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Improving Functional Outcomes of Veterans with PTSD and Tobacco Dependence

Study Protocol with Statistical Analysis Plan

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The present study will involve a randomized clinical trial of 50 Veterans with tobacco dependence and PTSD randomized to ACT-PT vs. the American Lung Association's Freedom From Smoking program [FFS]). This study has two primary aims:

AIM 1: Evaluate the relative feasibility and acceptability of ACT-PT vs. FFS.

AIM 2: Evaluate the preliminary efficacy of ACT-PT vs. FFS with the primary outcomes of tobacco use, PTSD symptoms, health-related quality of life, and functional impairment.

Treatment Procedures. 50 Veterans with PTSD and tobacco dependence will be randomized to ACT-PT (n=25) or FFS (n=25).

ACT Treatment Components. The following eight components are emphasized in ACT-PT: *1) Identifying Problems with Control:* Participants identify efforts to control or avoid smoking-related internal experiences and how this is problematic for quitting smoking. *2) Acceptance:* Participants face smoking urges and PTSD-related experiences with mindful acceptance rather than avoid them. *3) Mindfulness*: Participants engage in mindfulness exercises in order to practice nonjudgmental acceptance of internal smoking and PTSD-related experiences. *4) Valued living*: Participants clarify their values and goals (i.e., quitting smoking, work achievement, social connections), and identify barriers that prevent them from achieving life goals. *5) Triggers*: Internal (e.g., thoughts, feelings, bodily sensations) vs. external smoking triggers are identified, and Veterans practice acceptance and mindfulness to manage these experiences. *6) Exposure*: Participants create exposure hierarchies for PTSD-related triggers and other internal experiences related to smoking, face them with mindful acceptance, and become more comfortable with these experiences. *7) Cognitive Defusion*: Participants learn that they are not their anxieties or fears, and they mindfully observe and accept these internal experiences. *8) Behavioral Activation*: Participants identify life goals and increase activities to replace smoking as a behavior used to manage anxiety, stress, and to fill idle time. Participants commit to achieving valued goals.

ACT-PT procedures. Participants will receive nine 50-minute weekly individual counseling sessions, with a booster session one month following the final session. Session 1 is devoted to an explanation of the treatment rationale. Sessions 2-4 focus on acceptance, mindfulness, cognitive defusion, behavioral activation, and skills practice, with an emphasis on tolerance of PTSD-related triggers and replacing smoking with positive life activities. Session 5 is the scheduled quit week when the nicotine patch is started. Sessions 6-9 focus on acceptance and mindfulness of nicotine withdrawal, cravings, and PTSD symptoms, as well as behavioral activation. Sessions 1-6 will occur weekly; sessions 7-9 will take place every other week. A booster session will take place one month after the end of the main course of treatment.

Control Condition. The American Lung Association's Freedom from Smoking program (FFS) [49-51], commonly used in community treatment programs, will be the control condition. FFS will consist of the same dosage / intensity of psychosocial treatment or nine 50-minute individual counseling sessions, with a booster session one month following the final session. The first session will discuss the health effects of smoking. The second session will discuss coping strategies for smoking urges. Sessions 3-4 will focus on the benefits of quitting. The scheduled quit date for participants is Session 5 (when the nicotine patch is started) and will focus on managing nicotine withdrawal symptoms. Sessions 6-9 will focus on relapse prevention and non-smoking lifestyle choices (e.g., weight management, exercise). Sessions 1-6 will occur weekly, sessions 7-9 will take place every other week. A booster session will take place one month after the main course of treatment. FFS does not include mindfulness practices, places a greater focus on psychoeducation and less emphasis on affect regulation as an obstacle to quitting compared to ACT.

