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Pain and smoking study (PASS): A comparative effectiveness trial of smoking cessation counseling for veterans with chronic pain

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ABSTRACT

Introduction: Smoking is associated with greater pain intensity and pain-related functional interference in people with chronic pain. Interventions that teach smokers with chronic pain how to apply adaptive coping strategies to promote both smoking cessation and pain self-management may be effective.
Methods: The Pain and Smoking Study (PASS) is a randomized clinical trial of a telephone-delivered, cognitive behavioral intervention among Veterans with chronic pain who smoke cigarettes. PASS participants are randomized to a standard telephone counseling intervention that includes five sessions focusing on motivational interviewing, craving and relapse management, rewards, and nicotine replacement therapy versus the same components with the addition of a cognitive behavioral intervention for pain management. Participants are assessed at baseline, 6, and 12 months. The primary outcome is smoking cessation.
Results: The 371 participants are 88% male, a median age of 60 years old (range 24–82), and smoke a median of 15 cigarettes per day. Participants are mainly white (61%), unemployed (70%), 33% had a high school degree or less, and report their overall health as "Fair" (40%) to "Poor" (11%). Overall, pain was moderately high (mean pain intensity in past week = 5.2 (Standard Deviation (SD) = 1.6) and mean pain interference = 5.5 (SD = 2.2)). Pain-related anxiety was high (mean = 47.0 (SD = 22.2)) and self-efficacy was low (mean = 3.8 (SD = 1.6)).
Conclusions: PASS utilizes an innovative smoking and pain intervention to promote smoking cessation among Veterans with chronic pain. Baseline characteristics reflect a socioeconomically vulnerable population with a high burden of mental health comorbidities.

1. Introduction

Tobacco cigarette smoking is associated with the development and progression of many painful conditions [1–9]. In a conceptual synthesis, Ditre and colleagues hypothesized a reciprocal model of pain and smoking fueled by a myriad of social, biological, and physiological factors in which pain and smoking exacerbate each other, resulting in a positive feedback loop of more pain and increased smoking [10–13]. This model continues to be supported by recent studies showing that pain increases the urge to smoke in a dose-dependent relationship [14–16] and that smokers report significantly greater pain intensity, more frequent pain, and greater pain-related functional interference relative to non-smokers [17–19]. This is important to study in the Veteran population, where both chronic pain and current smoking are especially prevalent [20]. In a national cohort of Veterans, current smoking is associated with significantly higher pain intensity [21].

Smoking cessation substantially decreases morbidity and mortality [22–24], yet many patients (24–68%) with chronic pain continue to smoke [25,26]. Among patients with back pain, those who quit smoking reported significantly greater improvement in pain ratings compared to

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patients who continued to smoke [27]. Smokers with chronic pain report lower self-efficacy for smoking cessation [28], and emerging prospective data indicates that smokers with pain are less likely to initiate a quit attempt and maintain smoking abstinence than smokers without pain [29]. Accordingly, smoking cessation programs must be intensified to address the interaction of nicotine dependence and pain intensity among smokers with chronic pain.

Unique features of the co-occurrence of chronic pain and smoking make smoking cessation especially challenging. Pain-related anxiety serves as a trigger to smoke and diminishes smokers' self-efficacy to make a quit attempt [12,30–32]. Many smokers with pain report clinically significant levels of anxiety (e.g., fear of pain) as a reason for failing to maintain abstinence [33]. Smokers with chronic pain may have underdeveloped coping skills and may specifically benefit from adopting cognitive behavioral interventions (CBIs) for both smoking and pain [12,33,34]. Teaching smokers how to apply adaptive coping strategies to promote both smoking cessation and pain self-management can lead to increased confidence in ability to quit [35]. In addition, acquisition of these skills can improve pain-related anxiety.

A few pilot trials of CBIs for smoking cessation among patients with chronic pain have reported encouraging results [36–39]. However, to date, there have been no trials studying the long-term outcomes of smoking cessation with pain management counseling. Concomitant efforts to address smoking cessation and chronic pain, via established CBIs, have the potential to provide smokers with pain the requisite skills to navigate the smoking cessation process, manage associated anxiety-related cues that interfere with efforts to quit, and gain skills to manage chronic pain. The Pain and Smoking Study (PASS) was designed to evaluate telephone delivery of a smoking cessation program that combines behavioral pain management, nicotine replacement therapy (NRT), and smoking cessation counseling for smokers with chronic pain. In this report, we describe the methodological approach, recruitment flow, and baseline sample characteristics of the PASS Comparative Effectiveness Trial.

