Behavioral Activation for Smoking Cessation in Veterans with PTSD

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Project Summary

Aims and Rationale: The primary objective of this research is to produce an empirically validated treatment that increases smoking cessation in veterans with posttraumatic stress disorder (PTSD), one that can be easily integrated into smoking cessation clinics and/or mental health clinics within Veterans Administration (VA) facilities. PTSD is highly prevalent in the VA patient population and is associated with a rate of smoking (53% - 66%) that far exceeds that of VA enrollees in general (22%). PTSD is also associated with unusually high rates of smoking cessation treatment failure. The disparity in smoking cessation outcomes amongst veterans with PTSD may occur because standard smoking cessation treatment does not address PTSD-specific vulnerabilities. Veterans with smoking-PTSD comorbidity may respond optimally to treatment that addresses PTSD and associated affective symptoms, because such symptoms can both reinforce smoking and undermine quit attempts. Recent evidence shows that behavioral activation therapy (BA), a behavioral treatment that increases engagement in reinforcing activities, significantly reduces PTSD symptoms. BA may improve smoking cessation outcomes amongst veterans with PTSD because it reduces overall PTSD symptom severity and affective distress (low positive affect, high negative affect), which can cause smoking relapse. The proposed research will determine whether BA as an adjunct to standard smoking cessation treatment (ST+BA) is superior to a comparably intense combination of standard smoking cessation treatment + health and smoking education (ST+HSE) in improving smoking cessation outcomes among veterans with PTSD. The HSE intervention is intended to constitute a credible intervention that controls for contact time. Secondary objectives are to determine if BA improves PTSD symptomatology and associated affective distress, and to identify potential mediators of BA on smoking outcomes.

Methods: A total of 120 veterans with PTSD who are motivated to quit smoking will attend an initial diagnostic and baseline assessment session. Those who are interested, eligible, and who provide consent will be randomly assigned to receive ST+BA or ST+HSE and will be contacted by their individual study therapist to schedule the first treatment session. Participants will be stratified into treatment groups based on: 1) major depressive disorder (MDD; present versus absent), and 2) PTSD symptom severity. All participants will receive eight, individual sessions of ST+BA or ST+HSE. All participants will receive 20 minutes of identical standard smoking cessation treatment in each of the eight sessions. Those in the ST+BA condition will receive an additional 30 minutes of behavioral activation therapy; those in the ST+HSE condition will receive an additional 30 minutes of health education and information about smoking. All participants will receive 12 weeks of the nicotine patch and either nicotine gum or lozenge. Smoking cessation outcomes will be assessed 1, 2, 3, 4, 12, 20, and 26 weeks after the quit date.

Significance: This research has important clinical and public health significance because smoking is especially common among veterans with PTSD and it is the leading preventable cause of disease and disability. Reducing smoking rates among veterans with PTSD would result in substantially lower smoking-related illness and death in this vulnerable group of smokers. It would also reduce tobacco related healthcare costs charged to the VA. Study methods and findings may potentially be extended to smoking cessation treatment for patients with mental health disorders other than PTSD.

Background and Significance

PTSD is associated with an unusually high smoking prevalence and low cessation rates

The health, economic, and human costs of tobacco use are profound. Cigarette smoking remains the single largest preventable contributor to premature morbidity and mortality in the United States[20,21]. Approximately 443,000 Americans die prematurely each year from tobacco-

related cancer, cardiovascular, cerebrovascular, and respiratory diseases[22]. The economic costs of tobacco use are also substantial. In the US, the annual costs of medical expenses and lost productivity resulting from tobacco-related disease, disability, and death are estimated at more than $193 billion[22].

US veterans suffer disproportionately from smoking and smoking-related illness. Accordingly, a large portion of smoking-related healthcare costs are passed on to the nation's largest healthcare provider: the VA. PTSD, a highly prevalent mental health disorder among veterans (18%)[23], is associated with an especially high prevalence of cigarette smoking and low cessation rates[15,24,25]. Between 53-66% of veterans with PTSD smoke[14-16], nearly three times the rate of VA enrollees in general (22%)[17]. A greater proportion of veterans with PTSD smoke heavily (> 25 cigarettes per day), compared with VA patients who smoke but do not have PTSD (48% versus 28%)[15]. Moreover, there is evidence that smoking contributes to the significantly poorer physical health and higher use of medical care services for veterans with PTSD compared with those without the disorder[26-28]. Individuals with PTSD also have close to the worst quit rates in comparison with patients with 13 other mental health disorders[25]. Little is known about helping smokers with PTSD quit smoking, in part, because this group is typically excluded from smoking cessation clinical trials. We propose to examine whether behavioral activation (BA), a behavioral treatment that increases engagement in reinforcing activities, improves the efficacy of standard smoking cessation treatment (relative to a health and smoking educational adjuvant to standard cessation treatment: ST+HSE).

Standard smoking cessation treatment is *ineffective* for veterans with PTSD

Standard smoking cessation treatment is relatively ineffective for smokers with PTSD. A recent trial of 943 smokers with military-related PTSD compared the effectiveness of referral to a specialized VA smoking cessation clinic versus smoking cessation treatment that was integrated into mental health care (Integrated Care)[29]. McFall (co-investigator for proposed work) and colleagues found a 12-month prolonged abstinence rate of only 4.5% among veterans who received treatment from a VA smoking cessation clinic vs. a rate of 8.9% among veterans who received Integrated Care. Despite the boost in cessation achieved through Integrated Care, over 90% failed to maintain abstinence for a one-year period. In addition, only about a third of VA enrollees with PTSD engage in PTSD treatment[30]; thus, veterans with PTSD are insufficiently exposed to smoking treatment via Integrated Care. Clearly, there is a need to develop more effective smoking treatments for people with PTSD – especially treatments that can be delivered across diverse settings to increase treatment access. We aim to improve quit rates by augmenting standard smoking cessation treatment with BA, a novel and easily administered smoking cessation treatment for veterans with PTSD. Because BA selectively treats the components of PTSD that motivate smoking and may hinder quit attempts, it should be an especially efficacious smoking cessation treatment for veterans with PTSD.

Smokers with PTSD may smoke to regulate PTSD symptoms and affective distress

PTSD Symptoms. Regardless of the causal relation between smoking and PTSD (i.e., PTSD leads to smoking[31] or vice versa[32]), there is evidence that smoking may help regulate PTSD symptoms and associated mood states. PTSD is an anxiety disorder involving an extreme and often sustained psychological and biochemical stress response to trauma exposure. Pervasive efforts to avoid distress are central to PTSD symptomatology. Regular self-administration of nicotine may serve as one strategy for tolerating PTSD-related symptoms (re-experiencing, avoidance, emotional numbing, hyperarousal). VA PTSD patients, in particular, report being motivated to smoke in response to distressing military memories[14]. They have also been shown to experience nicotine withdrawal symptoms in response to encounters with trauma-related stressors[33], and they report that smoking reduces PTSD symptoms elicited by exposure to laboratory-based trauma cues[34]. In addition, research[35] including ours[36], shows that higher emotional numbing symptoms of PTSD (loss of interest, detachment from others) are associated with heavier smoking. These results suggest that smoking may be used to counteract the automatic blunting of positive emotion following trauma exposure.

Negative Affect. In addition to relatively specific PTSD symptoms, individuals with PTSD

also experience severe negative affective disturbances, and may smoke to regulate these events[37]. In fact, compared with other smokers, those with PTSD have extraordinarily high levels of negative affect[37,38], react more strongly to stressors[39,40], and have a greater perceived need to blunt or suppress negative affect[38]. Also, data show that smoking reduces negative affect among veterans with PTSD after they have been exposed to laboratory-based trauma cues[41]. If smoking helps regulate negative mood, quitting smoking may unmask heightened negative affect among smokers with PTSD. Negative affect is associated with failure to quit smoking (e.g., [5]), and those with PTSD may experience withdrawal-related negative affect as particularly intolerable[42], prompting a return to smoking.

Positive Affect. Smokers with PTSD may also self-administer nicotine to counter deficient positive affect, a deficit that is central to the emotional numbing component of PTSD. Evidence shows that individuals with PTSD report lower global positive affect than do those without PTSD[37], potentially because their pervasive pattern of avoidance disrupts contact with positively reinforcing activities that engender positive emotions. Nicotine administration stimulates brain reward systems[43] and produces positive mood improvement among smokers[44]. Thus, those with PTSD may rely on cigarettes as an accessible and reliable source of positive reinforcement. When veterans with PTSD attempt to quit smoking, they may be particularly likely to relapse because they miss the positive mood enhancing effects of cigarettes. Indeed, post-quit declines in positive affect have been implicated with difficulties quitting smoking[45,46]. We posit that veterans with PTSD may increase their likelihood of quitting smoking by learning to engage in new, non-smoking, sources of positive reinforcement that enhance positive emotions. BA was chosen as a smoking cessation adjuvant because it increases engagement in valued life activities in order to increase contact with positive reinforcement.

