UNM IRB PROTOCOL

TITLE:	Lorcaserin effects on smoking behaviors
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BACKGROUND/SCIENTIFIC RATIONALE

Despite declines in smoking prevalence in the United States, the likelihood of successfully quitting smoking has not improved [1, 2]. Roughly three in four smokers report the desire to quit, and up to half report past-year quit attempts [3, 4]. However, only 4-5% of smokers achieve sustained cessation in a given year [4], with relapse typically occurring within 5-10 days of a quit attempt [5, 6]. While the introduction of varenicline in 2006 was followed by marginally greater rates of pharmacotherapy utilization, no appreciable changes in sustained cessation have been observed since [4]. Given only three FDA-approved smoking cessation aids (varenicline, bupropion, and nicotine replacement therapy), advancing novel smoking cessation therapies is a critical aim [1, 7]. In principle, establishing a repertoire of medications will improve options for combination and personalized treatments [8-10]. Because the three FDA-approved smoking cessation medications each act on nicotinic receptors, identifying novel therapies with alternate pharmacological targets is a key priority [1,7].

The serotonin (5-HT) system is broadly implicated in the regulation of reward-related behavior, including drug seeking [11, 12], in part reflecting the role of 5-HT in regulating dopamine (DA) function [12, 13]. Historically, efforts to study the 5-HT system in relation to addiction have been complicated by the diversity of 5-HT receptors (7 distinct families and 14 receptor subtypes), as well as the opposing effects of some receptor subtypes on reward-related behavior [14]. Notably, selective serotonin reuptake inhibitors (SSRIs) have not proven efficacious for substance use disorders (SUDs) [11, 15]. However, given the diffuse action of SSRIs, and divergent effects of some 5-HT receptor subtypes on behavior, the evidence base on SSRIs does not rule out consideration of specific 5-HT receptors as therapeutic targets [11]. Importantly, 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 [11]. Of relevance to this application, substantial preclinical evidence supports the role of the 5-HT_{2C} receptor in reward-related behaviors, including drug-seeking [11, 12, 16].

Considerable evidence shows that targeted modulation of 5-HT_{2C} receptors alters reward-related behaviors, including food- and drug-related motivation, intake, and reinstatement [11, 17-19]. Generally, food- and drug-seeking behaviors are attenuated by 5-HT_{2C} agonists, and may be enhanced by 5-HT_{2C} antagonists [11, 14, 17]. The majority of work in preclinical models of addiction has concerned nicotine and cocaine. Notably, findings from several groups show that selective 5- HT_{2C} receptor agonists (including Ro 60-1075 and lorcaserin) reduce both nicotine self-administration and reinstatement [11, 16, 18, 20]. Fletcher and colleagues conducted much of the preclinical work on nicotine, demonstrating that 5-HT_{2C} receptor agonists attenuate nicotine self-administration and reinstatement, as well as hyperactivity and impulsive responding induced by nicotine [11, 18, 20, 21]. Notably, both acute

(single-dose) and chronic lorcaserin treatment reduces nicotine self-administration in non-human primates [22]. Moreover, treatment with 5-HT_{2C} receptor agonists attenuates self-administration of cocaine and other addictive drugs, raising the prospect of broader therapeutic applications for SUD [11, 16]. Clinical applications of 5-HT_{2C} receptor agonists. Reflecting the role of 5-HT_{2C} receptors in consumptive behaviors, selective 5-HT2C drugs were developed largely in pursuit of novel treatments for obesity. In 2012, lorcaserin (Belviq®) became the first FDA-approved selective 5-HT2C receptor medication for weight management. Approval of lorcaserin was based on three large Phase III trials totaling nearly 7800 subjects [23- 25]. In these studies, lorcaserin led to significant weight reduction with a favorable safety profile. Importantly, while the off-target side effects of non-selective 5-HT agents (e.g., fenfluramine) have prevented clinical translation, extensive Phase II/III work shows that lorcaserin has a favorable safety profile [26, 27]. Following from preclinical work with nicotine, an initial Phase II study of lorcaserin with smokers was reported recently [28]. Smokers were randomized to placebo or lorcaserin at one of two doses: 10mg QD (daily) or 10mg BID (twice daily). Relative to placebo, 10mg BID (the FDA-approved dose) significantly increased continuous abstinence rates (OR = 3.02, 95% CI = 1.47-6.22) [28]. Lorcaserin also had a favorable safety profile in smokers, with the most common side effects including headache, fatigue and nausea. As the only 5-HT2C medication with Phase III validation and FDA approval, lorcaserin has near-term potential for repurposing as a candidate SUD treatment [11, 16]. Further human work is needed to clarify lorcaserin's effects on smoking-related behaviors.

Clarifying mechanisms of treatment efficacy is critical for informing intervention design. Importantly, evidence that 5-HT2C receptor agonists reduce both food- and drug-seeking implies the possibility of one or more common mechanisms. Although the efficacy of 5- HT2C agonists for weight reduction was initially attributed to their effects on satiety, evidence that 5-HT2C agonists reduce operant responding for conditioned reinforcers strongly implicates motivational, appetitive and/or hedonic processes [17]. As reviewed recently by Fletcher and colleagues [17], a leading possibility is that 5-HT2C receptor agonists reduce responding for conditioned reinforcers by altering DA-mediated incentive motivation, consistent with the role of 5-HT2C receptors in 5-HT-related inhibition of DA function. Specifically, 5-HT2C agonists are shown to blunt DA release in the nucleus accumbens (NAc) under basal conditions [13, 29, 30]and, furthermore, to blunt drug-induced NAc DA release [31]. These data imply that 5-HT2C agonists could reduce drug-seeking by way of a generalized inhibitory effect on DA function, and/or by inhibiting DA activity associated with conditioned drug cues specifically. Consistent with the latter possibility, the first human imaging study of lorcaserin showed reduced BOLD response to hedonic food cues after one week of treatment [32].

Another explanation for 5-HT2C agonists' ability to reduce food and drug intake concerns their influence on impulsivity. Behavioral indices of impulsivity are generally attenuated by 5-HT2C agonists (and amplified by 5- HT2C antagonists), typically in the absence of altered baseline motor activity [17]. These findings have informed the hypothesis that the ability of 5-HT2C receptor agonists to reduce food/drug intake are partly mediated by reductions in impulsive responding (or conversely, improved inhibitory control) [17]. Given the central role of impulsivity in drug intake and relapse liability [33, 34], support for this hypothesis in human studies could carry significant implications: therapies that concurrently reduce drug intake while improving behavioral control would have particularly high appeal [35]. Of note, preclinical evidence indicates that 5-HT2C receptor agonists may have differential effects on measures of impulsive action (e.g., premature responding) versus impulsive choice (e.g., temporal discounting) [17]. While speculative at present, these findings could imply that specific impulsivity domains are involved in mediating drug effects on reward-related behavior. To date, no human studies have sought to characterize the effects of 5-HT2C agonists on impulsivity domains.