2. Methods/design

The goals of the study were to: 1) evaluate the impact of smoking cessation plus CBI (SMK-CBI) on cigarette abstinence rates (primary outcome) among Veterans with chronic pain at 6- and 12-months, compared to standard smoking cessation counseling (SMK-STD); 2) evaluate the impact of SMK-CBI on pain intensity and pain interference (secondary outcomes) among Veterans at 6- and 12-months, compared to SMK-STD; 3) assess whether change in self-efficacy and pain-related anxiety mediate the impact of SMK-CBI on smoking cessation in Veterans with pain at 6- and 12-months compared to SMK-STD. The trial is registered at www.ClinicalTrials.gov (NCT02971137). Protocols and consent documents were approved by the VHA Connecticut Institutional Review Board.

2.1. Setting

PASS is conducted in two northeastern VHA Healthcare facilities (VHA Connecticut and VHA Central Western Massachusetts).

2.2. Participants

Three hundred seventy-one Veterans who met the inclusion/exclusion criteria highlighted in Table 1 were consented. Enrolled Veterans were those who currently smoked >7 cigarettes in the past 7 days, were interested in making a quit attempt in the next 30 days, were currently experiencing chronic pain, and endorsed a pain intensity ≥4/10 at its worst for the past week.

Table 1
Inclusion and exclusion criteria.

Major inclusion criteria
Enrolled in care at VA Connecticut Healthcare System or VA Western Central Massachusetts Healthcare System
Current smoker (smoking ≥7 cigarettes in the past 7 days) and willing to quit in next 30 days
History of chronic pain defined as a pain intensity ≥4/10 for 3 or more months
Endorsed a pain intensity ≥4/10 at its worst for the past week.
Major exclusion criteria
Active diagnosis of psychosis or dementia or other memory loss condition
Severely impacted hearing or speech
Lack of telephone access
Enrollment in another research study that might affect the main outcomes of the study
Non-English speaking
Terminal illness

2.3. Participant screening and proactive recruitment

Proactive recruitment is an essential element of a successful evidence-based smoking cessation remote intervention [40]. Veterans with chronic pain and receiving VHA healthcare were identified from the electronic health record (EHR) based on vital signs (which in the VHA include 0 (no pain) −10 (worse pain imaginable) numerical pain rating scale scores) and standard annual primary care smoking status screeners. Study staff reviewed identified EHR records to ensure eligibility criteria. Utilizing proactive recruitment, potential participants were then sent an introductory letter signed by the principal investigator that described the study, urged patients to quit smoking, and informed them that they would be contacted to complete a telephone survey unless they opted out by calling a toll-free number to refuse participation. Approximately five business days after the mailing, patients who had not opted out were contacted by study staff to assess interest and screen for eligibility. Interested and eligible veterans then provided verbal informed consent and completed the baseline survey via telephone.

2.4. Randomization

Following consent and baseline assessment, Veterans were randomized to one of two treatment groups (SMK-CBI or SMK-STD). The statistical team created the entire study randomization sequence using REDCap before patient enrollment began. Randomization was stratified by sex. Statisticians used a permuted blocked randomization technique to ensure balance between groups.

2.5. Sample size

The sample size estimate is based on the primary hypothesis of the trial, which is that proportion of Veterans with prolonged abstinence at the 6-month follow-up will be significantly higher among Veterans in the SMK-CBI group as compared to the SMK-STD group. We will assign non-respondents to the primary outcome as continued smoking (no prolonged abstinence). The sample-size estimate is based on a Z-test for the difference in proportions, assuming a two-sided α of 5% and β of 80%. Standard smoking cessation interventions targeting smokers with chronic pain have found quit rates of 0–10%) [41]. The one intervention targeting both pain and smoking, to date, reported 20% prolonged abstinence [36], and a small pilot study (n = 7) found an estimated 29% 7-day point prevalence abstinence [37].