In summary, smoking may regulate PTSD symptoms as well as two affective vulnerabilities associated with PTSD: elevated negative affect and low positive affect. Quitting smoking may interfere with such regulation and further exacerbate these vulnerabilities, prompting a return to smoking. Thus, an optimal smoking cessation treatment for PTSD may be one that augments standard smoking cessation treatment with strategies that address PTSD symptoms as well as withdrawal-related affective distress. We propose to examine whether behavioral activation (BA), a treatment that targets these PTSD-associated vulnerabilities, improves the efficacy of standard smoking cessation treatment among veterans with PTSD.

Behavioral activation was first developed as a treatment for depression

The primary goal of Behavioral activation (BA) is to increase engagement in valued life activities in order to increase contact with positive reinforcement. BA was originally validated as a stand-alone treatment for depression. It has received very strong empirical support, with results equal to or better than cognitive therapy and antidepressant medications[47-51]. From the functional analytic framework of BA, depression is viewed as resulting from antecedent risk factors (e.g., environmental stressors) that initiate depression by disrupting contact with positively reinforcing activities. For example, a stressor like losing a job may lead to negative mood states. A common reaction to negative emotions is avoidance behaviors, because avoidance can reduce exposure to further stress. However, continued avoidance narrows the depressed person's behavioral repertoire and ultimately denies him/her access to sources of positive reinforcement. Entrenched patterns of avoidance result in depression. BA attempts to re-engage depressed individuals in their lives through focused activation strategies that encourage patients to approach sources of positive reinforcement that are consistent with their long-term goals.

Behavioral activation reduces symptoms of PTSD

BA may be an effective treatment for PTSD because of evidence that PTSD, similar to depression, results in a pervasive pattern of avoidance[38] that leads to disruption in contact with positively reinforcing activities. Behavioral theories of PTSD hold that PTSD develops by conditioning: a traumatic event becomes associated with the context in which the trauma occurred and generalizes broadly to other contexts. Individuals with PTSD then avoid situations and experiences (including those that would typically be experienced as enjoyable, such as

eating at a restaurant), to forestall negative affect. However, because of continued avoidance, the original conditioning remains intact (i.e., does not extinguish). Further, through the process of secondary conditioning (by which conditioned stimuli can create further conditioned associations), avoidance can become more pervasive and entrenched over time.

The application of BA for the treatment of PTSD is supported by both theory and research. As with depression, BA treats PTSD by re-engaging individuals in activities and experiences that are positively reinforcing by overcoming patterns of avoidance. Evidence suggests that BA should help regulate deficient positive affect and excessive negative affect associated with PTSD (including during tobacco abstinence). BA increases positive emotions resulting from engagement in appetitive events[52], and increased frequency of positively reinforcing activities is associated with increased positive affect and decreased negative affect[53]. Several open label, non-randomized trials support the efficacy of BA for treatment of PTSD. Civilians with PTSD (*n*=14) who received BA reported a significant pre- to post-treatment reduction in PTSD symptoms (assessed via Clinician Administered PTSD Scale; CAPS). The pre- versus post-treatment effect was large (d=1.29 [6]). Veterans with PTSD also reported a significant reduction in CAPS-assessed PTSD symptoms following BA treatment in two open-label trials (*n*=8, pre- versus post-treatment *d* = 1.44, [8]; *n*=11, pre-versus post-treatment d=.62 [11]). In addition, in a pilot randomized trial of BA versus treatment as usual (TAU) (*n*=8), BA produced greater PTSD symptom reduction than TAU[19]. The pre- versus post-treatment effect of BA was large (*d*=1.0), as was the BA versus TAU effect (*d*=1.19). The large average pre-versus post-treatment BA effect from these studies (*d*=1.10) is comparable to the large average pre- versus post-treatment effect for all evidence-based PTSD treatments (*d*=1.43; from a recent meta-analysis of evidence-based PTSD treatments[54]).

Finally, a recent open label trial of 117 veterans with PTSD[7] shows that BA produces reductions in PTSD symptoms (via PCL self-report) that are comparable to those produced by manualized Prolonged Exposure (PE) (i.e., β_{10}= -1.21: see [55]). Further, trauma imaginal exposure (the central element of PE) did <u>not</u> accelerate BA effects on PTSD[7]. These data add to the mounting evidence that BA can serve as an independent treatment for PTSD, producing effects that are similar to those produced by other evidence based treatments.

<u>Behavioral activation is ideal for integration with smoking cessation treatment</u>

Because BA treats PTSD and affective reactions that are implicated in cessation failure, we propose that it will improve the efficacy of standard smoking cessation treatment in veterans with PTSD. Several features of BA make it an ideal smoking cessation adjuvant. First, BA is inherently targeted at the challenges posed by quitting smoking; e.g., increased contact with nonsmoking reinforcers should mitigate the impact of nicotine abstinence on affect. That is, BA may facilitate cessation by reducing withdrawal symptoms such as negative affect (in addition to influencing cessation through reduction of PTSD symptoms). Second, the idiographic nature of BA allows it to be flexibly tailored to the unique needs of smokers with PTSD. Third, its uncomplicated nature allows it to be used with smokers varying in insight and intellectual capacity. Fourth, BA is straightforward to administer and extremely time-efficient, which facilitates its integration into smoking cessation treatment in diverse settings (e.g., BA has been effectively administered by nurses in primary care[56]). These latter features are especially promising regarding the potential flexibility and generalizability of BA for smoking cessation in different VA treatment settings. Therefore, BA is both feasible and functionally appropriate for smoking cessation without altering its central tenets or application.

Importantly, veterans who are interested in quitting smoking may accept BA more than they do other PTSD therapies such as prolonged exposure (PE). The primary goal of PE is to elicit fear and anxiety through exposing the individual to memories of the trauma. BA differs from PE in that the goal is to increase exposure to reinforcing activities vs. those that elicit fear or anxiety. In this respect, BA is a more suitable smoking cessation adjuvant treatment because it does not involve a trauma-focus component, and might therefore be less distressing and more acceptable to smokers with PTSD. This should also permit widespread use of BA in diverse treatment settings.

Behavioral activation improves smoking cessation outcomes

Dr. Lejuez (consultant for proposed research) and colleagues[9] found that BA plus standard smoking cessation treatment versus expanded standard smoking cessation treatment alone increased 6-month point prevalence abstinence among community smokers. Although the study was underpowered to detect treatment mediators (*n* = 42), importantly, smokers randomized to BA experienced a significant reduction in depressed mood at 6-months postquit relative to those who received a control therapy. This suggests that BA may have boosted cessation rates via its amelioration of post-quit affective distress. Because such affective distress hinders quit attempts in veterans with PTSD, we posit that BA will similarly improve cessation rates in this population.

The proposed treatment (ST+BA) is based on the BA treatment manual developed by Dr. Lejuez "Life Enhancement Treatment for Smoking". This treatment manual includes all the standard components of BA, but is made relevant for smoking cessation. For example, treatment goals are made relevant to developing a healthy non-smoking lifestyle; i.e., engaging in positively reinforcing activities in the absence of smoking. We have made minor adaptations to Dr. Lejuez's manual so that the BA exercises are also made relevant to PTSD. For example, the therapeutic exercises and examples have been tailored to address PTSD-specific barriers to engaging in reinforcing activities (e.g., tolerating anxiety while engaging in an activity in a public setting). Importantly, any adaptations to BA are psychoeducational and related to building a rationale for how BA addresses PTSD and smoking. The central tenets of BA remain unchanged: veterans increase engagement in positively reinforcing activities (see Appendix 3a; Session 1 of ST+BA treatment manual and Section D.8.e for detailed description of treatment protocol).

