking session	120
	Smoking break	15
	TQSU	1
	BAES	1
	AUQ	1
	DEQ	1
	Alcohol Purchase Task	2
	Cigarette Purchase Task	2
	Smoking break	15

VI. *Anticipated End Date*

We anticipate completing all data collection by March of 2021. At the time of study closure, after all follow-up data have been collected, all participant identifiers (name, address, etc.) will be made inaccessible to the research team. MRN retains the link between identifiers and URSI indefinitely for the potential future benefit to the research participant. Specifically, it may become medically advantageous in the future for a former participant to have access to the clinical information that may be present in the medical screening.

VII. *Project Location(s)*

All study procedures and participant interactions will take place at the Mind Research Network.

VIII. *Participant Compensation*

To compensate participants for their time, participants will receive cash. The payments will be allocated as follows: $50 for completing the consent/screening and medical screening session, $30 for the baseline visit; $130 for completing follow-up visit 1; $180 for completing the medication refill visit and follow-up visit 2. Participants will also receive a $30 bonus for completing at least 75% of scheduled phone-check-ins, up to $24 at each of the follow-up sessions (based on decisions about consuming alcohol or deferring drinks), and a final bonus of $50 for completing all of these study components (to be paid at the final visit). Therefore, the total possible compensation is $500 in base compensation for completing visits/questionnaires, plus up to $48 in additional payments at the laboratory visits, for a total maximum compensation of $548. In the event participants are not able to pick the final cash payment in person, we will offer the option of issuing the final payment via electronic gift card (e.g., Amazon) to the participant's email address.

IX. *Project Resources*

Five private, closed door rooms are available to research staff for study visits at MRN. These assessment rooms have white noise generators outside of the doors to prevent conversations from being overheard. These are reserved by investigators as needed, and are easily accessible. All MRN research staff are trained in regards to the HIPAA Privacy Rule. All individuals will be trained to administer the same consenting and study procedures. Further, all study personnel will have current CITI and HIPAA training throughout the period of the study.

EXPECTED RISKS/BENEFITS

I. *Potential Risks*

Safety and Side Effects Profile of Lorcaserin. Lorcaserin (Belviq®) received FDA approval in 2012 for the indication of weight reduction in patients with obesity (or patients with overweight status and at least one weight-related comorbid condition, such as diabetes). Lorcaserin received FDA approval based on the results of three large, Phase III randomized trials totaling nearly 7,800 subjects. In these trials, lorcaserin was efficacious for weight reduction (e.g., 47.1% of lorcaserin-treated patients had body weight reduction of 5% or more at 12 months, versus 22.6% of placebo-treated participants). The extensive evaluation of lorcaserin in Phase III trials, including subsequent pooled analyses of the safety/side effect data from Phase III trials [114, 115] has generated considerable data on lorcaserin's safety profile. These trials jointly comprise the largest obesity pharmacotherapy dataset in the United States to date.

In Phase III trials lasting up to one year in duration, the most commonly reported side effect/adverse event (AE) was headache (16.8% of lorcaserin participants vs. 10.1% of placebo participants). The next most common AEs were upper respiratory tract infection (13.7% lorcaserin vs.12.3% placebo), nasopharyngitis (13.0% vs. 12.0%), dizziness (8.5% vs. 3.8%), and nausea (8.3% vs. 5.3%). Side effects were generally time-limited, with differences in side effects between experimental groups being observed primarily during the first 1-2 weeks of medication. Rates of serious adverse events (SAEs) were 2.7% and 2.3% in lorcaserin and placebo groups, with 0.3% and 0.2% of participants in these respective groups experiencing treatment-emergent SAEs. None of the reported SAEs occurred in more than one participant. Study discontinuations due to AEs were slightly more common in the medication than placebo groups, however, the placebo-adjusted discontinuation rate of medication-emergent AEs was small (1.8%). Headache was the only single AE associated with a discontinuation rate of >1% (1.8% lorcaserin, 0.8% placebo). There was no evidence of treatment-emergent psychiatric side effects (e.g., increases in depression, suicidality) or symptoms of "serotonin syndrome." [114, 115] Pooled analyses from the Phase III trials also showed that lorcaserin-treated participants had significantly improved outcomes on several secondary measures relative to the placebo group, including significantly greater improvements in lipid profiles and glycemic indicators. Notably, the medication group also reported greater improvements on a measure of