We enrolled 371 Veterans to have 80% power to detect a 13% difference in prolonged abstinence (25.5% cessation rate for the SMK-CBI intervention and a 12.5% cessation for the SMK-STD arm). The 7-day point prevalence was approximately 25% higher than prolonged abstinence. Therefore, we estimated the 6-month, 7-day point prevalence abstinence to be approximately 16% in the SMK-STD group (12.5% x 1.25 = 16%) and 32% in the SMK-CBI group (25.5% x 1.25 = 32%). We have 80% power to detect a difference of 16% in 7-day point prevalence

at 6 months.

Given our planned sample size, we also examined the power and detectable difference for Hypothesis 2.1 (pain intensity using the Brief Pain Inventory) evaluated at 6-month follow-up. We have 90% power to detect a differential improvement of pain intensity of 30%, described as a clinically meaningful improvement in pain [42].

2.6. Treatment arms

Both groups receive five sessions of telephone-based smoking cessation counseling and smoking cessation content delivered at parallel times based on standard techniques informed by behavioral treatment principles, Social Cognitive Theory [43], and Motivational Interviewing [44] and shown to be efficacious for smoking cessation. The treatment protocol is consistent with the Public Health Service Clinical Practice Guide and was previously tailored to Veterans based on principles of evidence and consensus-based clinical practices [45].

2.6.1. Standard (SMK-STD)

The standard telephone counseling intervention includes five 30-min sessions focusing on motivational interviewing, how to manage cravings, how to handle slips, and rewards (Table 2).

2.6.2. Nicotine replacement therapy provided to both SMK and SMK-CBI

The United States Public Health Services Update of Clinical Practice Guidelines on the Clinical Treatment of Tobacco Use and Dependence recommends the use of NRT, typically a combination of a long-acting nicotine formulation (patch) and a short-acting nicotine formulation (gum or lozenge) [46,47]. At VHA specialty-based smoking clinics, counseling sessions with NRT are the standard of care for assisting Veterans to quit smoking. At the first telephone counseling session, counselors asked potential participants if they were interested in using NRT and contacted the Veteran's primary care physician to facilitate an NRT prescription.

Table 2
Intervention components.

	Smoking Cessation Counseling SMK-STD	*Smoking Cessation Counseling plus Cognitive Behavioral Intervention SMK-CBI*
#1	✓ Introduce counselor and study ✓ Check in ✓ Explore motivation to quit ✓ Set quit date if appropriate	✓ *All components of SMK-STD Session 1 (to the left, less the quit date discussion), plus the following:* ✓ *Introduce physical activity* ✓ *Use pedometer to record weekly step count* ✓ *Assign homework*
#2	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Discuss ways to manage cravings	✓ *All components of SMK-STD Session 2 (to the left), plus the following:* ✓ *Pleasant activities* ✓ *Set quit date* ✓ *Record weekly step count* ✓ *Assign homework*
#3	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Discuss how to handle slips	✓ *All components of SMK-STD Session 3 (to the left), plus the following:* ✓ *Introduce and practice progressive muscle relaxation* ✓ *Record weekly step count* ✓ *Assign homework*
#4	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Discuss rewards	✓ *All components of SMK-STD Session 4 (to the left), plus the following:* ✓ *Introduce Unhelpful Thoughts* ✓ *Introduce Mini Practices* ✓ *Record weekly step count* ✓ *Assign homework*
#5	✓ Check in ✓ Check in on patient's action plan on taking steps towards quitting ✓ Develop a post-counseling action plan	✓ *All components of SMK-STD Session 5 (to the left), plus the following:* ✓ *Review skills learned in previous sessions* ✓ *Record weekly step count*

2.6.3. Cognitive behavioral intervention (SMK-CBI)

In the SMK-CBI arm, evidence-based cognitive-behavioral pain management approaches were integrated into the evidence-based smoking cessation counseling (Table 2). CBI emphasizes psycho-educational and skills-based approaches and is informed by the VHA existing pain self-management program [48]. Specifically, the CBI developed for the study includes a focus on increasing physical activity, identifying pleasurable activities, relaxation practices, and thought monitoring/restructuring [49]. The CBI participant manual also included a PASS activity booklet, which provides Veterans with an opportunity to practice relevant behavioral and cognitive skills for both smoking cessation and pain self-management. Consistent with standard CBT for pain protocols, participants in the SMK-CBI arm were encouraged to increase their physical activity. To facilitate this, they were given pedometers and instructed to track and record their daily steps in the PASS activity booklet, and to report their weekly steps average to the PASS counselor during each of the 5 telephone counseling sessions. They were encouraged to increase their steps by 10% each week. As in the SMK-STD arm, Veterans in this arm received five 30-min telephone sessions.