Human laboratory studies play a pivotal role in drug development by providing an efficient, cost-effective bridge between preclinical studies and full-scale randomized trials [36-43]. By allowing

efficient cross-validation of both preclinical and Phase III results, human experimental studies serve a cornerstone role in translational drug development [7, 36, 37, 44]. An ancillary advantage of these studies is the ability to test putative mechanisms of pharmacotherapy effects under controlled experimental conditions [41]. As noted, clarifying treatment mechanisms is a critical goal that ultimately informs treatment design, and can also inform selection of clinical endpoints for Phase III trials [36]. Notably, most candidate SUD medications are tested in Phase III trials without prior or subsequent study in human laboratory models [36]. Despite lorcaserin's appeal as a candidate therapy for smoking cessation [11, 16], no human laboratory investigations of lorcaserin have been reported. Importantly, recent reviews have also highlighted areas in which laboratory studies can be improved. First, many laboratory studies are limited by a sole focus on self-report outcomes (e.g., craving), which lack a direct analogue in animal models [45, 46]. Relative to self-report outcomes, drug self-administration outcomes appear more sensitive to pharmacotherapy effects, and may improve consistency in findings across preclinical and human studies [36]. Additionally, self-reported craving - while undoubtedly a clinically important construct - is neither necessary nor sufficient for self-administration, supporting the need to prioritize objective self-administration outcomes [47]. Another limitation of most human lab studies concerns their discordance with Phase III trials in terms of sample characteristics. A key limitation, as highlighted in a recent systematic review, is that human laboratory studies of smoking pharmacotherapy typically recruit non-motivated smokers, limiting comparisons with Phase III trials [44]. Importantly, evidence shows that recruiting non-motivated smokers undermines the ability to detect medication effects, whereas recruiting smokers with some motivation to quit (even if not engaged in an active quit attempt) improves effect sizes in medication screening trials [39].

OBJECTIVES/AIMS

The proposed project will leverage human laboratory methods to study behavioral processes by which 5-HT2C receptor agonism might alter cigarette consumption and relapse. Using a double-blind, within-subjects, counterbalanced laboratory design, we will randomize smokers to short-term treatment with lorcaserin (10mg twice-daily) or placebo prior to completing human laboratory sessions. Laboratory endpoints will include both nicotine-specific (e.g., reinstatement, self-administration) and nicotine-nonspecific (e.g., impulsivity) outcomes selected on the basis of preclinical studies of 5-HT2C receptor medications.

Aim 1. To examine the effects of lorcaserin vs. placebo on laboratory indices of nicotine reinstatement (lapse) and self-administration.

Aim 2. To examine the effects of lorcaserin vs. placebo on nicotine-nonspecific behavioral processes implicated in preclinical studies of 5-HT2C receptor drugs.

PROJECT DESIGN

I. *Target Population and Inclusion/Exclusion Criteria*

A final sample of 42 nicotine-dependent cigarette smokers will be recruited from the community.

Inclusion Criteria
a) age 18-65 [28]
b) smoking 5+ cigarettes per day (average) over the past year, with no period of abstinence > 90 days
c) biochemical verification of smoking status, based on expired CO $\geq$ 8 at baseline
d) baseline Fagerström (FTND) score of 5+ (indicating at least moderate nicotine dependence)

e) reporting long-term motivation to quit smoking (defined as interest in a quit attempt within the next 12 months [39])
f) willingness to take study pills and complete study procedures
g) willingness to complete lab sessions involving cigarette smoking

Exclusion Criteria
a) meeting DSM-5 criteria for substance use disorder aside from tobacco use disorder and mild cannabis use disorder
b) recent (30 day) illicit drug use (except marijuana), based on self-report and urine drug screen
c) Past 30-day use of tobacco cessation aids or nicotine/tobacco products other than cigarettes
d) Past 30-day use of SSRIs, other psychiatric medications, or weight control medications
e) lifetime diagnosis of severe mental illness (e.g., psychotic or bipolar I disorder)
f) significant medical or neurological illness based on the medical staff (i.e., physician or nurse practitioner) evaluation including severe hepatic impairment or cirrhosis, insulin dependent diabetes
g) actively engaged in smoking cessation treatments or a smoking cessation attempt (or intent to start an attempt in the next 90 days)
h) interested in quitting smoking immediately (i.e., in the next two months)
i) Medications which are contraindicated for use with lorcaserin (bromocriptine, cabergoline, dapoxetine, dihydroergotamine, ergoloid mesylates, ergonovine, ergotamine, methylene blue, methylergonovine, nicergoline, pergolide, thiorizadine) or which have a significant interaction with lorcaserin (bupropion, doxorubicin, eliglustat, linezolid, perhexiline, rasagiline, safinamide, selegiline, tamoxifen)
j) body mass index (BMI) under normal range (BMI < 18 kg/m^2)
k) history of significant cardiovascular conditions including history of arrhythmias or heart block, heart failure, valvular heart disease, heart attack, stroke, unstable angina
l) abnormal electrocardiogram (ECG) results
m) 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 consent up to 100 participants in order to obtain a final sample of 42 eligible participants who complete all study sessions.

III. *Recruitment and Screening Procedures*

Participants will be recruited from the community. Participants will be recruited through flyers, radio/TV ads, movie theaters, word of mouth, press releases, newspaper ads, business cards, online postings (e.g. Craigslist, Google Adwords, Facebook, Instagram, clinicaltrials.gov) within the Albuquerque metro area, and email communications directed towards community groups. 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 other than those from the MRN Participant Recruitment Registry, 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. No coercion or undue influence will be used. 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 18 hours over a period of approximately 5 weeks. This includes a screening visit (up to 3 hours), a baseline visit (up to 3 hours), and two follow-up visits (up to 5 hours each). In addition, participants will complete a follow-up medication refill visit (1 hr.) and daily questionnaires online (using Redcap) every day (1-2 minutes per day), and will receive calls twice from staff during each of the medication phases to check in on side effects (up to 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 cigarette, alcohol, and drug use, medications, and medical history. Potential participants will be given a brief description of the study, following a designated script. 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. The initial telephone contact is estimated to take roughly 10-15 minutes. Included in the phone screen will be a series of questions about interest in quitting (e.g. are you interested in making an attempt to quit in the next 3, 6, or 12 months?). This question is to ensure that a) participants are not planning to make an imminent quit attempt in the next 3 months (given the laboratory smoking sessions), and b) that participants report some degree

of long-term motivation to quit (which has been shown to increase effect sizes in medication screening studies).

Screening and Baseline Data Collection Visits

Prior to any assessments, we will obtain informed consent from all participants. The in-person screening visit will include both a clinically-oriented screen by a medical staff member (study physician or nurse), and self-report and interview questions, conducted by the research assistant or medical staff member. The staff will administer a urine drug screen (for females, the test will also include a pregnancy screen), and then briefly review and verify information collected over the phone. In all cases in which the pregnancy test shows a positive result, the results of the test will be given to only the participant in a private room. We will also measure expired alveolar carbon monoxide (CO) at the screening visit.

Additional screening criteria, including symptoms of nicotine and alcohol dependence, and aspects of medical history (see criteria listed above) will be assessed. The **Structured Clinical Interview for DSM-V** [76] will be used to assess inclusionary and exclusionary diagnoses. The **Timeline Follow-Back (TLFB)** [77] will be used to assess cigarette, alcohol, and other drug use in the 90 days prior to baseline, and the **Fagerström Test of Nicotine Dependence** [78] will be used to assess nicotine dependence. Consistent with prior studies [39], motivation for cessation at screening will be measured by asking participants about **intent to quit** in the next 3, 6, and 12 months (intent to quit within 12 months serves as the index of motivation, whereas intent to quit within 3 months will be exclusionary). 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, and a hepatic function panel. The baseline blood sample will also serve as the sample for DNA analysis. Blood draws will be performed by trained research staff. Participants will also complete an ECG test. 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. The initial consent and eligibility interview session is projected to take up to 3 hours.

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. 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.

