Cover Page

Title: Smoking Cessation & Opioid Dependence Treatment Integration

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Study Protocol

Lay Summary (6th grade reading level):
Many people who abuse drugs also smoke cigarettes. Little is known about when in a person's drug treatment would be best to help them quit smoking. In this study, opioid dependent smokers will be asked to use a medication for 12 weeks. Each day, participants will respond to text messages related to quitting smoking. We will see participants once each month (4 visits) to ask about how ready they are to quit smoking. We plan to assess the feasibility of using this program in an opioid treatment clinic. We also plan to compare outcomes based on their clinic group.

Purpose and Objectives: Early evidence suggests that outcomes for substance use disorders (SUDs) may be improved for those who also smoke cigarettes, if smoking cessation is integrated with SUD treatment (Mannelli et al., 2013). Debate remains, however, over when to implement the smoking cessation treatment: immediately (to present a consistent treatment message) or after a delay (to allow patients to stabilize on their SUD pharmacotherapy). Thus, researchers have called for more work to determine whether the timing of treatment integration affects outcomes for both smoking and SUDs. At WVU, the Comprehensive Opioid Addiction Treatment (COAT) program provides access to a relatively large population of opioid-dependent smokers in various stages of SUD treatment: Days 1 to 90 (weekly group), Days 91 to 180 (biweekly group), and Days 181 to ≥365 (monthly group). In the proposed study, all three groups will receive varenicline pharmacotherapy and take varenicline per label instructions for 12 consecutive weeks. They will also provide a blood sample at one study visit for assessment of genetic markers for drug use. The goals of this work include:

> **Primary Aims**. Demonstrate the feasibility of implementing smoking cessation treatment within an outpatient opioid-dependence treatment program via recruitment rates, adherence to treatment components, compliance with study requirements, and overall retention rates.
>
> **Secondary Aims**. Compare COAT groups on outcomes related to drug use, including tobacco abstinence rates, days until successful cigarette abstinence, relapses for all drugs, withdrawal-related effects, and genetic markers for drug use.

Study results will shed light on the feasibility of implementing smoking cessation therapy within the COAT clinic, results that may generalize to other treatment programs for opioid dependence. Results will also provide initial evidence for whether smoking cessation timing affects abstinence outcomes for both tobacco and opioid use. Such data are directly relevant to communities within the state of West Virginia, which are disproportionately affected by the harms of these drugs. Among all states, WV ranks 50th for tobacco use prevalence, as well as 49th for deaths related to recreational use of opioids. Ultimately, this line of work may lead to recommendations for improving outcomes associated with opioid dependence treatment, as well as improving outcomes for a population of smokers that may otherwise not quit tobacco.

Explain the Scientific Rationale: Early evidence suggests that outcomes for substance use disorders (SUDs) may be improved for those who also smoke cigarettes, if smoking cessation is integrated with SUD treatment (Mannelli et al., 2013). For instance, among opioid-dependent smokers maintained on methadone (opioid pharmacotherapy) for up to 3 months, varenicline (tobacco pharmacotherapy) may promote an earlier successful cigarette quit day (de Dios et al., 2014) and improve long-term smoking abstinence rates (Nahvi et al., 2014), relative to placebo. Additionally, duration of smoking abstinence is associated positively with duration of opioid abstinence (Shoptaw et al., 2002), and changes in opioid pharmacotherapy dose are associated with changes in smoking behavior (Mello et al., 1985; Schmitz et al., 1994). Debate remains, however, over when to implement the smoking cessation treatment: immediately (to present a consistent treatment message) or after a delay (to allow patients to stabilize on their SUD pharmacotherapy). Thus, researchers have called for more work to determine whether the timing of treatment integration affects outcomes for both smoking and SUDs. At WVU, the Comprehensive Opioid Addiction Treatment (COAT) program provides access to a relatively large population of opioid-dependent smokers in various stages of SUD treatment: Days 1 to 90 (weekly group), Days 91 to 180 (biweekly group), and Days 181 to >365 (monthly group). In the proposed study, all three groups will receive varenicline pharmacotherapy for 12 consecutive