Rationale for FFS. After reviewing the literature, and carefully weighing pros and cons of many options [52-57], FFS was chosen as the comparison condition for several reasons: 1) FFS and similar treatments are usual care in many VA smoking cessation clinics [58]; 2) FFS is an effective treatment [49, 59]; and 3) this control condition has been previously used in other mindfulness smoking cessation studies [60]. We considered many alternatives, including historical controls, a no-treatment group, a minimal treatment condition, waitlist controls, or a nonspecific ("placebo") therapy [54, 55, 61]. A 16-week waitlist is likely to lead to significant attrition, and it would be problematic to ask Veterans to wait over 4 months for treatment. We decided it best to focus on evaluating ACT-PT compared to one of the most common tobacco treatments.

Therapists and therapist training procedures. Four psychology postdoctoral fellows will be trained and treat Veterans (two in Year 1 and two in Year 2). We will use a systematic procedure for teaching therapists to deliver ACT-PT and FFS in a competent and reliable fashion. Training components include: 1) reviewing the

manual; 2) listening to portions of selected treatment tapes that illustrate methods; 3) role playing techniques; 4) participating in a structured workshop to enhance familiarity with the theory of the treatment; and 5) ongoing supervision. After the didactic training in both ACT-PT and FFS, therapists will participate in three mock therapy sessions and the PI will provide them with feedback. The therapists' first two cases will be closely monitored through weekly supervision and reviews of session videotapes.

Inclusion/Exclusion Criteria *Inclusion Criteria:* 1) Current DSM-5 PTSD, 2) Minimum score of 38 (clinical cutoff for PTSD) on the PTSD Checklist for DSM-5, 3) A regular smoker for at least 3 years, 4) Currently smoking at least 10 cigarettes per day, 5) Able to communicate meaningfully with the investigator, 6) Competent to provide written informed consent, 7) Ages 18 and older. *Exclusion Criteria:* 1) Current unstable DSM-5 bipolar disorder (i.e., instability characterized by two or more manic or depressive episodes in the past 12 months, and a current Young Mania Rating Scale total score ≥ 13 or a current BDI score ≥ 19), 2) Any lifetime DSM-5 psychotic disorder, 3) Current or recent (within 1 month of study entry) moderate or severe DSM-5 alcohol or drug use disorder, 4) Use of other tobacco products, 5) Current use of any smoking cessation medications (including bupropion), 6) a cognitive impairment that would interfere with participation, 7) A suicide attempt or severe suicidal ideation within the past 3 months, 8) Presence of any clinical features requiring inpatient or partial hospital treatment, 9) Pregnant or lactating women, or women of childbearing age that are not using a medically acceptable form of contraception, 10) Severe generalized skin disorder, 11) Nicotine patch allergy, 12) Recent myocardial infarction within the past 3 months, and 13) Unstable angina.

Recruitment. Participants will be 50 Veterans recruited from the PI's Tobacco Cessation Program at the Bedford VAMC. Based on the rate of PTSD and characteristics of Veterans in our clinic, 320 Veterans would meet eligibility criteria for the study during the two-year study period. Of note, if needed, 2800 other Veterans in the Bedford system would meet study criteria. Therefore, we do not anticipate difficulty recruiting the proposed number of participants. If recruitment fails to proceed at the expected rate in the first 3 months, we will modify recruitment procedures and/or add more recruitment sites (e.g., Primary Care, Mental Health Clinic).

Screening Procedures. Callers will be screened by phone. Eligible participants will be scheduled for an in-person assessment with the PI, who will confirm study eligibility and obtain informed consent. After consent, participants will complete clinician-rated assessments and self-report measures (see below). As in our stage 1a trial, a psychiatrist will assess participants to determine whether they are medically cleared for the study.

Assessment Measures. A broad range of reliable and valid measures will be used (see Table 2).