Participants who meet all study eligibility procedures will be provided with a study overview, and locator and collateral contact information will be obtained.
A **Demographic Screening Questionnaire** will assess basic demographic factors (e.g., age, education, income). The **Timeline Follow-Back (TLFB)** [77] will be used to assess cigarette, alcohol, and other drug use since the screening visit, and during the study phase. Other baseline measures will include the **Nicotine Dependence Syndrome Scale** [79], the **Wisconsin Inventory of Smoking Dependence Motives** [80], and the **Alcohol Use Disorders Identification Test** [81]. To assess stages of motivation during the study, and a **Contemplation Ladder** [82]. The **PROMIS** Depression scale and **Beck Depression Inventory-II** will be administered to assess potential negative effects on 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** will be administered to obtain an estimate of IQ. The **Yale Craving Scale** will be used to measure craving/withdrawal over the past week. When possible, baseline questionnaires will be collected using a computerized system (i.e., Redcap). Any measures that would be expected to show change across sessions (or in response to medication) will be repeated at follow-up visits. Participants will also be asked to provide a saliva sample for genetic analyses. The primary objective of these analyses is to examine functional variants in the *CYP2A6* gene. The CYP2A6 enzyme is primarily responsible for the metabolism of nicotine. Several *CYP2A6* variants have been identified that alter nicotine metabolism, and some have been linked to smoking outcomes. Because *CYP2A6* variation has also been linked to responses to nicotine pharmacotherapy, we will examine genetic moderators of response to medication effects on smoking outcomes. We may also investigate genetic variants implicated in substance use and related traits (e.g., impulsivity, which is another focus of the present application).

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. These tasks include: Stop Signal, Continuous Performance Test, Monetary Choice Questionnaire, Cigarette Discounting Task, Food Discounting Task, Cigarette Purchase Task, and a Reward Responsiveness Test.

The baseline session will require up to 3 hours to complete. 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). On Day 7 participants will return to complete the human laboratory session described below. This visit will also include a repeat of the medical tests/measurements (noted above), a calendar-based assessment of interim cigarette use, other substance use, and medication adherence, and a pill count. Following the laboratory visit on Day 7, participants will undergo a washout phase of at least 7 days. Next, they will repeat the same 7-day sequence in the alternate pill condition, culminating in a second, identical human laboratory 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 physician, participants may be provided with additional days of medication as needed. During the medication phases, side effects will be assessed with the **SAFTEE questionnaire** [106] and an **Adverse Events Checklist** [107]. 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 of cigarettes smoked; 2) peak prior-day craving; 3) any emergent side effects; and 4) medication adherence for the prior day. Participants will have the option of completing the brief survey via smart phone. If participants do not own a smart phone, we will provide an email link to the survey, or if preferable, a text message containing the survey questions.

Follow-up Sessions 1 and 2. At each of two identical sessions (corresponding with the end of the medication weeks), participants will report to MRN in the morning, after receiving instructions to abstain from cigarettes (overnight) and from and alcohol (for 24 hours). Expired alveolar carbon monoxide (CO), breath alcohol concentration (BrAC), body weight, and heart rate/blood pressure will be collected at each in-person visit. Upon arrival, overnight smoking abstinence will be verified based on expired CO of <6ppm (or <50% of the initial screening reading). Participants will then provide a urine sample for riboflavin detection (as an index of adherence). A blood sample (up to 20 ml) will then be taken in order to assess metabolite levels of the medication. Blood draws will be performed by trained research staff. Participants will take that day's medication dose under supervision. Sessions will include three main elements: 1) computerized measures of impulsivity and reward sensitivity, 2) follow-up self-report (e.g., cigarette use, craving, self-efficacy) and medical (e.g., side effects, body weight) assessments, and 3) laboratory measures of smoking cue reactivity, reinstatement, and self-administration, as detailed below. The latter tasks will occur in a place equipped with a ventilated system for smoking studies.

Computerized behavioral tasks. Participants will complete validated behavioral tasks assessing impulsive action and impulsive choice, as described below. Selection of these constructs is based on preclinical observations that 5-HT_{2C} receptor agonists reduce impulsive responding, and may preferentially influence measures of impulsive action, as opposed to impulsive choice. Because another possible mechanism by which lorcaserin influences consumptive behaviors is through reduced sensitivity to reinforcers generally [17], we will also include a validated behavioral assay of reward responsiveness. Tasks will be administered twice at the follow up visit (prior to and following the lapse procedure) to assess possible changes following nicotine exposure. These tasks include: Stop Signal, CPT, Monetary Choice Questionnaire, Cigarette Discounting Task, Food Discounting Task, Cigarette Purchase Task, and a Reward Responsiveness Test.

Cue-elicited craving. Human studies of the effects of 5-HT_{2C} agonists on cue-elicited drug craving have not been reported. To address this objective, we will utilize an established cue reactivity task to assess peak provoked craving (PPC). This procedure, which involves assessing craving during a cue exposure task (lighting a cigarette and attending to cues) while in a period of short-term abstinence, has been demonstrated to reliably induce acute craving [71]. Given the potential for differential medication effects on tonic vs. phasic craving [74], tonic craving will also be assessed as a component of the repeated self-report assessments (noted below).

Simulated lapse. The cue reactivity task will lead directly into the simulated lapse procedure developed by McKee, who is a consultant on this project [38, 75]. Importantly, preclinical evidence shows that lorcaserin reduces both nicotine reinstatement and self-administration. The McKee paradigm is the only validated laboratory procedure that models each of these outcomes [38]. In this procedure, a nicotine deprivation period (e.g., overnight abstinence) provides a context to study medication effects on reinstatement [38]. Participants will be presented with a package of their preferred cigarettes (participants will be asked to bring one unopened pack in to the session). Participants will given the choice to initiate cigarette smoking, or to delay smoking for up to 50 minutes in exchange for monetary reinforcement. Prior studies show that a reinforcement schedule of $1 for every 5 minutes results in participants resisting, on average, for 25 minutes, providing ideal variability in time to reinstatement [38]. If no lapse occurs (i.e., the participant resists for 50 minutes), participants will not be forced to smoke a cigarette. Following the initial decision to smoke, participants will complete assessments of craving, withdrawal, and subjective effects (described below).

Next, a 60-minute period of ad libitum smoking will ensue [68]. Participants will be presented with a tray containing 8 cigarettes from the package, and will have the opportunity to smoke additional cigarettes at their discretion [68]. Again, participants will not be forced to smoke a cigarette. Repeated ratings of craving, withdrawal, and subjective effects will be taken at 15-minute intervals during the self-administration period. A follow-up measure of expired CO will be taken at the end of the session to measure CO "boost", an additional index of cigarette intake.

The primary outcomes for the human laboratory sessions consist of 1) nicotine reinstatement (i.e., minutes of resistance to smoking reinstatement), and 2) nicotine self-administration (i.e., cigarettes consumed during ad libitum smoking). These primary outcomes are selected because they reflect objectively defined behaviors analogous to those reported in preclinical studies of 5-HT_{2C} medications. Secondary human laboratory outcomes will include peak-provoked craving during the cue exposure task, CO boost, and subjective effects during nicotine self-administration, e.g., assessed by the **Modified Cigarette Evaluation Scale** [90] and the **Drug Effects Questionnaire** [91]. The **Positive and Negative Affect Scale** [92] will also assess change in mood.

To assess lorcaserin's effects on behavioral measures of impulsivity, we will use validated measures of impulsive action (a Continuous Performance Test, CPT), and impulsive choice (the Monetary Choice Questionnaire, MCQ, assessing temporal discounting). The Connors' CPT II task [93] requires participants to attend to a sequence of numbers and press a button for every letter that appears on the screen except the letter 'X'. The task outcomes include number of correct detections, (a measure of attentional capacity), reaction time (processing speed), omission errors (distractibility), and commission errors (a measure of impulsivity and the key outcome for this study). Importantly, preclinical studies have found effects of 5-HT2C drugs on impulsivity when using the 5-choice Serial Reaction Time Task [94, 95], which was originally designed as a rodent analogue of the CPT. The MCQ [96]is a measure of temporal discounting (or impulsive choice). Participants indicate their preferences on each of 27 items that present an immediate and delayed reward (e.g. $19 today or $25 in 53 days). From these choices, it is possible to derive a discounting value, k, reflecting the extent to which one discounts future rewards in favor of immediate rewards. A similar Cigarette Discounting Task [103], and a Cigarette Purchase Task [104] will further serve as behavioral indices of drug-related impulsive choice. Finally, given the additional possibility that 5-HT2C agonists may reduce aspects of reward-based responding generally, a Reward Responsiveness Test [97] will be included. In this task, participants must discern between two similar, briefly presented (i.e. 100ms) stimuli. During each block of 100 trials, participants receive rewards on 40 of the correct trials; however, unbeknownst to participants, the two stimuli are rewarded on different reinforcement ratios, leading to systematic bias in responding. The key outcome is response bias (indexing bias towards reward-based learning).