BA treats PTSD-specific smoking relapse risk factors

In addition to examining whether BA affects smoking outcomes (the "Intervention Hypothesis": see Figure 1), a secondary objective of the proposed research is to examine the treatment effects of BA on PTSD symptoms and affective distress. Examining these treatment effects will also identify potential mediators of BA on smoking outcomes. Although this initial research is not powered for mediation analyses, such analyses may nevertheless suggest how BA works for smokers with PTSD and provide critical pilot data for future treatment process research. A secondary benefit is that the proposed work will produce additional data on BA as a treatment for PTSD. The following are hypothesized treatment effects of BA that may promote smoking cessation:

PTSD Treatment Effect. Consistent with prior research[6,7,8,11,19], we posit that BA will reduce overall PTSD symptom severity. Exploratory analyses will also examine the BA effects on each PTSD symptom cluster (re-experiencing, avoidance, emotional numbing, hyperarousal) to refine analyses of potential mediators. Self-report PTSD symptom severity will be measured at treatment visits and at each follow-up visit. In addition, a structured clinical assessment of PTSD (via the Clinical Administered PTSD Scale; CAPS) will occur at baseline and end-of-treatment.

Negative Affect Treatment Effect. BA has been shown to reduce depressed mood during smoking cessation[9], and increased engagement in reinforcing activities is associated with decreased negative affect[51]. Thus, we posit that BA will decrease negative affect following quitting smoking. We will also explore the effects of BA on other tobacco withdrawal symptoms (e.g., craving) since negative affect may be causally linked with such symptoms. In addition, exploratory analyses will examine the influence of BA on depressed mood because depression often co-occurs with PTSD[59]. Negative affect, depressed mood, and withdrawal symptoms will be assessed at every study visit and follow-up visit. A structured clinical assessment of current depression, in addition to PTSD, will occur at baseline and end-of-treatment.

Positive Affect Treatment Effect. Evidence suggests that increasing the frequency of engagement in reinforcing activities elevates positive affect[51]. Therefore, we posit that BA will lead to increased global positive affect. In general, there is evidence that BA modulates reward functioning (i.e., approach toward rewarding events). Administration of BA results in functional

changes in brain structures that mediate both reward anticipation (incentive value) and reward feedback[60]. It is unclear how BA's enhancement of the brain reward system maps onto actual behavior. It is possible that BA will also increase the sensitivity of the Behavioral Activation System (BAS), one of the major motivational systems associated with goal attainment and reward seeking. Thus, exploratory analyses will examine whether BA increases the sensitivity of the Behavioral Activation System. Positive affect and sensitivity of the Behavioral Activation System will be measured at every study visit (albeit, with only questionnaire measures).

Exploratory Mediation Analyses. Separate treatment effect hypotheses address whether BA, on top of a common smoking cessation base, affects PTSD symptoms, negative affect, and positive affect. Separate analyses will determine the relations of these latter variables with likelihood of smoking abstinence (the outcome hypotheses). We will conduct exploratory mediation analyses for variables that are influenced by BA and that also predict smoking outcomes. Although the proposed research is not powered for mediation, detecting treatment or outcome effects will provide relevant information about how BA works (or does not work), and how it can be improved. Finally, while not a meditational analysis, exploratory analyses will analyze the extent to which improvement in PTSD symptoms and affect in the ST+BA condition depends upon execution of behavioral assignments (e.g., engaging in reinforcing activities). This is an important test of the model by which BA is thought to work.

Significance

Smoking in persons with PTSD is common, hard-to-treat, and refractory, and exacts incredibly high human and health costs. This work is significant because it will contribute to the development of a smoking cessation treatment tailored for people with PTSD that could boost quit rates in this hard-to-treat comorbid population. Stopping smoking would reduce the elevated risk of tobacco-related cancer, cardiovascular, cerebrovascular, respiratory diseases and premature death in smokers with PTSD, and associated healthcare costs. The rapidly expanding number of veterans returning from deployment to Iraq and Afghanistan with comorbid nicotine dependence and PTSD[62] presages an increasing demand for smoking cessation services and medical care from these veterans for years to come. Failure to develop more effective smoking cessation treatments for this large and expanding group of smokers will result in unnecessary tobacco-related disease, disability, and death in a vulnerable, comorbid population.

BA holds a great deal of promise for smoking cessation in veterans with PTSD. First, BA is extremely time-efficient and easily integrated with standard smoking treatment. Second, BA affects factors that are central to both PTSD and smoking cessation. Third, BA has already been shown to successfully increase cessation rates among smokers with symptoms of depression. Fourth, BA is feasible for delivery in VA settings and is acceptable to veterans. Adding to the significance of this work is evidence that suggests BA will not only boost smoking cessation rates in this population, but will also ameliorate symptoms of PTSD. Finally, this work will provide additional insight into how BA works, which will guide future treatment development and evaluation research.

In sum, we posit that BA — used as an adjuvant to standard smoking cessation treatment — will overcome major shortcomings of tobacco use treatment provided for veterans with PTSD by the VA (i.e., poor outcomes). It will do so by treating PTSD symptomatology that motivates smoking and undermines quit attempts using a treatment that is highly acceptable to veterans with PTSD.

Innovation

It is imperative to develop innovative, more effective smoking cessation interventions that accommodate the unique treatment needs of smokers with PTSD. No clinical trials have tested a smoking treatment tailored for this vulnerable comorbid population. The present research will, therefore, build on limited previous research and constitute the only trial that compares a novel treatment (BA) versus a contact control condition on long-term smoking abstinence. This research is highly innovative because BA is designed to treat both the symptoms of PTSD as well as enhance smoking outcomes. Thus, BA is a rare or unique

smoking cessation adjuvant because it could promote cessation by simultaneously treating both PTSD and tobacco withdrawal symptoms (e.g., negative affect).

In addition, BA's simplicity and lack of aversive elements should enhance its clinical delivery in health care contexts and enhance patient acceptance and participation. Finally, the measures of mechanism of action (e.g., affect, PTSD symptoms) should produce unique information on why smoking is so highly comorbid with PTSD, and why veterans with PTSD are unable to quit.

Relevance to Veteran Health

Smoking claims 443,000 lives each year, making it the leading cause of death in the US[22]. **In fact, smoking kills more people each year than AIDS, drugs and alcohol, homicide, suicide and motor vehicle accidents *combined***[63]. US veterans suffer disproportionately from smoking and smoking-related illness. Accordingly, a large portion of smoking-related healthcare costs are passed on to the VA. In 2008, the VA spent over $5 billion to treat chronic obstructive pulmonary disease (COPD) alone, a condition that is highly linked with tobacco use[17]. Stopping smoking before the age of 50 reduces risk of death by 50% over the ensuing 15 years[64], and health benefits extend to older smokers who stop as well[64].

Veterans with PTSD represent a large group of patients who would reap the known health benefits of stopping smoking[64] if the effectiveness of cessation treatment is improved. The VA has placed high priority on providing specialized care to approximately 560,217 veterans with PTSD[65]. Stopping smoking would reduce the risk of tobacco-related cancer, cardiovascular, cerebrovascular, and respiratory diseases in those with PTSD[22]. In addition, the rapidly expanding number of veterans returning from deployment to Iraq and Afghanistan with comorbid nicotine dependence and PTSD[62] suggests there will be an increasing demand for smoking cessation services and medical and psychiatric care from these veterans for years to come. A decline in smoking in veterans with PTSD would result in substantially lower smoking-related illness and death in this vulnerable clinical population. It would also dramatically reduce tobacco-related healthcare costs charged to the VA. The relevance of this research is further enhanced because the tested intervention targets both PTSD symptoms as well as smoking cessation. Finally, the relevance of the proposed work is underscored by the fact that BA is a brief and easily administered treatment that is readily accepted by veterans with PTSD[8,11]. Thus, ST+BA could easily and readily be translated into VA clinical practice.

Research Design and Methods

Study Objective

The primary goal of the proposed research is to examine whether behavioral activation as an adjuvant to standard smoking cessation treatment (ST+BA) improves smoking cessation outcomes among veterans with PTSD relative to a comparably intense combination of standard smoking cessation treatment + health and smoking education (ST+HSE).

Specific Aims/Study Objectives

Primary Aim:

Aim 1: Compare the effects of behavioral activation (BA) and health and smoking education (HSE) on abstinence rates, when each is used as an adjuvant to standard smoking cessation treatment (ST+BA vs. ST+HSE).

Secondary Aims:

Aim 2: Compare the effects of behavioral activation (BA) and health and smoking education (HSE) on PTSD symptoms and affective distress when each is used as an adjuvant to standard smoking cessation treatment.

Aim 3: Identify potential mediators of the effects of BA on smoking cessation outcomes.