2.6.4. Training and fidelity

The PASS study counselor was trained by a doctoral-level clinician on both SMK-STD and SMK-CBI counseling sessions, provided with videos and readings on CBI, smoking cessation, and pain, and was audio-recorded using a mock patient. Counseling session fidelity was assessed using audio-taped recordings of sessions. We recorded approximately 20% of sessions (all sessions in the first 3 months of the study and then one week out of every 2 months for the remainder of the study). Investigators rated 10% of the sessions in both arms to ensure protocol fidelity over time.

2.7. Measures

Study measurements were obtained via telephone at baseline, 6 months, and 12 months post baseline. Participants were given a $25 thank-you payment for completing each follow-up questionnaire. Medical data, including co-occurring medical and mental health diagnoses, were collected from the Veteran's EHR.

2.7.1. Primary outcome

In keeping with the Society for Research on Nicotine and Tobacco's recommendations for measuring abstinence, we use prolonged abstinence as our main outcome and allowed for a 2-week window around quit date. During the 6- and 12-month follow-ups, Veterans were asked about prolonged abstinence, "In the past 6 months, have you smoked at least a part of a cigarette on each of 7 consecutive days?" and "In the past 6 months, have you smoked any cigarettes in each of 2 consecutive weeks?" [50]. We will assign non-respondents to the primary outcome as continued smoking (no prolonged abstinence).

2.7.2. Secondary outcomes

Point prevalent abstinence: At each follow-up (6-and 12-month), patients were asked whether they have smoked a cigarette, even a puff, in the past 7 days. If no, they were asked whether they have smoked a cigarette, even a puff, in the past 30 days.

Pain intensity and pain related functional interference: At baseline, participants completed the Brief Pain Inventory (BPI), which includes 2 multi-item scales measuring pain intensity and pain-related functional interference [51]. Pain intensity in the past week is measured in 4 items—worst, least, current, and usual—each using a validated 11-point *numerical rating* scale (0–10). A rating of 0 indicates no pain, while 10 indicates the worst pain imaginable. Items are averaged to create an intensity composite; a score of 4 or above is considered clinically

significant according to VHA treatment guidelines [52,53]. The functional interference subscale consists of 7 items measuring self-rated pain interference related to general activity, mood, walking ability, normal work (inside or outside the home), relations with other people, sleep, and enjoyment of life. Respondents rated how much pain has interfered with these aspects of their lives in the past 24 h on a scale of 0 (does not interfere) to 10 (completely interferes). A composite average of these 7 items is then calculated.

2.7.2.1. Biochemical verification. Saliva samples were collected from participants who reported not smoking in the prior 7 days (7-day point prevalence) in order to biochemically validate their self-reported smoking status. This process has been shown to improve the validity of self-reported smoking cessation [45]. Samples are collected at next clinic visit following the telephone interview [54]. Saliva samples measure cotinine levels using NicAlert dipsticks with a standard cut point of 16 ng/ml to determine abstinence. Participants receive a $10 incentive for providing each saliva sample at 6- and 12-month follow-up surveys.

2.7.3. Background measures

2.7.3.1. Demographic characteristics. Information on age, race/ethnicity, gender, education, marital status, and employment status were gathered from the baseline survey.

2.7.3.2. Tobacco Use history and dependence. Veteran smoking history was assessed by asking the number of cigarettes currently smoked per day on average and the number of serious quit attempts (quitting for at least 24 h) within the last six months. Use of other tobacco or nicotine products including smokeless tobacco (e.g., snuff, dip), cigars, regular pipe, and electronic cigarettes was also queried. To assess nicotine dependence, the one-item Fagerström Test for Nicotine Dependence was administered [55]. This measure assesses how soon after waking the person smokes their first cigarette (within 5 min; 6–30 min; 30–60 min; or after 60 min).