Table 1. Study Measures

VISIT	MEASURE/PROCEDURE	TIME (MINS)
Screening	Consent	30
	Urine drug screen	5
	Urine pregnancy test (females)	5
	Blood draw	5
	Expired CO	2
	Intention to quit/treatment status	2
	FTND	1
	TLFB	30
	SCID	60
	The Wechsler Test of Adult Reading (WTAR)	10
	Physical Exam	10

VISIT	MEASURE/PROCEDURE	TIME (MINS)
Medical screen (may occur on different day than screening depending on availability)	Medical History	15
	EKG	20
Baseline/First Dispensing Visit	Demographics form	5
	Locator form	10
	AUDIT	2
	TLFB (since last visit)	10
	NDSS	3
	WISDM	10
	Yale Craving Scale	5
	TQSU	1
	UPPS-P	5
	Contemplation Ladder	1
	Three Factor Eating Questionnaire	3
	Reward-Based Eating Drive Scale	2
	Simplified Nutritional Appetite Questionnaire	2
	PROMIS Depression/BDI-II	4
	Cigarette Self-efficacy Questionnaire	1
	Stop signal	10
	CPT	10
	Reward Responsiveness Test	15
	Monetary Choice Questionnaire	2
	Cigarette Discounting Task	2
	Food Discounting Task	4
	Cigarette Purchase Task	2
	SAFTEE/Adverse Effects Checklist	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 smoking session)	Expired CO/Breath Alcohol	4
	Weight	2
	Blood draw	5
	Take dose of medication	2
	Pill count	2
	PROMIS Depression/BDI-II	4
	Cigarette Self-efficacy Questionnaire	1
	Cigarette Purchase Task	2
	Cigarette Discounting Task	2
	Monetary Choice Questionnaire	2
	Stop Signal task	10
	CPT	10
	Food discounting task	4
	Yale Craving Scale	5
	Reward Responsiveness Test	15
	PANAS	2
	Heart rate/blood pressure	5
	Three Factor Eating Questionnaire	3
	Reward-Based Eating Drive Scale	2
	Simplified Nutritional Appetite Questionnaire	2
	SAFTEE questionnaire	8
	Adverse Effects Checklist	5
	Cue elicited craving	10

VISIT	MEASURE/PROCEDURE	TIME (MINS)
	Simulated lapse paradigm	120
	Drug Effects Questionnaire	2
	Modified CEQ	5
Washout	7 days with no medication	
	Weight/Blood Pressure	5
	TLFB (since last visit)	5
	SAFTEE/Adverse Effects Checklist	2
	Simplified Nutritional Appetite Questionnaire	2
	Dispense 2nd medication	10
Follow up visit 2 (including smoking session)	Expired CO/Breath Alcohol	4
	Weight	2
	Blood draw	5
	Take dose of medication	2
	Pill count	2
	PROMIS Depression/BDI-II	4
	Cigarette Self-efficacy Questionnaire	1
	Cigarette Purchase Task	2
	Cigarette Discounting Task	2
	Monetary Choice Questionnaire	2
	Stop Signal task	10
	CPT	10
	Food discounting task	4
	Yale Craving Scale	5
	Reward Responsiveness Test	15
	PANAS	2
	Heart rate/blood pressure	5
	Three Factor Eating Questionnaire	3
	Reward-Based Eating Drive Scale	2
	Simplified Nutritional Appetite Questionnaire	2
	SAFTEE questionnaire	8
	Adverse Effects Checklist	5
	Cue elicited craving	10
	Simulated lapse paradigm	120
	Drug Effects Questionnaire	2
	Modified CEQ	5

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 compensation. The payments will be allocated as follows: $50 for completing the eligibility and medical screening visit; $60 for completing the baseline visit; $100 completing the first experimental session; and $150 for completing the second experimental visit. For each of the experimental sessions, participants will receive a $30 bonus for having a breath CO < 6 or less than half of the baseline CO reading, which are indicative of overnight abstinence. In addition, during the smoking lapse task at each follow-up session, it is possible for participants to earn up to an additional $10 for resisting smoking for the entire 50 minutes. Participants will also receive a $30 bonus for completing at least 75% of daily Redcap assessments, and a final bonus of $50 for completing all of the study visits (to be paid at the final visit). Therefore, the total possible compensation is $520. 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 to the participant's email address.

IX. *Project Resources*

Five private, closed door rooms will be 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 studies where lorcaserin was taken for a longer period of time (at least one year), the most commonly reported side effects (i.e., greater than 5% of participants and more common than placebo) included:

- headache
- dizziness
- fatigue
- nausea
- dry mouth
- constipation
- nasopharyngitis (nasal/throat irritation, similar to a common cold)

Additionally, the less common side effects (reported by 2% or more of patients) included:

- diarrhea
- vomiting
- upper respiratory tract infection
- urinary tract infection
- back pain
- musculoskeletal pain
- cough
- oropharyngeal pain (e.g., sore throat)
- sinus congestion
- rash

The most commonly reported side effect/adverse event (AE) in Phase III trials of lorcaserin 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. A full list of registered randomized trials of lorcaserin can be found at ClinicalTrials.gov.

While we have no reason to expect adverse effects specific to our study population, we plan to carefully assess potential side effects to inform the safety profile for this population, and the inclusion of a DSMB will maximize safety. 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 physician reviewers and an external reviewer. 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 Smoking Sessions. Other potential risks include those related to participation in smoking sessions. For example, it is possible that participants may experience dizziness/nausea from smoking in the laboratory setting. The might experience temporary discomfort or craving while abstaining from cigarettes leading up to the smoking cession. However, the purpose of the laboratory procedures is to investigate drug effects on craving, and these procedures are commonly used in human laboratory studies. There is also the possibility that participants may experience demand characteristics (e.g., feeling obligated to smoke) in laboratory sessions. However, all participants will be regular daily smokers, and we have taken measures to protect against ethical concerns by excluding treatment-seekers or those engaged in an active quit attempt. Participants will also have the option not to smoke if they choose not to.

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).

There may also be side effects or risks to study participation that are unforeseen and not known at this time.

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 MRN for repeat follow-up examinations (including weight, heart rate/blood pressure measurements, ECG) 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 Smoking Sessions. To ensure participant safety, a member of the study staff will be present for the duration of all smoking sessions, and a member of the study medical staff will be on call during smoking sessions. Several steps will be taken to ensure that a potential long-term

cessation attempt is not undermined by participation in the study. First, participants will be screened twice (once by phone, and again in person) to ensure that those reporting the intent of an imminent quit attempt (i.e., during the next 90 days) are not enrolled. Participants who express desire to engage in a permanent quit attempt will be screened out and referred to treatment resources. Additionally, any participants who change quit intentions during the study (e.g., initiate a permanent quit attempt sooner than anticipated) will be excused from further participation and provided with cessation resources. Finally, as a component of informed consent, participants will be informed that a) the study involves laboratory cigarette smoking, b) participants are free to withdraw at any time if they wish to initiate a permanent quit attempt, and c) participants will be provided with cessation resources upon request at any point during the study. Co-I Wilcox, an addiction psychiatrist, will provide participants with cessation advice and direct referrals as needed.