Design Overview

A total of 120 veterans with PTSD who are motivated to quit smoking will attend an initial diagnostic and baseline assessment session. Those who are interested and eligible and who provide consent will be randomly assigned to receive ST+BA or ST+HSE and will be contacted by the study therapist to schedule the first treatment session. Randomization of participants into treatment will be stratified on: 1) major depressive disorder (MDD; present vs. absent), and 2) bupropion use. All participants will receive eight, individual sessions of ST+BA or ST+HSE. All will receive 20 minutes of identical standard smoking cessation treatment in each of the eight sessions. Those in the ST+BA condition will receive an additional 30 minutes of behavioral activation therapy; those in the ST+HSE condition will receive an additional 30 minutes of health education and information about smoking. All participants will receive 12 weeks of the nicotine patch and either nicotine gum or lozenge. Smoking cessation outcomes will be assessed 1, 2, 3, 4, 12, 20, and 26 weeks after the quit date.

Recruitment

The proposed research will be conducted at the Madison VAMC in collaboration with the UW-CTRI. Due to challenges associated with recruiting a specialized population, we have devised a recruitment plan using two major recruitment pipelines.

Pipeline 1: We will recruit veterans from the Madison VAMC and other local VAMCs (e.g., Tomah, Milwaukee, and community-based outpatient clinics). During regular mental health treatment, primary care visits, and other medical appointments at VAMCs, veterans will be queried by providers not affiliated with the study about their interest in the study. Clinicians who identify potential subjects will co-sign study staff to a note. Study staff will then call the interested study candidate for an initial telephone screening. Additionally, approved recruitment fliers will be posted within the Madison and other local VAMCs. . Potential subjects may call study staff directly. An automated list of VA patients who have both PTSD and tobacco dependence in their medical record will be generated. Informational letters may be mailed to veterans who meet these two basic eligibility criteria for the study. Data will be reviewed from the Mental Health Research Cooperative (MHRC) registry and informational letters may be mailed to veterans who have previously joined the registry and meet basic criteria. Veterans who receive the informational letter may call study staff directly if interested, and study staff may place a follow-up phone call to letter recipients if they do not reply.

Pipeline 2: We will also recruit veterans from the greater Madison area and Southern Wisconsin. who may *not* be receiving VA care. We will use our ongoing collaboration with the Wisconsin State Department of Veterans Affairs (DVA) to recruit non-VA enrolled veterans. As in the past, the DVA has agreed to provide information about the proposed research program within *Mission Welcome Home* packets. Research program information will include a flier and interested veterans can contact study staff. As part of our collaboration with the Wisconsin DVA, we will also continue collaborating with County Veteran Service Officers (CVSOs) in southern Wisconsin, who work directly with veterans and who will refer veterans to the research program. Approved recruitment fliers will be posted in the community and potential subjects may call study staff directly.

In addition to screening for smoking status and interest in quitting, the phone screen will include a validated four-item PTSD screening questionnaire used by the Department of Defense Post-Deployment Health Assessment Program, which identifies veterans with possible PTSD[88].

Inclusion and Exclusion Criteria

One hundred and twenty participants will be enrolled. For inclusion in the study, participants must: 1) report smoking an average of 6 or more cigarettes daily for at least six months; 2) report a desire to quit smoking; 3) meet criteria for *current* PTSD; 4) speak and read English; 5) agree to participate in the study; and 6) be ≥ 18 years old.

Participants will be excluded from the study based on the following: 1) meeting criteria for psychotic or bipolar disorder; 2) psychoactive substance abuse or dependence (excluding nicotine dependence) within the past 6 months; 3) inability to give informed, voluntary, written consent to participate; 4) current use of any pharmacotherapy for smoking cessation not

provided by the researchers during the quit attempt; 5) use of non-cigarette tobacco or nicotine products as a primary form of tobacco/nicotine use; 6) being currently suicidal or homicidal, as assessed by VA suicide/homicide template questions administered to all veterans; 7) being medically unable to use the nicotine patch or nicotine gum/lozenge; 8) psychotropic medication changes within 2 months of study initiation and during active treatment; 9) current engagement in evidence-based therapies for PTSD or depression; 10) pregnant or trying to become pregnant; or 11) incarceration.

In addition, we will inform participants that, for research purposes, we prefer that they remain on the same psychotropic medication regimen throughout the trial. However, if it is necessary for a participant to alter treatment for his/her welfare, we will ask the participant to notify us immediately. Such participants will remain in the trial, but primary study analyses will be conducted with such participants excluded.

Any concerns regarding nicotine patch, gum, or lozenge use will be reviewed by the study clinician, who may interview patients should further information be required. All women of childbearing potential will be required to agree to use an approved method of birth control to prevent pregnancy during the period of nicotine replacement therapy (NRT) use. Participants with suicidal or homicidal ideation at screening will be referred for VA psychiatric care, and they will be excluded from the study. Study candidates who express imminent intent for harm to self or others at any point in the study will be referred for VA emergency care.

Assessments

The following assessments will be conducted during the study: 1) Screening/diagnostic assessments used to determine inclusion into the study, 2) baseline descriptive assessments, 3) smoking status assessments, 4) treatment effect assessments, and 5) treatment adherence assessments. See Table 1 for the schedule of assessments.

Table 1. Therapy and Assessment Schedule for the Study

	Baseline	Therapy Sessions									Follow-ups	
	V1	**V2** Wk -4	**V3** Wk -3	**V4** Wk -2	**V5** Wk -1	**V6** Target Quit Day	**V7** Wk 1 Post-quit	**V8** Wk 2 Post-quit	**V9** Wk 3 Post-quit	**V10** Wk 4 Post-quit	**PA1, 2** Wk 12,20 Post-quit	**V11** Wk 26 Post-quit
In-person Counseling (ST+BA or ST+HSE)		TS1	TS2	TS3	TS4	TS5	TS6	TS7	TS8			
Screening/Diagnostic Assessments												
PTSD phone screen (PC-PTSD)	X*											
Axis I Disorders (SCID-I)	X											
PTSD (CAPS)	X									X		
Depression (SCID-I)	X									X		
Suicidal/Homicidal Ideation Assessment	X											
Medical History	X											
Baseline Descriptive Measures												
Demographics	X											
Smoking history	X											
FTND	X											
WSWS	X											
Smoking Status Assessments												
Smoking/Alcohol use Status		X	X	X	X	X	X	X	X		X	X
Calendar data		X	X	X	X	X	X	X	X		X	X
CO assessment	X					X	X	X	X			X
Cotinine Assessment												X
Treatment Effects Assessments												
PANAS	X	X		X		X	X	X	X	X	X	X
PTSD symptoms (PCL)	X			X			X	X		X	X	X
Depressed mood (PHQ-9)	X								X			
Behavioral Activation (BAS)	X				X		X		X		X	X
WSWS-11	X					X		X		X	X	X

Tripartite Pleasure Scale	X				X		X			X		X
Snaith-Hamilton Pleasure	X			X		X		X		X	X	X
Stress and Pleasure	X								X		X	X
Treatment Adherence Measures												
Therapist adherence to treatment												
Adherence to nicotine patch and side effects						X	X	X	X		X (Wk 12 only)	
Participant adherence to BA		X	X	X	X	X	X	X	X			

*Occurs at the phone screen, prior to the in-person screening visit; **Follow-ups at Weeks 5 and 26 are in-person, to permit PTSD and depression assessments and abstinence bioverification, respectively. Other follow-ups, at Weeks 12 & 20, are phone assessments (PA).

Screening/Diagnostic Assessments

Primary Care PTSD Screen (PC-PTSD). The PC-PTSD[88] is a validated, four-item measure of PTSD with yes-no response options used by the Department of Defense Post-Deployment Health Assessment Program to identify veterans with possible PTSD. Two yes answers have been shown to yield sensitivity of .96 and specificity of .78[89]. Study candidates who yield one or more yes answers on the PC-PTSD at the phone screen will be further assessed by an in-person diagnostic interview.

Clinician Administered PTSD Scale (CAPS). The CAPS[90] will be used to determine PTSD diagnostic status and severity. It will be administered at baseline and at the end of treatment (V10; see Table 1). The CAPS is a widely used and validated clinician interview for the assessment of PTSD. PTSD diagnosis on the CAPS is based on meeting the symptom criteria as defined in the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM). The CAPS shows strong internal validity[90]. In addition, time since trauma, number of traumatic exposures, type of trauma, and time since original PTSD diagnosis will be assessed to aid in identifying factors that may be associated with treatment outcomes.

Structured Clinical Interview for DSM Axis I Disorders (SCID-I). The SCID[91] is a widely used structured interview that assesses psychiatric disorders. The SCID-I has been shown to have very good reliability and validity[92]. The SCID-I will be administered at baseline, and only the depression module of the SCID-I will administered at the end of treatment (V10). If depression is noted in the SCID and participants are not already receiving clinical care, they will be referred to a clinical care provider. Questions pertaining to illicit drug use will be asked, but not recorded to protect participant privacy.

