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Design considerations for a pilot trial using a novel approach for evaluating smoking-cessation medication in methadone-maintained smokers

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ABSTRACT

The prevalence of smoking in methadone-maintained (MM) patients is over 80% and smoking-abstinence rates are strikingly low, even with the use of first-line smoking-cessation medications. Research has found that cigarettes increase the reinforcing properties of methadone; this interaction may be an additional, daily, challenge to smoking cessation in MM-smokers. This paper describes a novel approach in which patients who experience a particular barrier to achieving smoking abstinence are selected, and the impact of smoking-cessation medications on the identified barrier is evaluated. This is a 7-week, outpatient, randomized, within-subject, placebo-controlled, crossover trial with a follow-up visit at week 8. MM-smokers, who smoke ≥40% of their total daily cigarettes in the 4-h post-methadone-dosing period, as assessed with a Quitbit electronic cigarette lighter, will be recruited from a methadone program in Cincinnati, Ohio. Eligible participants will be randomized to receive four interventions (nicotine nasal spray (1 mg per dose, up to 40 times per day), placebo nicotine nasal spray, varenicline (2 mg/day), and varenicline placebo) in one of four orders to mitigate potential order effects. The primary outcome analysis will consist of two sets of statistical analyses, one comparing the effect of nicotine nasal spray to its placebo, and one comparing the effect of varenicline to its placebo, on the proportion of daily cigarettes smoked during the 4-h post-methadone-dosing period. This trial is of interest both as an efficient, precision-medicine-based approach to testing smoking-cessation interventions and as a specific strategy for identifying effective smoking-cessation treatment for MM-smokers.

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1. Introduction

Cigarette smoking, which accounts for more than 480,000 deaths annually in the United States [1], has an estimated prevalence of over 80% in methadone-maintained (MM) patients, a rate four times higher than the general population [2], and significantly higher than the rate observed in other outpatient substance use disorder treatment populations [3]. Despite interest in quitting smoking [4–7], smoking-abstinence rates in MM-smokers are strikingly low, even with the use of first-line smoking-cessation medications [8–14].

The disappointing rates of smoking abstinence in clinical trials with MM-smokers [8], along with the significant expense associated with these trials [15], suggest that an alternative approach should be taken to evaluating smoking-cessation medications for this patient population. During the past several years, within-subject crossover designs with relatively brief medication exposure periods have been used to screen smoking-cessation medications both in human laboratory [16] and clinical [15] studies; these designs lower costs by requiring fewer participants and by decreasing the length of the trial. When testing medications for particularly difficult-to-treat populations, such as MM-smokers, medication screening efficiency might be increased if barriers to smoking abstinence could be identified and used as proximal outcome measures. Such an approach would be consistent with precision medicine in which patient characteristics (e.g., genetic, psychosocial) are used to determine treatment [17] and would serve to increase the homogeneity of the sample, allowing for smaller sample sizes while maintaining adequate statistical power.

Several explanations for the low quit rates in MM-smokers have been offered, including poor medication adherence [8,14], high rates of psychiatric co-morbidity [8,11], and poor social support [8]. Another, compelling, explanation for the low quit rates lies in the interaction between opioids and smoking [11,14]. Specifically, research has found that administration of opioids, including methadone [18,19], buprenorphine [20,21], and heroin [22], significantly increases smoking. In MM-smokers, cigarette smoking significantly increases methadone's attenuation of opioid withdrawal [23] and participants work harder to receive a methadone dose when cigarettes are available concurrently than when methadone is offered alone [24]. In addition, MM-smokers report smoking around the time of their methadone dose to increase the pleasant effects of methadone [25]. A study by Richter and colleagues indicates that the 2–4 h following methadone dosing is associated with greater levels of smoking, with greater rates of smoking observed in the 2 h following

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dosing compared to the first 2 h after waking [26], which is the period of greatest smoking in non-MM smokers [27]. Thus, in addition to the usual challenges faced by smokers trying to quit, MM-smokers may have an additional, daily, challenge associated with methadone dosing. In the study by Richter and colleagues [26], 70% of MM-smokers had elevated smoking following methadone-dosing, which suggests that the interaction between methadone and smoking may be a smoking-cessation barrier for the majority of MM-smokers. Identifying treatments that can alleviate this challenge is of critical importance given the number of patients affected, with the number of these patients growing due to the opioid-use epidemic that has characterized the recent years [28,29]. To our knowledge, no study has evaluated the ability of smoking-cessation interventions to mitigate increased smoking following methadone dosing in MM-smokers. This paper describes a pilot trial designed to address this gap in the literature.