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.

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 enhance smoking cessation efforts, 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 server. Electronic data captured by RedCap are stored on a secure server at MRN, 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 outcomes are 1) minutes of resistance to smoking reinstatement and 2) number of half cigarettes smoked during the ad lib session. Using the same model, we will also examine secondary outcomes including: impulsive choice (k value from monetary discounting task and cigarette discounting task), impulsive action (commission errors on CPT), and reward response bias as measured by the Reward Responsiveness Test.

Statistical Power. To achieve adequate power (.80) to detect medium effects of medication on our primary outcomes, we will recruit a sample of 42 smokers in order to arrive at a final sample of 34 (allowing for up to 20% attrition). Given no prior data on lorcaserin's effects on laboratory outcomes, we reviewed effects reported in similar screening studies with other medications. In a study using the lapse paradigm proposed here, varenicline had a medium to-large effect on duration to reinstatement (Cohen's d = .72) and a large effect for self-administration (d = 1.5). To account for the possibility of stronger effects for varenicline relative to lorcaserin, our power analyses assumed a medium effect size. We assumed a within-subjects correlation of 0.60 for laboratory outcomes (as reported in prior human laboratory screening studies) and an alpha level of .05. We estimated power in G*Power software using a fixed effects, within-subjects design and two time-points. Conservatively, a sample of N = 34 allows sufficient power (.80) to detect a medium effect on the primary outcomes (Specific Aims 1 and 2). Although human data are not available to inform the predicted effect size for Aim 2, preclinical studies using this medication, and an analogous behavioral task, suggest large effects of medication. For our supplementary aim (evaluating indirect effects on the primary outcomes via impulsivity and craving), simulation studies indicate that the proposed analysis, utilizing a bootstrap procedure, will provide sufficient power (.80), given the planned sample size, to detect mediated effects in medium-to-large effect size range.

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

REFERENCES

1. Koob GF, Kenneth Lloyd G, Mason BJ: **Development of pharmacotherapies for drug addiction: a Rosetta stone approach**. *Nat Rev Drug Discov* 2009, **8**(6):500-515.
2. Litten RZ, Egli M, Heilig M, Cui C, Fertig JB, Ryan ML, Falk DE, Moss H, Huebner R, Noronha A: **Medications development to treat alcohol dependence: a vision for the next decade**. *Addict Biol* 2012, **17**(3):513-527.
3. Litten RZ, Falk DE, Ryan ML, Fertig JB: **Discovery, development, and adoption of medications to treat alcohol use disorder: Goals for the phases of medications development**. *Alcohol Clin Exp Res* 2016, **40**(7):1368-1379.
4. Litten RZ, Wilford BB, Falk DE, Ryan ML, Fertig JB: **Potential medications for the treatment of alcohol use disorder: An evaluation of clinical efficacy and safety**. *Subst Abus* 2016, **37**(2):286- 298.
5. Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF: **Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment**. *Alcohol Clin Exp Res* 2015, **39**(4):579-584.
6. Heilig M, Goldman D, Berrettini W, O'Brien CP: **Pharmacogenetic approaches to the treatment of alcohol addiction**. *Nat Rev Neurosci* 2011, **12**(11):670-684.
7. Falk DE, Yi HY, Hiller-Sturmhofel S: **An epidemiologic analysis of co-occurring alcohol and tobacco use and disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions**. *Alcohol Res Health* 2006, **29**(3):162-171.
8. McKee SA, Weinberger AH: **How can we use our knowlegde of alcohol-tobacco interactions to reduce alcohol use?** *Annu Rev Clin Psychol* 2013, **9**:649–674.
9. World Health Organization: **Global Health Risks. Mortality and Burden of Disease Attributable to Selected Major Risks**. Geneva, Switzerland: World Health Organization; 2009.
10. Dawson DA: **Drinking as a risk factor for sustained smoking**. *Drug Alcohol Depend* 2000, **59**(3):235-249.
11. Yardley MM, Mirbaba MM, Ray LA: **Pharmacological options for smoking cessation in heavy- drinking smokers**. *CNS Drugs* 2015, **29**(10):833-845.
12. Prabhu A, Obi KO, Rubenstein JH: **The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis**. *Am J Gastroenterol* 2014, **109**(6):822-827.
13. Pelucchi C, Gallus S, Garavello W, Bosetti C, La Vecchia C: **Cancer risk associated with alcohol and tobacco use: focus on upper aero-digestive tract and liver**. *Alcohol Res Health* 2006, **29**(3):193-198.
14. Kahler CW, Spillane NS, Metrik J: **Alcohol use and initial smoking lapses among heavy drinkers in smoking cessation treatment**. *Nicotine Tob Res* 2010, **12**(7):781-785.
15. Roche DJ, Ray LA, Yardley MM, King AC: **Current insights into the mechanisms and development of treatments for heavy drinking cigarette smokers**. *Curr Addict Rep* 2016, **3**(1):125-137.
16. McKee SA, Harrison EL, O'Malley SS, Krishnan-Sarin S, Shi J, Tetrault JM, Picciotto MR, Petrakis IL, Estevez N, Balchunas E: **Varenicline reduces alcohol self-administration in heavy-drinking smokers**. *Biol Psychiatry* 2009, **66**(2):185-190.
17. King A, Cao D, Vanier C, Wilcox T: **Naltrexone decreases heavy drinking rates in smoking cessation treatment: an exploratory study**. *Alcohol Clin Exp Res* 2009, **33**(6):1044-1050.
18. O'Malley SS, Krishnan-Sarin S, McKee SA, Leeman RF, Cooney NL, Meandzija B, Wu R, Makuch RW: **Dose-dependent reduction of hazardous alcohol use in a placebo-controlled trial of naltrexone for smoking cessation**. *Int J Neuropsychopharmacol* 2009, **12**(5):589-597.
19. King A, Cao D, Zhang L, Rueger SY: **Effects of the opioid receptor antagonist naltrexone on smoking and related behaviors in smokers preparing to quit: a randomized controlled trial**. *Addiction* 2013, **108**(10):1836-1844.
20. Anton RF, Latham PK, Voronin KE, Randall PK, Book SW, Hoffman M, Schacht JP: **Nicotine-use/smoking is associated with the efficacy of naltrexone in the treatment of alcohol dependence**. *Alcohol Clin Exp Res* 2018, **42**(4):751-760.
21. Fucito LM, Park A, Gulliver SB, Mattson ME, Gueorguieva RV, O'Malley SS: **Cigarette smoking predicts differential benefit from naltrexone for alcohol dependence**. *Biol Psychiatry* 2012, **72**(10):832-838.