quality of life [115]. Based on Phase I research with lorcaserin, the drug received a Schedule IV designation upon its FDA approval in 2012, due to potential perceptual or quasi-hallucinogenic effects of the drug. However, in a Phase III project examining lorcaserin as an obesity treatment involving roughly 3,400 participants, no reports of hallucinogenic effects emerged in lorcaserin-treated participants, and only six participants reported mild-to-moderate euphoric effects while taking the drug [116]. Further, subsequent experimental research has suggested no effects on perceptual outcomes, and that the drug has very low abuse potential [116]. Acute doses of 40mg and 60mg (considerably higher than the FDA-approved twice-daily 10mg dose) were associated with higher reports of disliking the drug, again indicating unlikely abuse potential [116]. As noted above, there were no unusual safety concerns noted in a Phase II trial of smokers [51]. Following FDA approval in 2012, Belviq® entered the U.S. market in 2013. Since then, no new safety concerns have been noted [114,115]. Overall, based on extensive Phase II and III research with obesity, and initial Phase II research in substance use disorder populations, lorcaserin is proposed as a promising treatment option for substance use disorders [72].

Absence of side effects associated with nonspecific serotonergic agents. Past efforts to advance non-selective serotonergic agents (e.g., *fenfluramine/phentermine, fen-phen*) for obesity - as well as efforts to investigate their efficacy for addiction - were halted due to adverse side effects. However, it is important to note that cardiac and psychiatric side effects of *fenfluramine/phentermine* are attributable to activation of 5-HT_{2B} and 5-HT_{2A} receptors. These side effects are not part of the profile of lorcaserin, which is highly selective for the 5-HT_{2c} receptor. This finding was borne out in the Phase III obesity trials: pooled data that included 20,000 echocardiogram readings over two years of medication exposure found no evidence for increased risk of cardiac valvulopathy [114,115].

Safety profile in participants with substance use disorder. Findings from the first trial of lorcaserin for substance use disorder, which aimed to examine the efficacy and safety profile of lorcaserin in smokers, were consistent with the aforementioned findings [51]. Smokers in this study were either normal weight or overweight, under-weight participants (<18kg/m^2) were ruled out due to a lack of safety studies in this population. The most commonly reported side effects included headache, nausea, dizziness, and constipation. Most AEs were mild or moderate, with no AEs in lorcaserin groups exceeding the rate of the placebo group by more than 3.5%. Rates of any AEs and AE-related discontinuations were 62%/2.5% and 55%/3.0% in the lorcaserin 10mg BID and placebo groups, respectively [51]. No unique safety risks were noted in smokers relative to the results from obesity trials. Overall, neither the Phase III obesity trials (totaling nearly 7,800 participants) nor the Phase II smoking cessation trial (involving 603 smokers) reported any potential interactions or contraindications with nicotine, alcohol or other commonly used drugs. Notably, *there are now a number of randomized trials underway examining lorcaserin in participants with drug use and substance use disorder,* including trials on tobacco, cocaine, and cannabis. A full list of registered randomized trials can be found by searching for “lorcaserin” at ClinicalTrials.gov. While we have no reason to expect adverse effects specific to our study population, we plan to carefully monitor participants to assess potential side effects, and will form a DSMB prior to initiating recruitment.

Monitoring will be the primary responsibility of the PIs and the study physician, who will meet weekly to discuss the status of the trial. In addition, we will establish a Data and Safety Monitoring Board to maximize safety. The DSMB will include two physicians, and the head of the IRB,. This board will meet at least every six months to review data quality, recruitment and retention, and to review all serious or clinically significant adverse events. In addition, the board will review safety data following any serious adverse event that appears to be study related. Patterns of adverse events as well as individual events may indicate the need for operational changes, protocol modifications, a decrease in dose, or, conceivably, discontinuation of the trial.

Pharmacokinetic and pharmacodynamic profile. According to the prescriber's brochure, lorcaserin reaches peak plasma concentrations in 90 - 120 minutes after oral dosing. Steady-state plasma levels are achieved after 3 days of twice-daily dosing, and the plasma half-life is roughly 11 hours.

Human studies have demonstrated that lorcaserin distributes to cerebrospinal fluid and the CNS. Lorcaserin is metabolized via multiple enzymatic pathways in the liver and excreted primarily (92%) in urine. Its metabolites shows no activity at 5-HT receptors.

Selected dosage and medication duration. The current study will use the FDA-approved dosage of 10mg twice- daily (BID). This dosage was used in the recent smoking cessation trial noted above. We will use a 7-day medication schedule because a) this allows more than adequate time to reach steady-state plasma levels, and b) this time frame allows us to capture short-term changes in naturalistic smoking/craving in this sample. Of note, recent data suggest that lorcaserin has acute effects on reducing nicotine intake when administered 15 min. prior to testing [45] , suggesting that short-term medication exposure is adequate to observe effects on addiction-related outcomes. In addition, the first neuroimaging study of lorcaserin found differences in neural reactivity to hedonic food cues following one week of treatment [117].