2. Research design and study organization

2.1. Research objectives

The primary objective of the pilot trial is to test the ability of two pharmacological treatments, the nicotine nasal spray (NNS) and varenicline, relative to their placebos, to reduce cigarette smoking during the 4 h following methadone dosing in MM-smokers who experience elevated levels of smoking. An exploratory objective is to compare the efficacy of the NNS and varenicline in reducing cigarette smoking during the 4-h post-methadone dosing.

2.2. Research design

The study schema is provided in Fig. 1. This is a 7-week, outpatient, randomized, within-subject, crossover trial with a follow-up visit at week 8. The portion of the study evaluating the NNS and placebo nasal spray (PNS) will be single-blind due to the inability to source a matching placebo for the NNS. The portion of the study evaluating varenicline and its matching placebo will be double-blind. Eligible participants will be randomized to receive the four interventions in one of four orders (see Fig. 1); this design will serve to mitigate potential order effects. The NNS/PNS are fast-acting medications that do not require titration and, thus, will be taken for one full week each, which will constitute the evaluation week. A dose escalation period is required for Varenicline/Placebo and, thus, each will be taken for two full weeks, with the second week being the evaluation week (see Fig. 1). It should be noted that the study design is not fully counterbalanced in that varenicline and its placebo will always follow NNS and PNS. While it would be ideal to have a fully counterbalanced design, utilizing such a design would require an 11-week study, due to the dose escalation and washout periods required for varenicline/varenicline placebo. Given that the lack of a fully counterbalanced design impacts only the comparison of NNS and varenicline, which is an exploratory objective, the decision was made to use the more efficient 7-week design.

2.3. Study population

Twenty participants, recruited from the University of Cincinnati (UC)-affiliated methadone clinic, will be randomized. Participants will be recruited through flyers at the UC-affiliated methadone clinic and through word-of-mouth from the clinic staff. To be eligible for the present study, a MM-smoker must experience elevated levels of smoking in the 4 h following methadone dosing, defined as smoking ≥40% of total daily cigarettes in that 4 h time-frame as assessed during a one week screening period; participants ruling out on this criterion will not be informed of the specific pattern of smoking required for study eligibility. The timing of cigarette smoking will be assessed by instructing participants to light their cigarettes with a Quitbit electronic cigarette lighter (manufactured by Quitbit, Inc.; Providence, RI), which records the time and date each time the lighter is activated. Based on the study by Richter and colleagues [26], we anticipate that a majority of MM-smokers (approximately 70%) will have their greatest level of smoking in the 4 h post-methadone-dosing period but, to our knowledge, this finding has not yet been replicated. The process of screening patients for this study will provide valuable information about the relative frequency of patients who experience this level of elevated smoking during the post-methadone-dosing period. Table 1 lists all study eligibility criteria.

2.4. Blinding and randomization

Pfizer, Inc. (NY, NY 10017) will provide varenicline and matching placebo to the University of Cincinnati (UC) Investigational Drug Services (IDS) Pharmacy. The Pharmacia & Upjohn Co. Division of Pfizer, Inc. (NY, NY 10017) will supply Nicotrol®NS to the UC IDS Pharmacy. Because of the inability to source a matching placebo for the Nicotrol®NS, the IDS pharmacy will fill and assemble single-blind placebo NNS bottles. The placebo NNS formulation will consist of a commercial saline product (e.g., Ocean® saline nasal spray). The Pharma division of Aptargroup, Inc. (Congers, NY 10920) will supply bottles and pumps for the placebo NNS that are similar (though not identical) to the Nicotrol®NS in size, shape, and mechanism. All nasal spray bottles will be over-labeled to ensure that original Nicotrol®NS labeling cannot be seen. These measures should be adequate to ensure that the participants are blind to their nasal spray assignments. Because of discrepancies in appearance between the PNS bottle and the Nicotrol®NS bottle, research staff will be considered to be non-blinded for this phase of the study. Eligible participants will be randomized to receive the four interventions in one of four orders (see Fig. 1) in a 1:1:1:1 ratio, with 5 participants randomized to each order. The IDS Pharmacy will create all participant drug kits, and the kits will be assigned to participants according to a randomization scheme available only to the study pharmacist and statistician, neither of whom will have any participant contact.

Randomization to 1 of 4 orders:	Week 1 Evaluate	Week 2 Evaluate	Week 3 Escalate	Week 4 Evaluate	Week 5 Wash-out	Week 6 Escalate	Week 7 Evaluate	Week 8 Follow-up
1	PNS[a]	NNS[a]	Varenicline	Varenicline		Placebo	Placebo	
2	PNS	NNS	Placebo	Placebo		Varenicline	Varenicline	
3	NNS	PNS	Varenicline	Varenicline		Placebo	Placebo	
4	NNS	PNS	Placebo	Placebo		Varenicline	Varenicline	

[a] PNS= Placebo Nasal Spray; NNS= Nicotine Nasal Spray

Fig. 1. Study schema.

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