2.7.3.3. Additional psychosocial measures. The 12-item Short Form Survey (SF-12) [56] assessed quality of life. Perceived health quality was rated in five categories from excellent to poor at baseline only. Determination and desire to change their smoking behavior was assessed by the following item, "On a scale from 1 to 7 where 1 is "not at all" and 7 is "very much" how much do you want to quit smoking in the next 6 months?" The Patient Health Questionnaire (PHQ-9) assessed depressive symptoms; the PHQ-9 can be used to calculate a mean score, the percent of patients with PHQ-9 scores $\geq$10, and the percent of patients with suicidal ideation [57]. Other measures included the Alcohol Use Disorders Identification Test (AUDIT-C), which is an alcohol screening tool that can help identify people with hazardous drinking or alcohol use disorder [58].

2.7.3.4. Process/mediator measures. Global self-efficacy to quit smoking was assessed via a single item, "How confident are you that you will be able to quit smoking in the next 6 months?" (1 = Not at all confident to 7 = Very confident) [59]. The use of a global measure is supported by previous studies in which multiple-item questionnaires formed an unifactorial construct [60]. The 20-item Pain and Anxiety Symptom Scale (PASS-20), assessed fearful and anxious responses to pain such as "I think that if my pain gets too severe, it will never decrease" and "when I feel pain, I am afraid that something terrible will happen" [61].

2.7.3.5. Engagement and satisfaction with intervention components. Reported use of/adherence to study-administered interventions (e.g. smoking cessation self-help materials, number of sessions attended) were assessed. Patients in the CBI arm were asked how much of the self-help manual they read and how useful the self-help manual was in helping them to try to quit smoking. Patients were also asked how useful the counseling calls were in helping them to try to quit smoking and if they would recommend the program to a friend who was trying to quit smoking. Veterans were also asked about the use of NRT, including what type and their adherence to this medication.

2.8. Data analysis and statistical considerations

This study is a randomized, two-arm parallel group trial. The primary analysis is based on intention-to-treat principles.

Hypothesis 1.1. Prolonged abstinence will be significantly higher among Veterans in the SMK-CBI group compared to those in the SMK-STD group.

Hypothesis 1.2. The 7-day prevalence abstinence will be significantly higher among Veterans in the SMK-CBI group compared to those in the SMK-STD group.

Cigarette abstinence will be assessed at 6- and 12-month follow-up. Abstinence will be measured as a dichotomous variable that indicates whether patients have been abstinent or not. The same analysis approach will be used to test both prolonged (30 day) and 7-day point prevalence abstinence rates. Self-report of abstinence will be validated with cotinine saliva testing.

Logistic regression will be used to test for a between-group difference in abstinence at 6 months [62]. For each of the outcomes, we will evaluate the intervention effect by testing that parameter estimate differs from zero and report the odds ratio (OR) and its 95% CI. With SMK-STD as the reference group, an OR significantly greater than 1.0 will provide evidence that SMK-CBI group patients have higher odds of prolonged abstinence. The model will also include stratification variables (e.g. gender) as recommended in the Committee for Proprietary Medicinal Products guidelines [63].

Sustainability, or longer-term effects of the intervention, will be examined by comparing abstinence between groups at 12 months. We will model change in abstinence at baseline, 6, and 12 months using generalized linear models with a logit link fit with generalized estimating equations with autoregressive covariance structure [64]. The regression coefficients from this model have essentially the same interpretation as those from a cross-sectional regression analysis (e.g. logistic regression) but are more appropriate as they properly incorporate the within-subject correlation that is inherent in the longitudinal structure of the data. The model will be fit using the SAS procedure GENMOD (SAS Institute, Cary, NC).

Hypothesis 2.1. Veterans in the SMK-CBI will report significantly lower usual pain intensity and pain interference compared to the SMK-STD group.

We will use a linear mixed effect models procedure for analyzing repeated-measures data with fixed and random effects to evaluate study group assignment effects on our continuous and repeated outcomes (pain intensity and pain interference). The statistical procedure is designed for unbalanced repeated measures with missing data, allowing for intra-participant serial correlation. It provides tests of the overall between-participant effects, repeated measures (time) effects, tests of fixed and random effects, and analysis of reduced models that can provide detailed tests of specific pattern of results [65]. Additionally, the model will include the stratification variables. We will use the SAS procedure MIXED (SAS Version 9.2, Cary, NC).