Table 2. Outcome Measures for the RCT

Measure	Rater	Self	Baseline	Weekly	Monthly	End of Tx	1-month Follow-Up	3-Month Follow-Up
Tobacco Use								
Number of Cigarettes		X	X	X		X	X	X
CO Level	X		X	X		X	X	X
QSU		X	X	X		X	X	X
Contemplation Ladder		X	X	X		X	X	
Quality of Life								
SF-36		X	X		X	X	X	X
Q-LES-Q		X	X		X	X	X	X
SCQoL		X	X	X		X	X	X
SDS		X	X		X	X	X	X
WSAS		X	X		X	X	X	X
Psychiatric								
PCL		X	X	X		X	X	X
BDI-II		X	X	X		X	X	X
Process								
AAQ		X	X		X	X	X	X
MAAS		X	X		X	X	X	X
VLQ		X	X		X	X	X	X
Satisfaction								
CSQ-8		X				X		

Diagnostic Measures: The *Structured Clinical Interview for DSM-V (SCID-5-RV)* is a reliable semi-structured instrument that is the gold standard for diagnosing mental health disorders [63, 64]. The Young Mania Rating Scale is a reliable and validated measure that will be used to screen for bipolar disorder [65].

Tobacco Use: The *Smoking History Questionnaire* (SHQ)[66] is a measure of smoking history and patterns. The *Questionnaire for Smoking Urges-Brief* (QSU-Brief) [67, 68] is a 10-item measure that evaluates

the structure and function of smoking urges. The QSU-Brief has very good reliability (α=.78–.89).*The Fagerström Test for Nicotine Dependence* (FTND) [69] is a 6-item self-report measure of nicotine dependence, with good internal consistency and test-retest reliability [69, 70]. *Smoking outcomes* will include a self-report of the number of cigarettes smoked, verified by carbon monoxide (CO) breath tests (< 8 ppm) [71]. Periods of sustained continuous abstinence and survival time to lapse and relapse will also be analyzed. Lapse will be defined as an episode of smoking that interrupts continuous abstinence, and a relapse is a return to regular smoking [72, 73]. A *Timeline Follow-back* (TLFB) procedure will be used to assess time to first smoking lapse and time to first relapse, defined as the seventh day after quit date on which smoking occurs [74]. The *Contemplation Ladder* is an 11-point self-report measure of readiness to quit smoking. It has good predictive and concurrent validity with the likelihood of a serious quit attempt within 6 months [75].

Social, Occupational, Mental Health and Physical Functioning: The *Short Form 36 Health Survey* (SF-36) is a 36-item self-report measure of current physical, mental health, and social functioning [76, 77], with excellent psychometric properties [76]. The *Quality of Life Enjoyment and Satisfaction Questionnaire* (Q-LES-Q) [78, 79] is a commonly used self-report measure to assess quality of life in several domains: general activities, physical health, subjective feelings, leisure time activities, social relationships, work, and household duties. The *Smoking Cessation Quality of Life Questionnaire* (SCQoL) is a self-reported measure designed to quantify to quantify the impact of smoking cessation on perceived functioning and well-being [80]. The *Sheehan Disability Scale* (SDS) is a reliable and valid 3-item self-report measure of overall disability, and assesses social life, work/study, and family life functioning [81]. The *Work and Social Adjustment Scale* (WSAS) is a 5-item measure of leisure activities, relationships, and home and work functioning [82].

Psychiatric Symptoms: The *PTSD Checklist for DSM-5* (PCL-5) is a popular 20-item measure of PTSD symptoms [83]. The *Beck Depression Inventory (BDI-II)* is a 21-item measure of depression severity [84].

Process Measures: Experiential avoidance will be measured with the *Acceptance and Action Questionnaire (AAQ)*[85], a 7-item self-report measure of emotional avoidance and inaction. The *Mindful Attention Awareness Scale* (MAAS) is a 15-item scale of the ability to mindfully observe the present moment [86]. The *Valued Living Questionnaire* is a self-report measure of the extent to which a person is living in accordance with one's values in everyday life [87]. All measures possess good internal consistency, and construct validity. These measures will be used for mediation analyses in the future clinical trial.

Treatment Satisfaction: *Client Satisfaction Questionnaire-8 (CSQ-8*; [88]): This 8-item scale measures patients' perceived satisfaction with treatment and has good internal consistency (α=.83-.93) [89]. The CSQ will be administered at the end of treatment (Session 10).