Suicidal Ideation/Homicidal Ideation (SI/HI) Screening Form. Participants will be asked standard VA clinical questions regarding suicidality and homicidality (e.g., “In the last month, have you thought about harming or killing anyone?” “Are you feeling hopeless about your future?”). Participants who endorse homicidal ideation or suicidal ideation with intent or plan will be excluded from the study, thoroughly evaluated for safety, and referred for VA mental health care. Dr. Cook, a VA psychologist, will be available via pager at all times so that study staff can consult with her about assessing risk for harm and making appropriate referrals. In addition, all study staff will receive standard VA suicide prevention training.

Medical History. Participants will complete a brief medical history questionnaire used in our prior research that focuses primarily on contraindications for using the nicotine patch, gum, and lozenge. Positive responses will be followed up by the study clinician, Maria Wopat. All women will receive additional questions regarding current pregnancy/nursing, plans to become pregnant during the period of medication use, and use of birth control.

Baseline Descriptive Measures

Demographic Information Questionnaire. Standard demographic information will be gathered via self-report at baseline to describe the study sample and to allow examination of any systematic differences between the two treatment groups.

Smoking History Questionnaire and Nicotine Dependence Assessment. Standard smoking history information such as number of previous quit attempts and years smoked will be

collected. The Fagerstrom Test for Nicotine Dependence (FTND)[93] will be used as a continuous measure of nicotine dependence.

Smoking Status Assessments

Measures of Smoking Status**.** Number of cigarettes smoked each day will be assessed at baseline and every visit. Abstinence (both point-prevalence and continuous) will be assessed on the quit day and at 1, 2, 3, 4, 12, 20, and 26-weeks post-quit day. We will assess long-term outcomes in a manner consistent with the recommendations of the Society for Research on Nicotine and Tobacco (SRNT) Workgroup on Biochemical Confirmation[1]. The main outcome analyses are based on 7-day point prevalence abstinence (i.e., reported abstinence for at least the 7 days prior to the assessment). Time-line follow-back (TLFB)[95] procedures will be used, as in our previous work, to assess continuous abstinence and to establish dates of initial lapse (smoking the first postquit cigarette), relapse (smoking for 7 consecutive days), and total days smoking.

Biochemical Verification. Self-reported abstinence will be biochemically verified at every in-person visit (from the Quit Day through 4 Weeks postquit and at 26-Weeks postquit) by carbon monoxide (CO) analysis of breath samples (8 ppm cutoff[96]). We chose the 26-week postquit follow up to biochemically verify abstinence as this is the smoking cessation outcome time point used in major meta-analytic studies (e.g., [86]), and it serves as a good index of later smoking outcomes[86].

In addition to CO verification, urinary cotinine (cutoff value of 20 ng/ml) for stated abstinence of 2 weeks or more (cotinine may be incompletely metabolized before this time) will be assessed at 26-Weeks postquit. All participants will be queried as to NRT use as this could affect cotinine levels. Expired air CO levels will be assessed with a carbon monoxide monitor[96]. Detected values above the stated cutoff scores will be considered indicative of smoking.

Treatment Effect Measures

Positive and Negative Affect. The Positive Affect-Negative Affect Schedule (PANAS)[97] will be used to assess positive and negative affect. The PANAS is a self-report state mood questionnaire consisting of 10 adjectives describing positive mood states and 10 adjectives describing negative mood states that are rated on 5-point scales ranging from 1 (very slightly or not at all) to 5 (extremely). The PANAS possesses good reliability and validity[97]. Positive and negative affect will be measured at all treatment and follow-up sessions. Anhedonia, the ability to experience pleasure will also be assessed by the Pleasure Activity Scale and Hedonic Tone questionnaires.

PTSD Symptoms. Posttraumatic Stress Disorder Checklist-Military Version (PCL)[98] is a 17-item self-report scale that assesses PTSD symptom severity. Items are rated on a 5-point Likert scale according to how much the symptom bothered the respondent over the past month. The psychometric properties of this measure are excellent[98]. In addition, a structured clinical assessment of PTSD via the CAPS will occur at baseline and end-of-treatment (V10).

Depressed Mood. We will use the Personal Health Questionnaire Depression Scale (PHQ) to assess depression. The PHQ is a well-validated tool for the assessment of depressive symptoms. The PHQ will be administered during active treatment and follow-up assessments. The depression module of the SCID-I will also be administered at baseline and end of treatment (V10).

Behavioral Activation. The Behavioral Activation Scale[100] assesses the sensitivity of the Behavioral Activation System, an index of the strength of motivation to engage in reinforcing activities (including goal-directed activity). Although those in the ST+BA group will record the actual *frequency* of engagement in reinforcing activities, self-monitoring is an important component of the ST+BA and could introduce poor treatment fidelity if utilized in the ST+HSE group. Thus, we have chosen to measure sensitivity of the Behavioral Activation System, which theoretically is the primary factor affected by BA. Sensitivity of the Behavioral Activation System will be assessed during active treatment and follow-up sessions. The psychometric properties of the Behavioral Activation Scale are strong[100].

Withdrawal. We will monitor withdrawal severity at baseline, throughout treatment, and

follow-up using the Wisconsin Smoking Withdrawal Scale, a 28-item scale that assesses nicotine withdrawal. It will allow for the assessment of the frequency, duration, severity, and temporal variability in withdrawal symptoms.

Ecological Momentary Assessment (EMA). For 2 weeks (1 week prior to the quit date and 1 week after the quit date), participants will receive automated assessment calls every evening (14 calls) at a pre-arranged time. Two calls will also be made prior to initiating therapy and two calls after completion of therapy. The Interactive Voice Response (IVR) assessments will evaluate: 1) PTSD symptoms, 2) positive and negative affect, 3) withdrawal, 4) use of NRT (after the quit date), 5) number of cigarettes smoked that day, and 6) activity engagement (e.g., Did you engage in a recreational activity today?). Four activity engagement EMA items will provide an additional measure of adherence to the behavioral exercises, as well as a measure of the primary mechanism through which BA is thought to work; i.e., whether BA leads to reduction in PTSD as a result of increased activity level. Moreover, EMA will provide information about whether symptom improvement is related to the overall level of activity and/or type of activity (e.g., social versus non-social reinforcers). EMA data will also allow us to examine whether increased activity is directly associated with smoking abstinence (in addition to PTSD reduction). Finally, we will be able to examine whether BA's effects on PTSD symptoms (assessed via EMA) influence smoking abstinence.

The brief assessment items—Ecological Momentary Assessment (EMA)—have been shown in our prior work to sensitively reflect treatment effects, predict relapse, and reveal treatment mediation[47,64]. The calls will last approximately 4 minutes; this assessment burden is much less than has been used successfully in many other studies, including our own, using EMA assessments[46,98]. Importantly, research shows that veterans with PTSD have similar EMA compliance rates as individuals without PTSD[34,65]. Participants will use either their own cell phone or one provided by the study. They will earn $2.00 for completing each EMA assessment.

We believe the EMA assessment schedule will produce the data needed for the study although it is less intensive (only one assessment per day) than other EMA protocols. In contrast to most research involving EMA , we are not attempting to characterize the relationships among measures at particular points in time (e.g., examining affect before and after individual cigarettes), which would require a much more frequent assessment schedule. Instead, we are interested in whether BA exerts effects on behavior and ratings on a more tonic basis, consistent with BA's putative mechanisms of action, and are using EMA in order to obtain time-stamped measures.

Treatment Adherence Measures

Therapist Competence and Adherence to Treatment. All treatment sessions in both conditions will be audiotaped, and a random selection of 25% (about 2 tapes per participant) of the audiotapes will be rated shortly thereafter by Drs. Cook and Messina to assess therapist adherence to and competence with the treatment protocol. Audio tapes will be maintained in a locked area accessible only the study staff and will be stored at the VA indefinitely, per VA policy. Separate rating checklists developed for the ST+BA and ST+HSE protocols will be used. Kappa will be reported for rated variables.

Adherence to Nicotine Replacement Therapy and side effects. Adherence to the nicotine patch, gum, and lozenge will be queried at each visit following initiation of NRT (Visits 6–9) and during the 12-week post-quit follow up call. Participants will be asked to return unused patches and gum/lozenge, which will be counted at each visit before dispensing new medication. NRT side effects will also be assessed at each visit. Potential differences in NRT use between treatment groups will be examined and incorporated into statistical models if a meaningful relation with outcomes is detected.