Questionnaire and Interview Assessments. There are potential psychological risks associated with assessment procedures. Participants may find the battery of psychiatric and psychological assessments tedious or intrusive. Participants may experience discomfort resulting from questions about personal histories or substance use patterns.

Participation in Alcohol Administration Sessions. Other potential risks include those related to participation in alcohol administration sessions. For example, it is possible that participants may experience dizziness/nausea from drinking during these visits, or during smoking breaks. Our group has considerable experience with alcohol administration and self- administration procedures [74-78], and the safety precautions required in these studies. These procedures will follow the NIAAA recommended guidelines for administering alcohol to human subjects (https://www.niaaa.nih.gov/Resources/ResearchResources/job22.htm). In particular, we have taken measures to protect against ethical concerns by excluding treatment-seekers or those engaged in an active quit attempt.

Confidentiality/Privacy. Risks from potential breaches of confidentiality include invasion of privacy, as well as social and economic risks. Economic risks include alterations in relationships with others that are to the disadvantage of the subject, and may involve embarrassment, loss of respect of others, labeling with negative consequences, or diminishing the subject's opportunities and status in relation to others. There is also a risk of breach of data confidentiality (uncommon).

Risks Related to DNA Collection. The purpose of collecting saliva for DNA in this study is to allow secondary analyses to examine whether medication effects might be different according to certain genetic factors. The main aim of this analysis will be to examine the *CYP2A6* gene, which is related to nicotine metabolism. These analyses may also focus on genetic factors potentially associated with drug use or related behaviors, such as impulsivity. Potential risks associated with DNA collection involve potential identification, and there may be risks with genetic (DNA) tests that are as yet unknown. Genes may be shown at some point in the future to be related to mental illnesses or tendency to addiction. Samples will be labeled with participant ID only, and analyzed at an outside laboratory. Samples will be destroyed upon completion of the analyses. We will not conduct any whole genome sequencing of the DNA samples. Additionally, the consent form will state that participants have the option to opt out of DNA collection, and to request that their samples are destroyed at any time during the study. Participants will not receive any feedback from any of the genetic tests from study staff.

Plan for Preventing/Minimizing Risks:

Provisions to Monitor the Data to Ensure the Safety of Subjects:

Medication and Side Effects Monitoring. Although we anticipate the risk of adverse events to be low based on the safety profile of the medication, several steps will be taken to track and report medication-related side effects. A project staff member will contact participants during medication weeks to assess potential side effects. Participants will be given a contact number for study medical staff in case of serious emergent side effects. Participants will return to the lab for repeat follow-up examinations (including weight, heart rate/blood pressure measurements) following the 7-day medication phase. All adverse events will be documented and reported in accordance with UNM OIRB and MRN policies, applicable FDA regulations, and the regulations of NIH.

Confidentiality/Privacy. Any computerized data will be password protected and contained on a secure, password-protected computer or a secure server. Recruitment data (de-identified) will be stored in a secure, password-protected file accessible only to the study investigators and personnel. At the end of recruitment, eligible subject files will be separated from those failing to meet eligibility criteria, and records of ineligible recruitment subjects will be anonymized. Data pertaining to screening failures will be tabulated in an anonymized fashion. Data collected in other formats (e.g., medical screening notes) will be labeled only by study identifier and stored in binders in secure, locked cabinets while the study is taking place. Files will be stored and archived in accordance with Good Clinical Practice (GCP) standards. For all questionnaire and interview assessments, participants will be informed that they may decline to answer any question if they so choose.

Risks Related to Alcohol Administration Sessions. To ensure participant safety, a member of the study staff will be present for the duration of all alcohol administration sessions, and a member of the study medical staff will be on call during these sessions. As noted, we are recruiting participants who are non-treatment-seeking, due to the laboratory alcohol self-administration procedures. Additionally, any participants who express a desire to seek treatment during the study will be excused from further participation and provided with cessation resources. Co-I Wilcox, an addiction psychiatrist, will provide participants with referral advice as needed.