22. Hartmann-Boyce J, Stead LF, Cahill K, Lancaster T: **Efficacy of interventions to combat tobacco addiction: Cochrane update of 2013 reviews**. *Addiction* 2014, **109**(9):1414-1425.
23. Kahler CW, Cioe PA, Tzilos GK, Spillane NS, Leggio L, Ramsey SE, Brown RA, O'Malley SS: **A double-blind randomized placebo-controlled trial of oral naltrexone for heavy-drinking smokers seeking smoking cessation treatment**. *Alcohol Clin Exp Res* 2017, **41**(6):1201-1211.
24. Mitchell JM, Teague CH, Kayser AS, Bartlett SE, Fields HL: **Varenicline decreases alcohol consumption in heavy-drinking smokers**. *Psychopharmacology (Berl)* 2012, **223**(3):299-306.
25. Fucito LM, Toll BA, Wu R, Romano DM, Tek E, O'Malley SS: **A preliminary investigation of varenicline for heavy drinking smokers**. *Psychopharmacology (Berl)* 2011, **215**(4):655-663.
26. Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, Green AI, Pettinati HM, Ciraulo DA, Sarid-Segal O *et al*: **A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence**. *J Addict Med* 2013, **7**(4):277-286.
27. Roche DJ, Bujarski S, Hartwell E, Green R, Ray LA: **Combined varenicline and naltrexone treatment reduces smoking topography intensity in heavy-drinking smokers**. *Pharmacol Biochem Behav* 2015, **134**:92-98.
28. Ray LA, Courtney KE, Ghahremani DG, Miotto K, Brody A, London ED: **Varenicline, low dose naltrexone, and their combination for heavy-drinking smokers: human laboratory findings**. *Psychopharmacology (Berl)* 2014, **231**(19):3843-3853.
29. Higgins GA, Fletcher PJ: **Therapeutic potential of 5-HT2C receptor agonists for addictive disorders**. *ACS Chem Neurosci* 2015, **6**(7):1071-1088.
30. Kirby LG, Zeeb FD, Winstanley CA: **Contributions of serotonin in addiction vulnerability**. *Neuropharmacology* 2011, **61**(3):421-432.
31. Di Matteo V, Di Giovanni G, Di Mascio M, Esposito E: **Biochemical and electrophysiological evidence that RO 60-0175 inhibits mesolimbic dopaminergic function through serotonin(2C) receptors**. *Brain Res* 2000, **865**(1):85-90.
32. Hayes DJ, Greenshaw AJ: **5-HT receptors and reward-related behaviour: a review**. *Neurosci Biobehav Rev* 2011, **35**(6):1419-1449.
33. Muller CP, Homberg JR: **Serotonin revisited**. *Behav Brain Res* 2015, **277**:1-2.
34. Palacios JM, Pazos A, Hoyer D: **A short history of the 5-HT2C receptor: from the choroid plexus to depression, obesity and addiction treatment**. *Psychopharmacology (Berl)* 2017, **234**(9-10):1395-1418.
35. Higgins GA, Zeeb FD, Fletcher PJ: **Role of impulsivity and reward in the anti-obesity actions of 5- HT2C receptor agonists**. *J Psychopharmacol* 2017, **31**:1403-1418.
36. Higgins GA, Silenieks LB, Rossmann A, Rizos Z, Noble K, Soko AD, Fletcher PJ: **The 5-HT2C receptor agonist lorcaserin reduces nicotine self-administration, discrimination, and reinstatement: relationship to feeding behavior and impulse control**. *Neuropsychopharmacology* 2012, **37**(5):1177-1191.
37. Gobert A, Rivet JM, Lejeune F, Newman-Tancredi A, Adhumeau-Auclair A, Nicolas JP, Cistarelli L, Melon C, Millan MJ: **Serotonin(2C) receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat**. *Synapse* 2000, **36**(3):205-221.
38. Grottick AJ, Fletcher PJ, Higgins GA: **Studies to investigate the role of 5-HT(2C) receptors on cocaine- and food-maintained behavior**. *J Pharmacol Exp Ther* 2000, **295**(3):1183-1191.
39. Manvich DF, Kimmel HL, Howell LL: **Effects of serotonin 2C receptor agonists on the behavioral and neurochemical effects of cocaine in squirrel monkeys**. *J Pharmacol Exp Ther* 2012, **341**(2):424-434.
40. Kasper J, Tikamdas R, Kim MS, Macfadyen K, Aramini R, Ladd J, Bisceglia S, Booth R, Peris J: **The serotonin-2 receptor modulator, (-)-trans-PAT, decreases voluntary ethanol consumption in rats**. *Eur J Pharmacol* 2013, **718**(1-3):98-104.
41. Rezvani AH, Cauley MC, Levin ED: **Lorcaserin, a selective 5-HT(2C) receptor agonist, decreases alcohol intake in female alcohol preferring rats**. *Pharmacol Biochem Behav* 2014, **125**:8-14.

42. Tomkins DM, Joharchi N, Tampakeras M, Martin JR, Wichmann J, Higgins GA: **An investigation of the role of 5-HT(2C) receptors in modifying ethanol self-administration behaviour**. *Pharmacol Biochem Behav* 2002, **71**(4):735-744.
43. Cunningham KA, Fox RG, Anastasio NC, Bubar MJ, Stutz SJ, Moeller FG, Gilbertson SR, Rosenzweig- Lipson S: **Selective serotonin 5-HT(2C) receptor activation suppresses the reinforcing efficacy of**
44. Neelakantan H, Holliday ED, Fox RG, Stutz SJ, Comer SD, Haney M, Anastasio NC, Moeller FG, Cunningham KA: **Lorcaserin suppresses oxycodone self-administration and relapse vulnerability in rats**. *ACS Chem Neurosci* 2017, **8**(5):1065-1073.
45. Jacobs DS, Barkin CE, Kohut MR, Bergman J, Kohut SJ: **Effects of lorcaserin (Belviq®) on nicotine-and food-maintained responding in non-human primates.** *Drug Alcohol Depend* 2017, **181**:94-101.
46. Guy EG, Fletcher PJ: **Responding for a conditioned reinforcer, and its enhancement by nicotine, is blocked by dopamine receptor antagonists and a 5-HT(2C) receptor agonist but not by a 5-HT(2A) receptor antagonist**. *Pharmacol Biochem Behav* 2014, **125**:40-47.
47. Zeeb FD, Higgins GA, Fletcher PJ: **The serotonin 2C receptor agonist lorcaserin attenuates intracranial self-stimulation and blocks the reward-enhancing effects of nicotine**. *ACS Chem Neurosci* 2015, **6**(7):1231-1240.
48. Fidler MC, Sanchez M, Raether B, Weissman NJ, Smith SR, Shanahan WR, Anderson CM, BLOSSOM Clinical Trial Group: **A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: the BLOSSOM trial**. *J Clin Endocrinol Metab* 2011, **96**(10):3067-3077.
49. O'Neil PM, Smith SR, Weissman NJ, Fidler MC, Sanchez M, Zhang J, Raether B, Anderson CM, Shanahan WR: **Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study**. *Obesity (Silver Spring)* 2012, **20**(7):1426-1436.
50. Smith SR, Weissman NJ, Anderson CM, Sanchez M, Chuang E, Stubbe S, Bays H, Shanahan WR, Behavioral M, Lorcaserin for O *et al*: **Multicenter, placebo-controlled trial of lorcaserin for weight management**. *N Engl J Med* 2010, **363**(3):245-256.
51. Shanahan WR, Rose JE, Glicklich A, Stubbe S, Sanchez-Kam M: **Lorcaserin for smoking cessation and associated weight gain: A randomized 12-Week clinical trial**. *Nicotine Tob Res* 2017, **19**(8):944-951.
52. Hurt RT, Croghan IT, Schroeder DR, Hays JT, Choi DS, Ebbert JO: **Combination varenicline and lorcaserin for tobacco dependence treatment and weight gain prevention in overweight and obese smokers: A pilot study**. *Nicotine Tob Res* 2017, **19**(8):994-998.
53. Leeman RF, Bogart D, Fucito LM, Boettiger CA: **"Killing two birds with one stone": Alcohol use reduction interventions with potential efficacy in enhancing self-control**. *Curr Addict Rep* 2014, **1**(1):41-52.
54. Litten RZ, Fertig J, Mattson M, Egli M: **Development of medications for alcohol use disorders: recent advances and ongoing challenges**. *Expert Opin Emerg Drugs* 2005, **10**(2):323-343.
55. Bujarski S, Ray LA: **Experimental psychopathology paradigms for alcohol use disorders: Applications for translational research**. *Behav Res Ther* 2016, **86**:11-22.
56. Hendershot CS, Wardell JD, Samokhvalov AV, Rehm J: **Effects of naltrexone on alcohol self- administration and craving: meta-analysis of human laboratory studies**. *Addict Biol* 2016, **22**(6):1515-1527.
57. McKee SA: **Developing human laboratory models of smoking lapse behavior for medication screening**. *Addict Biol* 2009, **14**(1):99-107.