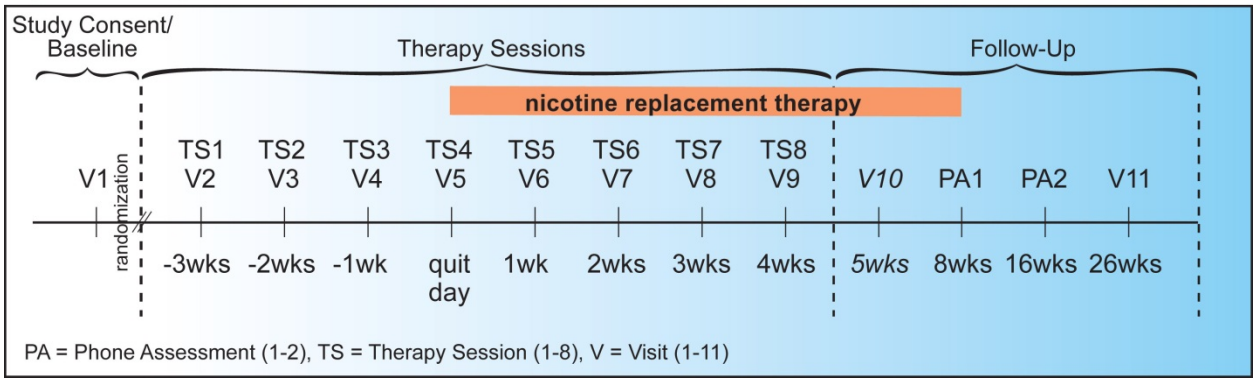
Adherence to BA. Patient treatment adherence to the ST+BA condition will be assessed by study personnel during weekly counseling sessions.

Study Procedures

Timing of Events

The study involves three basic phases:1) Study Consent and Baseline; 2) Therapy Sessions; and 3) Follow-up. Figure 4 illustrates the timing of study events, and the procedures associated with these phases are included in the text that follows.

Figure 4: Study Timeline



Study Consent and Baseline

Screening Telephone Call. Prior to entry into the study, participants will complete a screening phone call that will provide a brief overview of the study and ask preliminary screening questions. Study staff will obtain verbal consent to review the potential participant's VA medical chart to confirm that they meet basic criteria. The medical chart will be reviewed to confirm PTSD and depression diagnosis and treatment, other mental health disorders, current medications, and medication contraindications. Only information that is directly discussed with the potential participant will be recorded and no information regarding illicit drug use will be recorded. For those who are interested in learning more and who meet the criteria for entry into the study, an in-person screening session appointment (V1) will be scheduled.

In-Person Screening Assessment (V1). At the first visit, study staff will explain the study in detail and obtain written informed consent. Study staff will also obtain consent to audiotape treatment sessions on VA form 10-3203. For study candidates who provide informed consent, study staff will then proceed with screening and baseline assessments. All participants will complete an interview assessment including: 1) the Clinician Administered PTSD Scale (CAPS) for PTSD diagnostic status; 2) the Structured Clinical Interview for DSM (SCID) to assess for Axis I disorders (including depression); 3) assessment of suicidality or homicidality, and 4) medical history assessment. Any person who reports thoughts of suicide/self-harm or harm to others will be seen by VA Mental Health triage. Those judged to be at risk will be excluded and referred to appropriate VA treatment resources. Those who do not meet criteria for inclusion in the study will be referred to the VA smoking cessation clinic. Participants who meet inclusion/exclusion criteria will then be asked to complete a series of baseline self-report questionnaires including: 1) a demographic information questionnaire; 2) measures of PTSD symptom severity; 3) measures of proposed treatment effects; and 4) smoking history and dependence measures.

Randomization Process. After the in-person screening assessment is complete, the participant will be assigned into ST+BA or ST+HSE. The following variables will be blocked in this order: 1) severity of PTSD, 2) depression status (MDD versus no MDD), and 3) bupropion use. Separate randomization tables will also be developed for those presenting via the two different pipelines (VA vs. community [via DVA]). This will ensure that any characteristics that are related to such entities are counterbalanced across groups. Following randomization, study staff will contact the participant to schedule the first treatment session.

Treatment

All participants will attend eight study visits in which they will receive ST+BA or ST+HSE

(V2-V9). The quit day will occur on the same day as the fifth treatment visit (V6: see Figure 4). At the beginning of each visit (prior to the administration of therapy), participants will complete a series of self-report measures that may include assessments of: 1) positive and negative affect (PANAS), 2) PTSD symptom severity (PCL), 3) depressed mood (PHQ), 4) level of behavior activation (BAS), and 5) withdrawal symptoms. Some assessments will not be administered at every visit to reduce assessment burden (see Table 1 for specific assessment schedule). Smoking status (continuous and point prevalence) will be assessed at every in-person visit following the quit date. Sessions may be completed via telemental health (TMH) at a community based outpatient clinic (CBOC) that is closer to a Veteran's home or via phone in rare cases in which a Veteran is unable to travel a session in person.

Follow-up

All participants will receive follow-up phone calls at Weeks 12 and 20 (PA1 and PA2). They will also attend an in-person post-treatment follow-up visit to receive structured clinical assessments of PTSD and depression (V10). Participants will also attend an in-person follow-up visit at 26-weeks post-quit for nicotine abstinence bioverification (V11). Follow-up assessments will include measures of smoking status, positive and negative mood, PTSD symptom severity, depressed mood, sensitivity of the Behavioral Activation System, and withdrawal (see Table 1 for schedule).

Treatment Conditions

Treatment Conditions Overview

The experimental treatment group will receive ST+BA, and the contact control group will receive ST+HSE. BA is being examined as an adjunct to ST, with the latter an evidence-based treatment for smoking cessation. Both treatments will be delivered in eight, individual therapy sessions. Treatment sessions 1–4 (V2–V5) will occur prior to the quit day, therapy session 5 (V6) will occur on the quit day, and therapy sessions 6–8 (V7–V9) will occur each week until 4 weeks post-quit (see Figure 4). Participants in the ST+BA and ST+HSE conditions will participate in 20 minutes of identical, standard smoking cessation treatment during each session. The ST+BA condition will include an additional 30 minutes of behavioral activation therapy, and the ST+HSE condition will include an additional 30 minutes of health and smoking education. In addition to receiving ST+BA or ST+HSE, all participants will receive 12 weeks of the nicotine patch and either nicotine gum or lozenge.

Standard Smoking Cessation Therapy (ST)

Participants in both treatment groups will receive a standard, individual smoking cessation treatment based on the 2008 US PHS Clinical Practice Guideline, *Treating Tobacco Use and Dependence*[86]. The investigative team has considerable expertise in delivering behavioral and pharmacological treatments for smoking cessation. Treatment will be delivered in eight, 20-minute individual sessions over an 8-week period, with existing treatment manuals modified for this delivery format (see Table 2). The use of manuals will help ensure that the ST intervention does not differ between treatment arms (which will be checked with treatment fidelity assays). The same smoking cessation treatment has been used successfully in previous CTRI research (e.g., [4,46]). This cessation treatment is similar in content to that used at VA facilities[18], increasing the generalizability of the current research.

Table 2. Standard Smoking Cessation Treatment Overview

Therapy Session	Standard Smoking Cessation Therapy Content
Therapy Session 1 (V2)	• Provide reinforcement and support for quitting. • Discuss past quit experiences. • Address pros and cons of quitting. • Initiate self-monitoring. • Provide self-help materials (Clearing the Air USDHHS) [105]
Therapy Sessions 2 (V3)	• Identify high-risk situations. • Discuss abstinence violation effect. • Develop coping strategies.

	• Discuss link between alcohol use and smoking.
Therapy Session 3 (V4)	• Discuss how to enlist social support. • Demonstrate how to use nicotine patch and nicotine gum or lozenge. • Prepare for quitting.
Therapy Sessions 4 through 8 (V5–V9)	• Discuss past quitting experiences. • Provide intratreatment support and reinforcement. • Anticipate high-risk situations and generate coping plan. • Develop social support for nonsmoking.