As per the NIAAA guidelines, research studies involving alcohol administration are typically restricted to non-treatment-seeking participants in order to minimize ethical concerns, as will be the approach in this study. Regarding alcohol dose, we will use sex- and body-weight adjusted formulas [93] to ensure that the BrAC increments associated with the alcohol session beverages approximate the intended range (increment of .03g% for the priming drink, and average increments of .015g% for subsequent drinks). BrAC levels are estimated to decline at an approximate rate of .015g% to .020g% per hour (with variability across participants), thus, BrAC levels will remain within a safe range considering the two-hour self-administration period (with 4 drinks allowed per 1-hr. block). Participants will have undergone a medical screen prior to participation, and will be excluded if the study medical staff has reason to believe that alcohol is contraindicated (e.g., due to medical conditions or medications). Vitals signs (HR, BP) will be measured during the sessions. Following the completion of alcohol sessions, participants will be escorted to a private room designated for recovery purposes. Participants will only be discharged after their breath alcohol concentration is <.03g% (verified by at least two separate readings), consistent with NIAAA recommendations. Participants will also be provided with reimbursement for transportation if they have not arranged for a ride (participants will be instructed not to drive to the session).

Compensation for Research-Related Injury. No commitment is made by MRN to provide free medical care or money for injuries to participants in this study. This is clearly stated in the consent form.

Economic Burden to Subjects. Participants will not be charged for any of the experimental study procedures. If incidental findings from the study (e.g. abnormal EKG findings or abnormal hepatic/metabolic labs) result in the need for further evaluation/treatment, the participant or their insurance company will be responsible for additional clinical evaluation/treatment that may be

needed. Also, incidental finding information is disclosed only to the individual participant. However, if a participant chooses to disclose such information to their personal physician, this may become part of their medical record which may or may not have an effect in the future on getting health or life insurance.

II. *Benefits*

The participants in this study are not expected to benefit directly from their participation. However, the knowledge gained from this study could lead to a better understanding of a medication with potential to treat AUD, and potentially other substance use disorders. Given the use of an FDA-approved medication that has been deemed safe in the context of chronic administration for weight reduction, the risks to which participants will be exposed during this short medication screening trial are deemed relatively small in comparison to the potential benefits of the proposed research (i.e., demonstrating potential efficacy of a new medication).

III. *Privacy of Participants*

Five private, closed door rooms are available at MRN. The rooms have white noise generators outside the doors to prevent conversations from being overheard. All staff are trained in the HIPAA Privacy Rule.

IV. *Unanticipated Problems/Adverse Events*

All project staff will be trained to identify adverse events (AEs), which must be reported to the PI within 24 hours, and serious adverse events (SAE) must be reported to the PI as soon as possible after a staff member becomes aware of an SAE. In addition, any unanticipated participant issues will be discussed in weekly staff meetings, which will provide another opportunity to identify AEs. Anticipated problems and AEs will be reported to the OIRB within 7 calendar days.

V. *Participant Complaints*

If a participant wishes to issue a complaint or request information about the research, they may notify any study team member or the site PI, Eric Claus, at (505) 272-5028, Monday – Friday from 8am – 5pm. Participants may also contact the UNM Office of the IRB, (505) 277-2644, irbmaincampus@unm.edu. Website: http://irb.unm.edu/

Depending on the nature of the complaint, the problem will be resolved directly with the participant, if possible, in a confidential and timely manner. Complaints that constitute a reportable event will be submitted to the IRB within 7 days. Participant complaints will be coded with a unique research subject identifier and kept in their respective study folder in a locked office for record-keeping purposes.

PROJECT DATA

I. *Data Management Procedures and Confidentiality*

Consent Forms: Signed consent forms are stored in a locked cabinet in a locked office at MRN.

Questionnaire Data: All data are coded with a unique research subject identifier (URSI) number. Electronic data are stored on a drive only accessible by the research team on a secure MRN server and/or in the COINS database on a secure HIPAA compliant cloud based server. Electronic data captured by RedCap are stored on a secure server, and identified by participants ID only. For non-computer based forms, such as the neuropsychological assessments, the data collection sheets are stored in a locked cabinet in a separate locked data storage space at MRN.

Behavioral Data: All data are coded with the URSI, and collected and stored electronically. Electronic data is stored on a drive only accessible by the research team on a secure MRN server. De-identified data resulting from this study may also be presented at meetings, published in journals/books, used in classrooms for training/teaching purposes, and may be shared with other

researchers including scientists at other universities and institutions. In addition, this study will be registered at ClinicalTrials.gov, and de-identified information from this study will be submitted to ClinicalTrials.gov.

Data and safety monitoring plan: See attached plan.

Certificate of Confidentiality: In addition to the above protections, this study has a Certificate of Confidentiality from NIH to further protect participant confidentiality. Importantly, as stated in the consent, participants are informed that if they report current abuse of a child or an elder, we will report the person to the proper authorities, consistent with New Mexico state law.