Hypothesis 3.1. The relationship between pain-related anxiety intervention and smoking cessation will be mediated by self-efficacy and pain-related anxiety.

If there is a significant intervention effect on smoking cessation, then we will assess whether change in self-efficacy and pain-related anxiety mediate the impact of the intervention. This aim can be addressed under the general framework of mediation. We propose to conduct this

mediation analysis using the MacArthur approach, a modification of the traditional Baron & Kenny criteria, developed for use specifically in randomized clinical trials [66,67]. By the MacArthur definition, the potential mediator must be evident during or post-treatment; therefore, for example, the change in patient self-efficacy measures between baseline and 6 months will be considered as potential mediators. The outcome will be patients' abstinence at 12 months. We will first fit a model to examine the correlation between the mediator (C) and the SMK-CBI group: $C = \gamma 0 + \gamma 1 * \text{SMK-CBI}$. We also fit a model that examines the relationship between the mediator and the probability of abstinence (p): $\text{logit}(p) = \beta 0 + \text{SMK-CBI} * \beta 1 + C * \beta 2 + C * \text{SMK-CBI} * \beta 3$. Improvements in patient self-efficacy or pain-related anxiety will be considered to account for improvements in abstinence rates if there is evidence that $\gamma 1$ is not equal to zero, and if either $\beta 2$ or $\beta 3$ are not equal to zero.

Intention-to-Treat Analysis: All primary and secondary analyses focus on the effect of SMK-CBI as compared to control (SMK-STD). Therefore, we plan to use the intention-to-treat assumption for all analyses; participants will be analyzed as part of the group to which they are randomized, regardless of intervention adherence. Since participants can't cross arms of the trial, no per-protocol analyses will be conducted.

3. Results

3.1. Recruitment

Recruitment started in December 2017 and concluded in July 2020. Fig. 1 is the CONSORT diagram summarizing the recruitment process. We sent introductory letters to 3478 patients who were identified by an automated data pull and then underwent EHR review to confirm that they were current smokers and have a pain score >4 for 3 months. We were unable to reach 720 by telephone. Among the 2758 contacted, 2319 declined participation. The main reason that Veterans were not interested in participating in the study was they were not willing to quit smoking in the next 30 days. Among the 439 interested in participating, 50 failed the screener and 389 agreed to participate. Eighteen potential participants dropped out before randomization leaving a total of 371 enrolled.

3.2. Baseline characteristics

Of the 371 Veterans who were randomized, 186 were randomly assigned to SMK-CBI and 185 were randomly assigned to SMK-STD. At baseline, participants are 88% male, median age is 60 years old, and less than half are married/partnered (47.6%) (Table 3). Participants reported smoking, a median of 15 cigarettes per day. Participants are mainly white (61%) or black (26%); 7% are Hispanic. Participants are mostly (70%) not employed, 33% had a high school degree or less, and report their overall health as "Fair" (40%) and "Poor" (11%). Overall, mean pain intensity in past week was 5.2 (Standard Deviation (SD) = 1.6), and mean pain interference was 5.5 (SD = 2.2). Pain-related anxiety mean was 47.0 (SD = 22.2) which is high and self-efficacy was low (mean = 3.8 on a scale of 1–7). With regards to mental health, 59.0% scored above the clinical threshold of ≥10 on the PHQ-9 for major depressive symptoms and 11.3% endorsed suicidal ideations. Almost one-third (32%) screened positive for potential alcohol problems on the AUDIT-C.

4. Discussion

The PASS comparative effectiveness trial was designed to evaluate the telephone delivery of a smoking cessation program that integrated behavioral pain management, nicotine replacement therapy, and smoking cessation counseling among Veterans who smoke and have chronic pain. Teaching smokers how to apply adaptive coping strategies to promote both smoking cessation and pain self-management may be effective to promote smoking cessation. Following in the steps of previous trials that have studied smoking cessation in smokers with pain [36–39], our study offers a new look at long-term abstinence rates and changes in pain after a combined pain-smoking cognitive behavioral