Nicotine Replacement

Participants in both groups will begin using the nicotine patch and gum or lozenge starting on the morning of their assigned quit day. Nicotine patch and gum or lozenge will be provided to participants, at no cost, by the Madison VAMC. Consistent with the 2008 PHS Guideline[86], participants smoking ten or more cigarettes/day will receive 12 weeks of the following patch dosing: 6 weeks of 21 mg, 4 weeks of 14 mg, and 2 weeks of 7 mg nicotine patches. Participants smoking less than ten cigarettes/day will receive 12 weeks of the following patch dosing: 8 weeks of 14 mg and 4 weeks of 7 mg nicotine patches. Participants may taper down on patch dosage more slowly if needed as suggested by the 2010 VHA Tobacco Use Cessation Treatment Guidance. They will be instructed to apply one patch daily. As per the PHS Guideline, VHA Guideline, and package insert, gum/lozenge dose will be based on cigarettes smoked per day. Participants who smoke less than 25 cigarettes/day will only receive 2-mg gum/lozenge; participants smoking 25 or more cigarettes/day will receive 4-mg gum/lozenge. Participants will be told to try to use one piece of gum every 1-2 hours. However, participants will also be told that they may not be able to take a full, recommended dose of oral NRT given their conjoint use of the patch. Participants will be urged to use *at least* 5 pieces/day, unless this amount of use produces negative (toxic) effects. All participants will be given complete instructions on proper NRT use[86] and on signs of nicotine overdose/toxicity. Medication usage and side effects will be assessed at all visits. Maria Wopat, the VA smoking cessation coordinator, clinical pharmacist, and study clinician, will recommend dosage/use alterations as per good clinical practice if the participant experiences symptoms of nicotine toxicity or side-effects. Changes in recommended medication use will be considered in analyses of adherence outcomes. Participants will be asked to continue taking the medication for the full 12 weeks unless they are smoking regularly and heavily (≥ 10 cigarettes per day every day).

Standard Smoking Cessation Treatment Plus Health and Smoking Education (ST+HSE)

The ST+HSE treatment protocol will include all elements of standard smoking cessation treatment and nicotine replacement therapy (described above) along with health and smoking education. We will use a health and smoking education control treatment similar to that used by Hall and colleagues[84] — one that is currently being used successfully at UW-CTRI for a federally-funded grant (NIDA 5 P50 DA019706). The intervention includes information adapted from the Freedom from Smoking - American Lung Association, with additional information from the Mayo Clinic Nicotine Dependence Center Treatment Program Manual. This intervention is intended to produce the effects of a generic, extended cessation intervention and to control for clinical contact. We will present additional information beyond that presented in the ST intervention, so that the HSE intervention is not repetitive or boring. Participants will be encouraged to discuss presented information to reinforce what they are learning, and to discuss how the presented information is related to their situation and history (see [84]). Thus, while the HSE treatment will present more information than the ST intervention by itself, therapists will relate the information delivered in the HSE intervention to the patient's life situation, health status, desired quitting benefits, or self-reports (family history, withdrawal, level of nicotine dependence). This will be done because it is consistent with good clinical practice (also see[84]), and because the patient should not see the HSE intervention as being distinctly different/not integrated with the ST intervention. Therefore, in the ST+HSE condition, the first 20 minutes of

each session will have the same agenda as in the other conditions, but the rest of the agenda will present new information, encourage discussion of that information, and relate the information to the patient's situation and health. Thus, the ST+HSE intervention is designed to produce the effects of a generic smoking cessation intervention that has the same duration and clinical contact as does ST+BA (see Table 3; also cf. [83,84]). This intervention is not designed to be inert. But, because standard cessation interventions have had poor success in the PTSD population, we do not expect this intervention to produce significant benefit.

Table 3. Health and Smoking Education Overview

Therapy Session	Health and Smoking Education Content
Therapy Session 1 (V2)	• Smoking is a true addiction: the meaning and implications. • Symptoms of physical and psychological addiction and withdrawal and why it is so difficult to quit. • Smoking involves habitual behaviors: implications for heaviness of smoking and quitting. • Relate and discuss topics relative to participant's smoking history and experiences.
Therapy Session 2 (V3)	• Surgeon General Report: Health Consequences of Smoking (e.g., present data on health risks). • Immediate health benefits of quitting. • Delayed health benefits of quitting. • Relate to the patient's own health, smoking history, and concerns.
Therapy Session 3 (V4)	• Negative health effects of second-hand smoke and implications for family members. • Components of a cigarette (e.g., thousands of chemicals, 400 of which are toxic). • Nature and consequences of nicotine withdrawal symptoms, including urges (e.g., relapse), and the highly variable time course of symptoms. • Physical and psychological readiness for quitting smoking and the relation to cessation success. • Relate to patient's family/living context, withdrawal experiences, and readiness.
Therapy Session 4 (V5)	• The personal, social, and economic costs of smoking (time spent, money spent). • Relation of smoking to weight, and relation of quitting to weight gain. • Relative health effects of excess weight vs. smoking. • Relation of smoking to lifestyle, health behaviors (e.g., diet, exercise). • Relate to patient's reasons for quitting, concerns about costs of quitting, and lifestyle.
Therapy Session 5 (V6)	• Effect of quitting smoking on other behaviors (e.g., sleep). • Effects of quitting smoking on your physical appearance. • Importance of adherent use of nicotine replacement. • Information on safety of nicotine replacement products vs. smoking. • Relate to patient's concerns about appearance, use of NRT, and commitment to abstinence.

Therapy Session	Health and Smoking Education Content
Therapy Session 6 (V7)	• Effect of nicotine on the brain (e.g., time to reach brain, systems affected, risks for stroke, etc.). • Effect of quitting smoking on the brain (e.g., reduced risk of stroke). • Smoking and other health effects (e.g., infertility). • Threats to cessation that occur late vs. early in the cessation attempt.
Therapy Session 7 (V8)	• Relapse triggers and the course of a relapse. • Relate to patient's likely future encounters with triggers. • What a slip will do to health and smoking motivation (relation of slip to full relapse). • How smoking is related to psychological symptoms (e.g., may be triggered by anxiety). • Occurrence of unanticipated benefits of cessation.
Therapy Session 8 (V9)	• Years of potential life *gained* by quitting smoking. • Answer questions about cessation. • Reinforce success.

Standard Smoking Cessation Treatment Plus Behavioral Activation (ST+BA)

The ST+BA treatment will include all elements of standard smoking cessation treatment and nicotine replacement therapy (described above) along with the key elements of behavioral activation. Treatment will be delivered in eight, 50-minute (20 minutes of standard smoking treatment followed by 30 minutes of BA) individual sessions over an 8-week period. BA will be made relevant to smoking cessation, but this will occur within the BA portion of the treatment, ensuring that both conditions comprise the same smoking cessation base. As with the HSE treatment, therapists will make the BA relevant to the patient's life and will ensure appropriate integration with the ST. The following components of behavioral activation will be provided in ST+BA sessions:

Therapy Session 1 (V2)

Rationale for ST+BA and Monitoring. At the start of the BA component of Session 1, patients will receive a thorough rationale for the ST+BA treatment. Following this presentation, patients will discuss current activities (i.e., smoking lifestyle) and consider the reinforcing value of these activities. As homework, they will begin engaging in a self-monitoring exercise to examine already-occurring daily activities. The primary goals of this assignment are to: (a) provide a baseline measure to index progress following behavioral activation; (b) make the patient more cognizant of the quality and quantity of his/her activities; and (c) provide ideas for potential activities to increase during treatment. Psychoeducation information about how PTSD can undermine engagement in reinforcing activities will be presented.

Therapy Session 2 (V3)

Identification of Overall Values and Goals within a Nonsmoking Lifestyle. Following self-monitoring homework, the emphasis shifts to identifying a person's values and goals within a variety of life areas. This exercise will generate a target activity hierarchy (i.e., reinforcing activities). Next, the patient will be introduced to the Master Activity Log. Using the Master Activity Log, the therapist and patient will collaboratively determine the final goals regarding the frequency and duration of activities per week. The three easiest reinforcing activities from the hierarchy will be selected, and the patient will be given the Behavioral Checkout for use in monitoring engagement in these activities over the upcoming week. Study staff will not limit the type of activity in which the patient chooses to participate, and will encourage whatever activities the patient finds enjoyable, meaningful, and rewarding. Most likely, activities will be things that the patient has done in the past and study staff will encourage them to reinitiate activities or to increase the frequency. Common activities include gardening, going on walks, or doing volunteer work.

Therapy Session 3 (V4)

Monitoring Progress and Continuing to Reevaluate Nonsmoking Lifestyle. The session will begin with a discussion of the patient's weekly Behavioral Checkout. As a function of success in engaging in the previously selected activities, new activities will be added for monitoring in the upcoming week so that the patient moves through the hierarchy from the easier to the more difficult reinforcing activities. The session also focuses on the upcoming quit day and the importance of continuing with selected appropriate reinforcing activities in the absence of smoking.

Therapy Sessions 4–8: Quit Week and Beyond (V5–V9)

Maintenance. Participants will continue to monitor engagement in reinforcing activities in the absence of smoking. Based on their success, participants will continue to move through their activity hierarchy. As difficulties arise, participants will be encouraged to revisit their overall goals within a nonsmoking lifestyle and to work with their therapist to modify their activity hierarchy.