Retention and Noncompletion. We will use several strategies to increase retention: 1) We will ask participants to provide contact information and a release of information for people who will know how to get in touch with the participant; 2) We will call participants and remind them about their appointments, 3) We will pay participants for their time and travel for sessions and follow-up assessments. We will interview participants to determine reasons for study withdrawal and provide referrals for other services.

Data Management and Statistical Analysis. Participant files will be kept in a locked cabinet and data files will be password-protected and encoded with ID numbers. IDs will be unrelated to any identifying information. Data will be checked for values out of the normal range, inconsistencies, omissions and errors.

Preliminary analyses and handling missing data. Chi square and t-tests or non-parametric equivalents will be used to compare demographics, and baseline levels of tobacco dependence, PTSD severity, functional impairment, and motivation to quit smoking in both groups. If differences are detected, we will consider using these variables as covariates in subsequent analyses. To better characterize missing data, we will attempt to gather follow-up information for dropouts. If analyses show major differences between Veterans who complete the study or drop-out, we will explore methods for imputing data, and stratify analyses based on any bias [90].

Primary analyses. Primary analyses will involve examination of the feasibility and acceptability of a RCT of ACT-PT. Feasibility will be verified by adequate 1) recruitment rates (i.e., 3 Veterans per month), 2) >90% fidelity of clinician adherence to the treatment protocol, and 3) data retention (i.e., ≥70% of participants who attend at least 8 sessions of ACT-PT or FFS. An acceptable level of attrition will be <30% in each condition. We will also evaluate the number of ACT-PT and FFS sessions attended, by comparing the percentage of Veterans in each condition attending at least 80% of sessions (8/10). We will also examine the willingness of Veterans to be randomized with a goal of 80% of those approached who agree to randomization, the number of referrals from clinicians, ease of recruitment based on the average number of contacts needed to get consent and to schedule visits, the number of eligible participants from the pool of potential participants, and adherence and compliance to the treatment protocol (both counseling and nicotine patch) by comparison with the theoretical complete compliance. We will compare Veteran acceptability between groups by conducting an

independent samples t-test on the CSQ-8 [88]. We will compare attrition rates (<15% vs. >15%) between the two groups using a chi square and logistic regression analysis. We will also obtain qualitative data about the acceptability of the ACT-PT and FFS treatments.

Secondary analyses. Efficacy is not our major analytic aim, given the preliminary nature of this study [13]. We will examine differences in measures of tobacco use, PTSD severity and quality of life to identify empirical targets for further refinement of the treatment and inform the design of the future Merit Review. We will examine group differences for biologically verified abstinence, duration of sustained continuous abstinence and time to lapse and relapse [91, 92]. Based on the intent-to-treat principle, all participants randomized to treatment will be included in analyses. We will also look at individual trajectories of response to gain better insight into which participants do particularly well (or poorly) in the two interventions. Effect sizes and 95% confidence intervals will be used as only one element to estimate power and sample size to help plan for a Merit Review study [13]. In addition, we will explore differences in treatment groups over time using HLM [93] (time x condition) on other outcomes of interest, including PTSD symptoms, functioning and health-related quality of life. We will also examine the effects of treatment on the potential mediators (i.e., process variables), and the effect of these mediators on treatment outcome to identify candidate mediators for future study.

Power analysis. Given the caveats of Leon et al. [13], our primary outcome(s) are feasibility and acceptability. Consistent with the recommended stage model for behavioral therapy development [13, 14], the aim of this stage 1b pilot study is to inform future treatment development and evaluation plans. We expect ACT-PT will produce a medium treatment effect. In order to have .80 power to detect differences at a two-tailed alpha level of .05, a medium effect would require n=125. This is beyond the scope of a SPiRE, and more appropriate for a stage II trial. A total sample size of 50 (25 per cell) is feasible and consistent with the recommendation of 15-30 participants per condition for a stage 1b study [14].