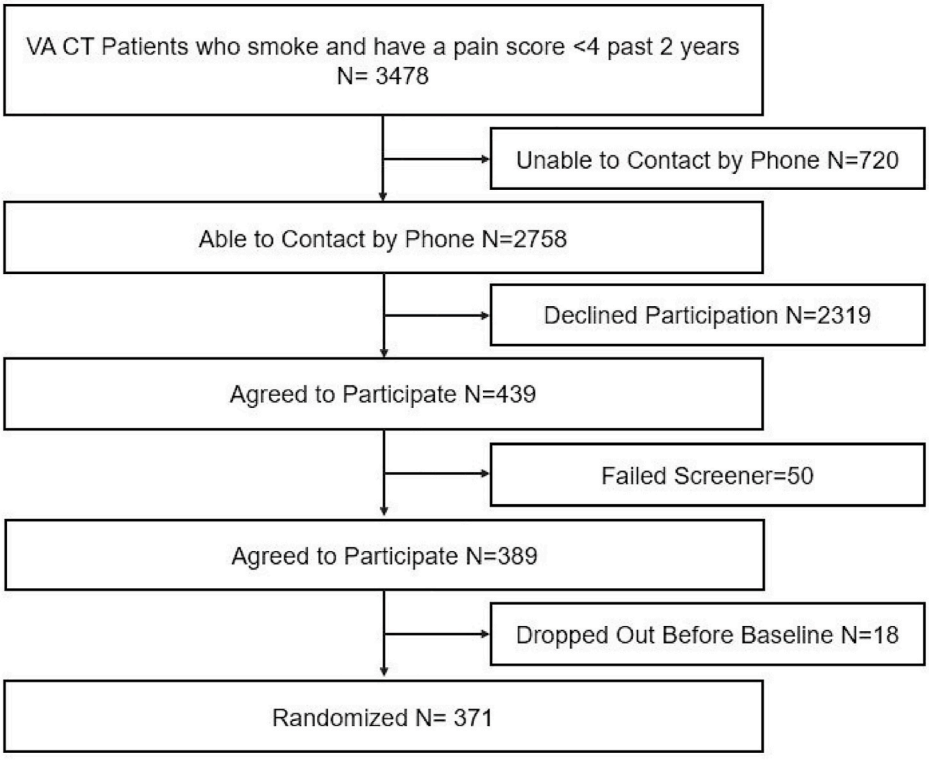

Fig. 1. CONSORT diagram for pain and smoking study.

Table 3
Baseline characteristics of the PASS sample (n = 371).

DEMOGRAPHICS	N = 371
Median age [IQR]	60 [52,65]
Men (%)	88.1
Race/Ethnicity	
White	60.6
Black	26.1
Hispanic	6.8
Asian/Pacific Islander	0.8
Biracial	3.2
Other	2.5
Married/Living with Partner (%)	47.6
High School Graduate or Less (%)	32.6
Self-Reported Work Status (%)	
Full Time	22.4
Part Time	7.3
Not Employed	70.3
SMOKING BEHAVIOR	
Cigarettes per Day (Median [IQR])	15 [8–20]
Years Smoking (Median [IQR])	40 [25–47]
Pack Years (Median [IQR])	22 [10–40]
Quit Attempts, Ever (Median [IQR])	5 [3–12]
Nicotine Dependence (%)	
Within 5 min	28.8
6–30 min	37.0
30–60 min	15.5
After 60 min	18.7
Desire to Quit Smoking (Mean, SD)	5.4 (1.1)
Global self-efficacy to quit smoking, next 6 m (Mean, SD)	3.8 (1.6)
Used E-Cigarettes in last week (%)	9.8%
PSYCHOSOCIAL MEASURES	
Overall Health, self-reported (%)	
Excellent	3.2
Very Good	12.4
Good	33.4
Fair	39.9
Poor	11.0
Mean PHQ-9 Score (Mean, SD)	11.4 (6.6)
PHQ-9 Scores≥10 (%)	59.0
PHQ-9 Suicidal Ideations (%)	11.3
Positive AUDIT-C (%)	32.1
PAIN MEASURES	
Pain Intensity in Last Week (1–10) (Mean, SD)	5.2 (1.6)
Pain Interference (Mean, SD)	5.5 (2.2)
Pain-Related Anxiety (Mean, SD)	47.0 (22.2)

SD = standard deviation, PHQ-9 = Patient Health Questionnaire-9, AUDIT-C = Alcohol Use Disorders Identification Test.

program.