Reasons for stopping assigned treatment

BA has been shown to improve mood and anxiety disorders. BA has not been associated with significant adverse events. However, we will monitor biweekly for patient reports of affective distress and PTSD symptoms to inform decisions to stop treatment early in consultation with the study Data Safety Monitoring Board (DSMB). In addition, as indicated in the informed consent, participants can choose to stop treatment at any time, and we will terminate individual treatment in the event of associated and concerning adverse events.

Retention of Participants

The integrity of the data is highly dependent on retention of a large proportion of participants. Our extensive experience with smoking cessation and PTSD intervention studies has shown that retention of participants is fostered by the following strategies that we will follow in the proposed research;

- Providing state-of-the-art smoking cessation interventions at no cost to participants;
- Willingness to negotiate scheduling of contacts to fit with the participant's schedule;
- Dispensing medications at in-person visits (i.e., not requiring additional trips to a pharmacy);
- Compensation of, and recognition for, completion of study milestones;
- Providing participant who would like to discontinue treatment the option of continuing to receive study assessments only.

We will also enhance retention via providing incentives for all phone assessment and in-person visits. Subjects will receive $30 for each in-person treatment visit (V2–V9) to help defray the costs of travel or potential child care, $25 for completing each follow-up phone assessment (at Weeks 12 and 20 post-quit (PA1–PA2)), and $50 for attending each in-person follow-up visit (at Weeks 5 and 26 post-quit (V10-V11)). Participants will also receive $2 for each automated call answered and an extra $24 if they answer 80% or more of the automated calls. Total subject payment is thus $450/subject if all visits, phone calls, and follow-ups are completed.

Data and Safety Monitoring Plan

To identify unanticipated problems or complications, study participants will be provided at enrollment with contact information for the study coordinator, principal investigator, and the VA hospital patient relations representative. Any unanticipated problems or complications will be reported to the MR IRB per UW-Madison campus policy. Corrective actions, such as changes to the research protocol or informed consent process, will be taken in order to protect the safety, welfare or rights of study subjects or others. Researchers will monitor biweekly for patient reports of affective distress and PTSD symptoms to inform decisions to stop treatment

early in consultation with the data monitoring committee. Additionally, the Clinical Science Research and Development (CSRD) Data Monitoring Committee will review safety data.

Safety and Protection of Human Subjects

Subject privacy will be protected during the course of this study and HIPAA regulation will be followed. Only relevant, applicable study data will be collected, and will be entered in a secure web-based system with restricted access. Any required paper data will be kept in a confidential locked area, with no personal identifying information in our data set. This will be available only to primary study staff directly responsible for this data, and to representatives of the VA Research and Development Committee or University of Wisconsin IRB. Access to data will be removed if study staff are no longer part of the study team. Informed consent will be obtained by study staff. A data and safety monitoring committee will review all adverse events. Medical emergency and safety plans will be established, and adverse events will be reported in a timely manner to appropriate committees.

In accordance with VA policy, in the case of reporting incidents, i.e. theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls, the Information Security Officer and Privacy Officer will be notified within one hour to determine an appropriate course of action.

Statistical Considerations

Power considerations

Estimated effect sizes for the primary treatment comparison and the power available to detect these effects with two-tailed tests are provided below for the total *N* = 120 participants with 25% attrition, using intent-to-treat approach. We computed power for the GLMM longitudinal analysis using a SAS macro developed by Dang and colleagues[108].

Specific Aim 1: Dr. Lejuez's recent trial of BA for smoking cessation in smokers with symptoms of depression showed that 19% of smokers who received ST+BA were abstinent at 6-months post-quit, relative to those who received a contact-control smoking cessation treatment (0% abstinence rate at 6-months post-quit). For a treatment of this intensity (ST+BA), we believe that an improvement of at least 15% at 26-weeks post-quit would be sufficiently large to support additional research. For the current study, we predict that 6-month point prevalence abstinence rates will be 20% for ST+BA and approximately 5% for ST+HSE. We computed power for the GLMM longitudinal analysis using a SAS macro developed by Dang and colleagues[109] with the following parameters: *N*=45 per group; 5 time-points; drop-out rate of 0.25; 5% vs. 20% treatment effect over time; random effects variance=1; and within-subject correlation=0.6. Power for this scenario is 0.85. Even though power estimates have accounted for an estimated 25% attrition for a sample of *N*=90, we increased the sample size by 30 participants (N=120) to ensure that we have sufficient statistical power (which accounts for 25% attrition). Thus, the current study will have strong statistical power in the GLMM analyses.

Data and Record Keeping

Data elements will be collected and stored during the screening assessment and all visits and phone assessments. During the screening session, data resulting from structured clinical interviews assessing Axis I Disorders will be collected and stored. In addition, questionnaires measuring mood, medical history, smoking characteristics, craving, withdrawal symptoms, CO levels, behavioral activation, and demographic information will be collected and

stored. During later visits, questionnaires measuring mood, craving, withdrawal symptoms, CO levels, cotinine levels, and behavioral activation will be collected and stored.

Screening assessment data will be collected and stored in paper format. A summary of the screening assessment and all study questionnaires at study visits will be administered to participants via a web-based computer program called Qualtrics that presents questions on the screen that are answered by entering keystrokes on the computer keyboard. Qualtrics is available and funded through UW DoIT and provides a HIPAA-compliant, encrypted data collection system that allows completion of questionnaires without paper data. Data are stored on a secure password-protected UW server but not on the computer on which the participant completes the Qualtrics questionnaires.

The study will utilize a unique study ID for storing all data related to individual participants. Information linking that study ID to participant identifying information will be maintained by the PI. Subject identifying information will only be available to those study staff with whom subjects have direct contact. Data being used for analysis will be identified with the study ID only. Aside from the screening assessment, the study will not routinely utilize any paper or non-electronic records; if paper records are used as a back-up during a period when a functioning computer is not available, they will be maintained in a locked area after their entry has been properly verified. Paper data will likely be kept in room G22 (VHAMADCookJ) or G13 (VHAMADWebstK) of the VA hospital. Electronic records may be obtained on a mobile device that is protected with VA approved encryption technology that is FIPS 140-2 validated.

The name, contact information, and study schedule for interested and enrolled participants will be kept in a separate database. The automated list of potential participants to whom informational letters will be sent will be maintained in a separate database as well. This identifiable information is maintained in order to contact and follow-up with interested potential participants or enrolled participants. No study data will be stored in these databases. All identifiable data will be stored on secure, password-protected servers located at the Madison VA and only study personnel will be granted access. All data that is not identifiable (forms collected after enrollment that are identified only by study number) is stored on a UW DoIT server with a copy of this data retained on a VA server.

Data will be maintained by the Madison, WI VAMC following the completion of the study.

Safety and Protection of Data Collected in Qualtrics

The research team will manage study data through Qualtrics. Qualtrics is an electronic data management system that will be used to capture, edit, manage, and export study data for analysis. Qualtrics is a HIPAA-secure survey tool obtained through licensing agreement with the University of Wisconsin System and promoted for research by DoIt. Subject identifiable information is restricted at multiple levels;

1. Access to the Qualtrics system is restricted to those that have been granted access by the software administrators. User access requires supervisor approval, completion of HIPAA and Human Subjects Protection training, and completion of role-based training in the Qualtrics system.
2. In addition, users' access is limited to protocols for which they have some responsibility of protocol, subject, or data management.
3. Within those protocols, the ability to view and modify data is restricted based on their role in the conduct of the research project (e.g. regulatory staff do not have the privilege to view subject identifiable information).

In addition, the technical components of this software are managed by the UW-Madison's Bioinformatics Computing Group (for server maintenance, software upgrades, etc.), and security and software support is provided by CTRI staff. CTRI staff are able to access subject information in order to help end users of the software program when questions arise.

All communication between the clients and the Qualtrics application takes place via Hypertext Transfer Protocol over Secure Socket Layer or HTTPS. HTTPS provide the ability for normal web based communication over an encrypted Secure Socket Layer (SSL) connection. This ensures that data passing between the client and Qualtrics is protected from unauthorized attempts to access the data.

The Qualtrics system is web-based software, with data stored on secure servers. Data exported from the Qualtrics System, is exported with indirect identifiers (i.e. with study ID number per subject) for statistical and data monitoring purposes in an MS Excel or SAS format. Upon exportation, the clinical research management system has no control over how it is manipulated or managed. Qualtrics data is backed up regularly. In addition, a copy of all Qualtrics data for the study is stored at the VA.

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