weeks. Study results will shed light on the feasibility of implementing smoking cessation therapy within the COAT clinic, results that may generalize to other treatment programs for opioid dependence. Results will also provide initial evidence for whether smoking cessation timing affects abstinence outcomes for both tobacco and opioid use. Such data are directly relevant to communities within the state of West Virginia, which are disproportionately affected by the harms of these drugs. Among all states, WV ranks 50th for tobacco use prevalence, as well as 49th for deaths related to recreational use of opioids (CDC, 2013). Ultimately, this line of work may lead to recommendations for improving outcomes associated with opioid dependence treatment, as well as improving outcomes for a population of smokers that may otherwise not quit tobacco.

Probability of Group Assignment: Participants will be assigned to one of three groups based on duration of illicit-drug abstinence and time in COAT program. Groups will be assigned by the COAT program at the Chestnut Ridge Center and will be: 0 to 90 days abstinent (weekly group), 91 to 180 days abstinent (biweekly group), and 181 to ≥365 days abstinent (monthly group). All groups will receive the same varenicline treatment regimen per the label instructions.

Inclusion criteria: Participants must report smoking ≥10 cigarettes per day for ≥1 year. An expired air CO reading of ≥10 parts/million (ppm) at screening will verify current tobacco use status. Individuals must also indicate interest in making a quit attempt in the next 1-6 months (*Contemplation* or *Preparation* stages), as measured via the Stage of Change (SOC; DiClemente et al., 1991). The SOC categorizes smokers into one of five stages: 1) no plans to quit (*Precontemplation*) 2) plans to quit in the next 6 months (*Contemplation*), 3) plans to quit in the next 30 days, with a recent attempt made (*Preparation*), 4) currently trying to quit (*Action*), and 5) have already quit (*Maintenance*). Individuals in the *Precontemplation* stage are likely too disinterested in quitting to consider the cessation program offered during the intervention, while individuals in the *Action* stage may have already begun changing their smoking behavior. Importantly, 70-90% of smokers are considering quitting but are *not* actively trying to quit (i.e., are in contemplation or preparation; Velicer et al., 1995).

Exclusion criteria: Exclusion criteria include current engagement in any form of tobacco cessation (e.g., pharmacotherapy); current use of contraindicated medications (e.g., theophylline, warfarin, insulin, etc.); reports of smoking < 10 cigarettes per day; expired air CO < 10 ppm; Stage of Change category as *Precontemplation* (no plans to quit), *Action* (actively trying to quit), or *Maintenance* (have already quit); self-reported seizures in the past year; untreated cardiovascular disease. Women will be excluded if they self-report breast-feeding or are pregnant (verified by urinalysis).

Justification for Equitable Enrollment of Subjects: No one will be excluded on the basis of gender, race, or ethnicity.

Data/Safety Monitoring: The PI (Dr. Melissa Blank, Ph.D.) will be responsible for executing the Data and Safety Monitoring Plan (DSMP), and complying with all reporting requirements.

Data Security: All data (questionnaires, CO samples, tobacco use behavior) will be treated with professional standards of confidentiality. Data will be identified by code number only and stored on password-protected computers kept within locked rooms. Participants' names are not directly associated with these data. The consent forms will be kept in the office of a PI (Dr. Blank), also in a locked cabinet.

Safety Monitoring Plan: In the unlikely event of adverse event(s) during the conduct of the study described in this application, the laboratory has a mechanism in place to ensure that the event(s) will be reported to the IRB in a timely manner. The PI will report events that are unexpected and possibly, probably, or definitely related to study participation a) within 24 hours if they are fatal, life-threatening, or serious, and b) within 10 calendar days if they suggest greater risk of harm to study participant(s) than was previously known or unrecognized.