58. Plebani JG, Ray LA, Morean ME, Corbin WR, MacKillop J, Amlung M, King AC: **Human laboratory paradigms in alcohol research**. *Alcohol Clin Exp Res* 2012, **36**(6):972-983.
59. Ray LA, Hutchison KE, Tartter M: **Application of human laboratory models to pharmacotherapy development for alcohol dependence**. *Curr Pharm Des* 2010, **16**(19):2149-2158.
60. Lerman C, LeSage MG, Perkins KA, O'Malley SS, Siegel SJ, Benowitz NL, Corrigall WA: **Translational research in medication development for nicotine dependence**. *Nat Rev Drug Discov* 2007, **6**(9):746-762.
61. Crabbe JC, Bell RL, Ehlers CL: **Human and laboratory rodent low response to alcohol: is better consilience possible?** *Addict Biol* 2010, **15**(2):125-144.
62. Leeman RF, Heilig M, Cunningham CL, Stephens DN, Duka T, O'Malley SS: **Ethanol consumption: how should we measure it? Achieving consilience between human and animal phenotypes**. *Addict Biol* 2010, **15**(2):109-124.
63. Roache JD: **Role of the Human Laboratory in the Development of Medications for Alcohol and Drug Dependence**. In: *Addiction Medicine.* Edited by Johnson BA. New York, NY: Springer; 2010: 129- 157.
64. Zimmermann US, O'Connor S, Ramchandani VA: **Modeling alcohol self-administration in the human laboratory**. *Curr Top Behav Neurosci* 2013, **13**:315-353.
65. MacKillop J, Murphy JG: **A behavioral economic measure of demand for alcohol predicts brief intervention outcomes**. *Drug Alcohol Depend* 2007, **89**(2-3):227-233.
66. Amlung M, McCarty KN, Morris DH, Tsai CL, McCarthy DM: **Increased behavioral economic demand and craving for alcohol following a laboratory alcohol challenge**. *Addiction* 2015, **110**(9):1421- 1428.
67. Green R, Ray LA: **Effects of varenicline on subjective craving and relative reinforcing value of cigarettes**. *Drug Alcohol Depend* 2018, **188**:53-59.
68. Murphy CM, MacKillop J, Martin RA, Tidey JW, Colby SM, Rohsenow DJ: **Effects of varenicline versus transdermal nicotine replacement therapy on cigarette demand on quit day in individuals with substance use disorders**. *Psychopharmacology (Berl)* 2017, **234**(16):2443-2452.
69. Enoch MA, Johnson K, George DT, Schumann G, Moss HB, Kranzler HR, Goldman D, National Advisory Council on Alcohol A, Alcoholism: **Ethical considerations for administering alcohol or alcohol cues to treatment-seeking alcoholics in a research setting: can the benefits to society outweigh the risks to the individual? A commentary in the context of the National Advisory Council on Alcohol Abuse and Alcoholism -- Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation (2005)**. *Alcohol Clin Exp Res* 2009, **33**(9):1508- 1512.
70. Motschman CA, Gass JC, Wray JM, Germeroth LJ, Schlienz NJ, Munoz DA, Moore FE, Rhodes JD, Hawk LW, Tiffany ST: **Selection criteria limit generalizability of smoking pharmacotherapy studies differentially across clinical trials and laboratory studies: A systematic review on varenicline**. *Drug Alcohol Depend* 2016, **169**:180-189.
71. National Institute on Alcohol Abuse and Alcoholism: **Recommended council guidelines on ethyl alcohol administration in human experimentation**. Rockville, MD: Department of Health and Human Services; 2005.
72. Collins GT, Gerak LR, France CP: **The behavioral pharmacology and therapeutic potential of lorcaserin for substance use disorders**. *Neuropharmacology* 2017, **S0028-3908**(17)30620-30622.
73. Wardell JD, Ramchandani VA, Hendershot CS: **A multilevel structural equation model of within- and between-person associations among subjective responses**

to alcohol, craving, and laboratory alcohol self-administration. *J Abnorm Psychol* 2015, **124**(4):1050-1063.
74. Hendershot CS, Wardell JD, Strang NM, Markovich MS, Claus ED, Ramchandani VA: **Application of an alcohol clamp paradigm to examine inhibitory control, subjective responses, and acute tolerance in late adolescence**. *Exp Clin Psychopharmacol* 2015, **23**(3):147-158.
75. Hendershot CS, Wardell JD, McPhee MD, Ramchandani VA: **A prospective study of genetic factors, human laboratory phenotypes, and heavy drinking in late adolescence**. *Addict Biol* 2017, **22**(5):1343-1354.
76. Hendershot CS, Claus ED, Ramchandani VA: **Associations of OPRM1 A118G and alcohol sensitivity with intravenous alcohol self-administration in young adults**. *Addict Biol* 2016, **21**(1):125-135.
77. Strang NM, Claus ED, Ramchandani VA, Graff-Guerrero A, Boileau I, Hendershot CS: **Dose- dependent effects of intravenous alcohol administration on cerebral blood flow in young adults**. *Psychopharmacology (Berl)* 2015, **232**(4):733-744.
78. Claus ED, Hendershot CS: **Moderating effect of working memory capacity on acute alcohol effects on BOLD response during inhibition and error monitoring in male heavy drinkers**. *Psychopharmacology (Berl)* 2015, **232**(4):765-776.
79. Stoner SA, Arenella P, Hendershot CS: **Randomized controlled trial of a mobile phone intervention for improving adherence to naltrexone for alcohol use disorders**. *PLoS One* 2015, **10**(4):e0124613.
80. Minian N, Baliunas D, Zawertailo L, Noormohamed A, Giesbrecht N, Hendershot CS, Le Foll B, Rehm J, Samokhvalov A, Selby PL: **Combining alcohol interventions with tobacco addictions treatment in primary care-the COMBAT study: a pragmatic cluster randomized trial**. *Implement Sci* 2017, **12**(1):65.
81. Dermody SS, Hendershot CS: **A critical review of the effects of nicotine and alcohol coadministration in human laboratory studies**. *Alcohol Clin Exp Res* 2017, **41**(3):473-486.
82. Littlewood RA, Claus ED, Arenella P, Bogenschutz M, Karoly H, Ewing SW, Bryan AD, Hutchison KE: **Dose specific effects of olanzapine in the treatment of alcohol dependence**. *Psychopharmacology (Berl)* 2015, **232**(7):1261-1268.
83. Littlewood RA, Claus ED, Wilcox CE, Mickey J, Arenella PB, Bryan AD, Hutchison KE: **Moderators of smoking cessation outcomes in a randomized-controlled trial of varenicline versus placebo**. *Psychopharmacology (Berl)* 2017, **234**(23-24):3417-3429.
84. Bogenschutz MP, Bhatt S, Bohan J, Foster B, Romo P, Wilcox CE, Tonigan JS: **Coadministration of disulfiram and lorazepam in the treatment of alcohol dependence and co-occurring anxiety disorder: an open-label pilot study**. *Am J Drug Alcohol Abuse* 2016, **42**(5):490-499.
85. Wilcox CE, Claus ED, Calhoun VD, Rachakonda S, Littlewood RA, Mickey J, Arenella PB, Goodreau N, Hutchison KE: **Default mode network deactivation to smoking cue relative to food cue predicts treatment outcome in nicotine use disorder**. *Addict Biol* 2018, **23**(1):412-424.
86. Wilcox CE, Tonigan JS, Bogenschutz MP, Clifford J, Bigelow R, Simpson T: **A randomized, placebo- controlled, clinical trial of prazosin for the treatment of alcohol use disorder**. *J Addict Med* 2018, Epub ahead of print, doi: 10.1097/ADM.0000000000000413.
87. Dermody SS, Donny EC: **The predicted impact of reducing the nicotine content in cigarettes on alcohol use**. *Nicotine Tob Res* 2014, **16**(8):1033-1044.
88. Dermody SS, Tidey JW, Denlinger RL, Pacek LR, al'Absi M, Drobes DJ, Hatsukami DK, Vandrey R, Donny EC: **The impact of smoking very low nicotine content cigarettes on alcohol use**. *Alcohol Clin Exp Res* 2016, **40**(3):606-615.

89. Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS *et al*: **Randomized trial of reduced-nicotine standards for cigarettes**. *N Engl J Med* 2015, **373**(14):1340-1349.
90. O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ: **Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo- pituitary-adrenocortical axis**. *Psychopharmacology (Berl)* 2002, **160**(1):19-29.
91. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO: **The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire**. *Br J Addict* 1991, **86**(9):1119- 1127.
92. Simpson TL, Malte CA, Dietel B, Tell D, Pocock I, Lyons R, Varon D, Raskind M, Saxon AJ: **A pilot trial of prazosin, an alpha-1 adrenergic antagonist, for comorbid alcohol dependence and posttraumatic stress disorder**. *Alcohol Clin Exp Res* 2015, **39**(5):808-817.
93. Brick J: **Standardization of alcohol calculations in research**. *Alcohol Clin Exp Res* 2006, **30**(8):1276-1287.
94. First MB, Williams JBW, Karg RS, Spitzer RL: Structured Clinical Interview for DSM-5—Research Version (SCID-5 for DSM-5, Research Version; SCID-5-RV). Arlington, VA: American Psychiatric Association; 2015.
95. Sobell LC, Sobell MB, Leo GI, Cancilla A: **Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations**. *Br J Addict* 1988, **83**(4):393-402.
96. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M: **Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II**. *Addiction* 1993, **88**(6):791-804.
97. Schuckit MA, Smith TL, Tipp JE: **The self-rating of the effects of alcohol (SRE) form as a retrospective measure of the risk for alcoholism**. *Addiction* 1997, **92**(8):979-988.
98. Schuckit MA, Tipp JE, Smith TL, Wiesbeck GA, Kalmijn J: **The relationship between Self-Rating of the Effects of alcohol and alcohol challenge results in ninety-eight young men**. *J Stud Alcohol* 1997, **58**(4):397-404.
99. Shiffman S, Waters A, Hickcox M: **The nicotine dependence syndrome scale: a multidimensional measure of nicotine dependence**. *Nicotine Tob Res* 2004, **6**(2):327-348.
100. Tiffany ST, Drobes DJ: **The development and initial validation of a questionnaire on smoking urges**. *Br J Addict* 1991, **86**(11):1467-1476.
101. Welsch SK, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB: **Development and validation of the Wisconsin Smoking Withdrawal Scale**. *Exp Clin Psychopharmacol* 1999, **7**(4):354-361.
102. DiClemente CC, Carbonari JP, Montgomery RP, Hughes SO: **The Alcohol Abstinence Self-Efficacy scale**. *J Stud Alcohol* 1994, **55**(2):141-148.
103. Gwaltney CJ, Shiffman S, Norman GJ, Paty JA, Kassel JD, Gnys M, Hickcox M, Waters A, Balabanis M: **Does smoking abstinence self-efficacy vary across situations? Identifying context-specificity within the Relapse Situation Efficacy Questionnaire**. *J Consult Clin Psychol* 2001, **69**(3):516-527.
104. Lesdema A, Fromentin G, Daudin JJ, Arlotti A, Vinoy S, Tome D, Marsset-Baglieri A: **Characterization of the Three-Factor Eating Questionnaire scores of a young French cohort**. *Appetite* 2012, **59**(2):385-390.

105. Epel ES, Tomiyama AJ, Mason AE, Laraia BA, Hartman W, Ready K, Acree M, Adam TC, St Jeor S, Kessler D: **The reward-based eating drive scale: a self-report index of reward-based eating**. *PLoS One* 2014, **9**(6):e101350.
106. Johnson BA, Ait-Daoud N, Roache JD: **The COMBINE SAFTEE: a structured instrument for collecting adverse events adapted for clinical studies in the alcoholism field**. *J Stud Alcohol Suppl* 2005(15):157-167; discussion 140.
107. George TP, Vessicchio JC, Termine A, Jatlow PI, Kosten TR, O'Malley SS: **A preliminary placebo- controlled trial of selegiline hydrochloride for smoking cessation**. *Biol Psychiatry* 2003, **53**(2):136- 143.
108. MacKillop J, Murphy JG, Ray LA, Eisenberg DT, Lisman SA, Lum JK, Wilson DS: **Further validation of a cigarette purchase task for assessing the relative reinforcing efficacy of nicotine in college smokers**. *Exp Clin Psychopharmacol* 2008, **16**(1):57-65.
109. Martin CS, Earleywine M, Musty RE, Perrine MW, Swift RM: Development and validation of the Biphasic Alcohol Effects Scale. *Alcohol Clin Exp Res* 1993, **17**(1):140-146.
110. Bohn MJ, Krahn DD, Staehler BA: **Development and initial validation of a measure of drinking urges in abstinent alcoholics**. *Alcohol Clin Exp Res* 1995, **19**(3):600-606.
111. Johanson CE, Uhlenhuth EH: **Drug preference and mood in humans: diazepam**. *Psychopharmacology* 1980, **71**(3):269-273.
112. Perkins KA, Stitzer M, Lerman C: **Medication screening for smoking cessation: a proposal for new methodologies**. *Psychopharmacology (Berl)* 2006, **184**(3-4):628-636.
113. McKee SA, Weinberger AH, Shi J, Tetrault J, Coppola S: **Developing and validating a human laboratory model to screen medications for smoking cessation**. *Nicotine Tob Res* 2012, **14**(11):1362-1371.
114. Greenway FL, Shanahan W, Fain R, Ma T, Rubino D: **Safety and tolerability review of lorcaserin in clinical trials**. *Clin Obes* 2016, **6**(5):285-295.
115. Aronne L, Shanahan W, Fain R, Glicklich A, Soliman W, Li Y, Smith S: **Safety and efficacy of lorcaserin: a combined analysis of the BLOOM and BLOSSOM trials**. *Postgrad Med* 2014, **126**(6):7-18.
116. Shram MJ, Schoedel KA, Bartlett C, Shazer RL, Anderson CM, Sellers EM: **Evaluation of the abuse potential of lorcaserin, a serotonin 2C (5-HT2C) receptor agonist, in recreational polydrug users.** *Clin Pharmacol Ther* 2011, **89**(5):683-692.
117. Farr OM, Upadhyay J, Gavrieli A, Camp M, Spyrou N, Kaye H, Mathew H, Vamvini M, Koniaris A, Kilim H *et al*: **Lorcaserin administration decreases activation of brain centers in response to food cues and these emotion- and salience-related changes correlate with weight loss effects: a 4-week- long randomized, placebo-controlled, double-blind clinical trial**. *Diabetes* 2016, **65**(10):2943-2953.

ATTACHMENTS

Advertisements:
Cig_Flyer_M1

Cig_Flyer_M2

Measures (listed alphabetical):
Alcohol Purchase Task
AUDIT
Cigarette Evaluation Scale
CES-D
Contemplation Ladder
Cigarette Purchase Task
Daily Survey
Demographics form
Fagerstrom Test for Nicotine Dependence
Locator form
Monetary Choice Questionnaire
Minnesota Nicotine Withdrawal Scale
Nicotine Dependence Syndrome 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

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