Finally, participants will be given the option of having all their data (behavioral assessments) stored in the MRN Data Repository (UNM HRRC# 06-387, PI: Roberts).

II. *Data Analysis/Statistical Considerations*

Primary and secondary outcomes will be evaluated using mixed linear effects models with condition (lorcaserin, placebo) as a within-subjects factor and medication order as a between-subjects factor. Maximum likelihood estimation will be used to account for missing data by analyzing all available cases. The primary outcome is number of laboratory drinks consumed. Using the same model, the secondary outcomes examined will be (1) cigarette and alcohol demand (based on corresponding purchase tasks) and self-reported craving after the priming alcohol dose, (2) levels of alcohol effects (stimulation/sedation) after the priming alcohol dose, and (3) cigarettes per day and drinking frequency/quantity during the 7-day medication phase. Exploratory analyses will also examine changes in alcohol stimulation/sedation and alcohol/cigarette demand and craving across all assessment time points (i.e., 30/60/90/120 minutes) by including time as an additional within-subjects factor and BrAC as a time-varying covariate. Mixed linear effects models will be adapted to examine medication effects on impulsivity/learning tasks constructs, and medication tolerability and side effect profiles. Sex will be examined as an exploratory moderator in all analyses.

Statistical Power. Because no human data on lorcaserin's effects on laboratory alcohol outcomes are available, we examined medication effect sizes in prior studies using similar populations involving the laboratory tasks that serve as our primary outcome (alcohol self-administration) and key secondary outcomes (subjective response to a moderate dose of alcohol). In studies of heavy-drinking smokers, varenicline yielded a large effect on number of laboratory drinks consumed (Cohen's d = 0.97; N = 10 per group, between- subjects [16] and small-to-large effects on subjective alcohol effects at doses of .03g% or .06g% (d ~ 1.00 [16]; d =0.18 to 0.93; N = 30 per group, between-subjects [28]). Taking into account the potential for a smaller effect size for locaserin relative to varenicline, power analyses assumed a medium effect size. We selected a within-subjects design, which is recommended to maximize power in medication screening studies [112], and assumed a within-subjects correlation of 0.60 for laboratory outcomes (as reported in prior cross-over human laboratory medication screening designs). Using these assumptions and an alpha of .05, we estimated power in G*Power software using a fixed effects, within-subjects design and two time-points. Conservatively, a final sample of N = 34 allows sufficient power (.80) to detect a medium within-persons medication effect on primary and secondary outcomes. To allow for roughly 20% attrition during the medication trial, we propose to randomize 42 participants to arrive at the final sample.

III. *Participant Withdrawal*

Participants may withdraw from the study at any time. The PI may choose to withdraw participants from the study if the participant's status changes (e.g., health change, becomes

incarcerated), is suspected of intentionally providing false data, or other reasons that would lead to poor data quality (e.g., very poor performance in impulsivity tasks). Data from withdrawn participants will be evaluated on a case by case basis. For participants that withdraw themselves from the study, we will use data they provided prior to withdrawing. If the PI chooses to withdraw the participant, data will only be used if it meets quality control standards (e.g., adequate behavioral performance, limited missing data).

PRIOR APPROVALS/REVIEWED AT OTHER IRBS

MRN Departmental Review

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ATTACHMENTS

Advertisements:
Lean_study_M1
Lean_study_M2

Measures (listed alphabetical):
ADS
Alcohol Purchase Task
AUDIT
BAES
CES-D
CIWA
Contemplation Ladder
Cigarette Purchase Task
Daily Survey
Demographics form
DEQ
Fagerstrom Test for Nicotine Dependence
Inventory of Drinking Situations
Locator form

Monetary Choice Questionnaire
Minnesota Nicotine Withdrawal Scale
Nicotine Dependence Syndrome Scale
Penn Alcohol Craving Scale
Positive and Negative Affect Scale
Reward Based Eating Drive Scale
Self Rating of the Effects of Alcohol Questionnaire
Simplified Nutritional Appetite Questionnaire
Three Factor Eating Questionnaire
Tiffany Questionnaire of Smoking Urges
UPPS-P Impulsivity Questionnaire
Wisconsin Smoking Withdrawal Scale

Data Collection Forms:
Study Med Count
Vitals
Conconcomittent Meds
Medical History
Physcial Exam
SAFTEE

Other
SAE Report
SAE Report follow-up
Adherece Handout
Belviq prescribing information
Lexicomp report for lorcaserin
MRN Departmental Review Form
Grant application
Data safety monitoring plan