How data will ensure safety for more than minimal risk: The inclusion/exclusion criteria ensure that we enroll only regular cigarettes smokers who are generally healthy. That is, we will exclude individuals whose breath tests reveal that they are not smokers, and who report severe medical conditions (i.e., untreated cardiovascular disease, seizures). Once enrolled, participants will be given varenicline (an FDA-approved tobacco-cessation pharmacotherapy) for 12 weeks. Participants who experience intolerable side effects from

the pharmacotherapy will have the freedom to stop use and withdraw from the study. For all participants, the health risks of study participation do not exceed those normally incurred in their own environment.

Subjects:

Participant Identification and Recruitment: Male and female smokers will be recruited from the Chestnut Ridge Center at WVU. Study enrollment will be open to any person who is enrolled in Comprehensive Opioid Addiction Treatment (COAT) at Chestnut Ridge Center for opioid dependence and is eligible based on screening procedures.

Protection of WVU employees/students: WVU employees and students are not specifically targeted. However, these individuals may be included in the study if they are enrolled in COAT at Chestnut Ridge Center and are deemed eligible based on inclusion/exclusion criteria. Of course, they will be assured the same rights and protections as all other participants. Informed consent will be performed by a trained staff member and individuals will be informed of the voluntary nature of their participation. Their protection will be maintained by keeping the consent forms, which contain their full name, separate from all session data. Specifically, consent forms will be kept in the office of the PI in a locked cabinet. Additionally, all computerized data will be stored on password-protected computers that are kept within a locked laboratory.

Additional Provisions of WVU employees/students: WVU employees and students will be informed that their participation will in no way affect their status at WVU as an employee or student. Additionally, any participants who are current students of Dr. Blank will be assured that their participation will in no way affect their status in her class. As always, they will be able to withdraw from the study at any time without any adverse consequence.

Consent Process (when, where, and how): Participants will be individuals enrolled in COAT at Chestnut Ridge Center at WVU. A trained member of our research team will visit Chestnut Ridge Center during regularly scheduled COAT meetings times for the informed consent process. Administration of the consent form will take place in a private room at the Chestnut Ridge Center by a trained staff member or co-investigator.

Sample size:

Justification: The sample size for this feasibility study is based on the estimated rate of attrition for the weekly group of COAT patients. The weekly group consists of those patients in the earliest stage of treatment, during which dropout rates would be greatest. The estimated dropout rate for this group is 20%. Thus, with 60 participants (n=20/group: weekly, biweekly, and monthly) we would be able to estimate a compliance rate for intervention of 80% within $\pm$ 10%.

Management of information relevant to human subjects protection: Any unanticipated problems experienced during the course of the study or other interim results will be reported appropriately to the IRB within the approved timeline. Moreover, as needed, interim results will be reported to participants prior to their enrollment into the study. Such interim results include any varenicline side effects that have not been commonly reported in the literature, including those outlined in the consent form (e.g., nausea, vomiting, sleep problems, and abnormal dreams).

Potential Risks/Discomforts:

Cigarette smokers who abstain from tobacco (i.e., those who choose to cut down or quit regular cigarettes) may experience an aversive withdrawal syndrome that includes irritability, restlessness, difficulty concentrating, hunger, and craving or urges to smoke. These effects can be uncomfortable but are not medically dangerous. These participants may also experience side effects reported of varenicline use: nausea, vomiting, sleep disturbance, abnormal dreams, gas, constipation. Notable is that these effects have been shown to dissipate with continued varenicline use, and do not appear to be significantly different from that incurred when using other nicotine replacement products like the patch (Bullen et al., 2013).

Participants may also experience some discomfort when the nurse inserts or withdraws the needle, or when blood samples are taken. We try very hard to minimize patient discomfort at these times, and the use of a trained nurse and sterile, disposable equipment enhances comfort while reducing the risk of bruising and infection.

Researcher interaction with participations kept private: Researchers will interact directly with participants in person. Individuals who are enrolled in the COAT program at Chestnut Ridge Center will be described the study requirements via the consent process. At each contact, study staff will be sensitive to collecting only that information that the person voluntarily reveals. Additionally, both the screening and session visits will occur in one of the Chestnut Ridge Center session rooms, which can only be accessed by trained personnel and current patients.

Potential Benefits to individuals:
Research participants may significantly reduce or quit their use of regular cigarettes as a result of their participation in this study.

Potential Benefits to Science/Society: This study has the potential to provide long-term benefits to society at large. Study results have the potential to reveal the influence of integrating smoking-cessation treatment with opioid-dependence treatment on abstinence outcomes of all substances. Given that tobacco and opioid use are significant problems in West Virginia, results form the current study may contribute to improved treatment packages for individuals with substance-use disorders. There is mixed evidence about when to integrate smoking cessation with substance-use disorder treatment. Specifically, we are interested in determining whether integrating smoking-cessation treatment at the beginning of opioid-dependence treatment, versus individuals are stabilized on opioid pharmacotherapy, will improve relapse rates for both substances.

Consent Procedures:
Why not PI or Co-I for conducting consent?: Co-investigators will be responsible for consenting participants. All staff will have passed the online CITI training modules, as well as will have completed additional training with the PI prior to working with participants.

Confidentiality:
How long will the data be kept? For participants that consent to participate, their screening and session data will be kept for no more than three years after the end of the study per recommendation of the American Psychological Association.

Where will data be securely located? Consent forms will be kept in a locked cabinet in the office of the PI (Dr. Blank), separate from the data. Other data will be kept on password protected computers kept in locked rooms within the laboratory. Additionally, the laboratory is only accessible by key, and only the PI and her research assistants will hold a key.

How will the data be destroyed? Hard copies of any forms (e.g., consent, screening documents, etc.) will be shredded, while electronic copies (e.g., session data) will be permanently deleted from any/all computers.

How maintain confidentiality and privacy? Privacy interests will be protected by assigning codes to participants' responses provided during screening and session visits. Names will not be associated with any of these data, and will be stored separately from consent forms that include participants' signatures. That is, consent forms will be kept in a locked file cabinet in the office of the PI (Dr. Blank), whereas screening and session data will be kept either in a locked file cabinet or on password protected computers located within session rooms in the laboratory. All data will be maintained for three years, as suggested by the American Psychological Association. Access to participants will come from word-of-mouth or study advertisements (flyers or electronic announcements to the WVU and greater Morgantown community).

Compensation:
Payment distribution? For intervention visits, participants will receive payments in equal amounts: $100 each for visits 2, 3, and 4. Participants will not be paid during the initial screening visit. All compensation will be in the form of Visa gift cards, and the total amount possibly earned for completing the entire study will be $300.

Statistical Analysis Plan

Primary outcomes. The primary outcomes will be those relevant to feasibility: 1) recruitment rates (i.e., number of patients enrolled relative to the number of patients screened), 2) adherence to treatment components (i.e., proportion of participants who complete the varenicline regimen), 3) compliance with responding to text message-based questions (i.e., number of responses to text message-based questions out of the total number asked), and 4) overall retention rates (i.e., completion rates for entire treatment program). These outcomes will be examined via descriptive statistics.

Secondary outcomes. Given that the proposed study is not powered to evaluate treatment efficacy, exploratory analyses will be employed to examine secondary outcomes. Using a one-way analysis of variance (ANOVA) groups will be compared on their proportion of relapses for all drugs, their proportion of smokers abstinent at each assessment, their average number of days until successful cigarette quit day, and their average ratings for tobacco withdrawal-related symptoms. Huynh-Feldt corrections will be used to adjust for violations of the sphericity assumption (Huynh & Feldt, 1976), and pairwise differences between means will be examined using Tukey's Honestly Significant Difference (HSD; Keppel, 1991) correcting for multiple comparisons. Comparisons for which $p<.05$ will be reported as significant.

Blood samples will be analyzed at the NIDA Center for Genetic Studies at Rutgers University.