Although the majority of smokers with chronic pain declined to participate, our enrollment rates are similar to prior smoking cessation studies using proactive recruitment [68,70,71]. The main advantage of proactive recruitment is to broaden the reach of effective interventions, but the accrual rates are typically low because smokers are not interested in quitting smoking. We successfully recruited a sample of middle-aged Veterans who smoke and have chronic pain. This population is medically and socioeconomically disadvantaged. Less than half are married/partnered, and 70% were not employed, and 33% had a high school degree or less. More than 50% reported that their overall health was fair or poor. In comparison, in the 2019 U S. Bureau of Labor's census of all Veterans, only 3.5% were unemployed [72]. Among the Veteran population in 2016, 33.9% had a high school diploma or less (Employment Situation of Veterans, 2020) and around 55% were married [73]. Our demographics are more comparable to previous smoking cessation trials. For example, in a study of 308 smokers with a chronic condition (i.e. heart disease, cancer, diabetes), 56.8% were married, 52.6% had no level of college, 80.3% were unemployed, average pain score was 4.9, and almost 60% rated their health as fair/poor [74]. Another study of Veteran smokers who had mental health clinic visits revealed that 40% had less than some college education and 24% were employed [69].

With regards to mental health conditions, nearly two-thirds of our participants exceeded the clinical cutoff for moderate depressive symptoms established by the PHQ-9. By comparison, a National Health and Nutrition Examination Survey revealed that the rate of depression in Veterans in 2011–2012 was 12.3% [75]. This is consistent with a meta-analysis showing that smoking is disproportionately higher in patients with depression [76], and smokers with chronic pain are more likely to report depression [25,77,78]. In our sample, around a third of the Veterans had a positive AUDIT-C score. In comparison, around 10% of Iraq and Afghanistan Veterans who are first-time users of VHA healthcare receive diagnoses of alcohol use disorder [79]. In terms of the relationship between alcohol and pain, in an integrative review, Zale et al. found evidence that heavy alcohol use was associated with greater pain severity [80]. Furthermore, alcohol may have acute pain-inhibitory effects, and situational pain may induce alcohol consumption [80,81]. The interplay of smoking, alcohol, and pain is a complex relationship that future studies should explore.

The average pain intensity in our study was moderately high at 5.2, while pain interference was also moderately high at 5.5. These scores are consistent with samples of Veterans seeking psychological interventions for chronic pain [71]. Higher pain intensity and interference scores may predict a lower smoking cessation rate. A 2017 study showed that in smokers with HIV, lower pain intensity predicted higher 24-h and 7-day abstinence rates [82]. Smokers with chronic pain are also more likely to report severe problems with mobility and with performing usual activities [77]. Furthermore, in a laboratory paradigm of smoking withdrawal, greater pain-related disability has been shown to predict shorter latency to lapse [83]. Our study also reported high rates of pain-related anxiety and low self-efficacy, with a mean pain-related anxiety score of 47.9 out of 100 points. In the validation study, the majority of individuals classified as having high pain-related anxiety had PASS-20 total scores greater than 30 [84].Self-efficacy is also important to consider, as previous studies have shown that higher confidence in quitting significantly predicts cessation rates [85]. Previous literature calls for transdiagnostic interventions that address pain-related anxiety in smoking cessation efforts and the treatment of pain [32]. Addressing both factors concomitantly has the potential to provide smokers with pain the requisite skills to navigate the smoking cessation process and manage the associated anxiety-related cues that interfere with efforts to quit.

While telephone quit lines are accessible to many smokers and can engage motivated smokers, proactive recruitment and proactive telephone counseling are essential elements of successful evidence-based telephone-delivered interventions. Studies have shown that proactive recruitment itself improves abstinence rates [86,87] and can reduce socioeconomic disparities in quitting [88]. We also endeavored to promote NRT use in our study. Adding pharmacotherapy can increase absolute tobacco quit rates by 3.1%, which results in a cost effectiveness ratio of $4,705 per quit [89]. Furthermore, in a 2016 meta-analysis, Ditre et al. found that nicotine administration, independent of method of administration (e.g. tobacco smoke, patch, nasal spray), produced acute analgesic effects on experimental pain threshold [90]. This means that NRT may provide similar acute pain relief as smoking, with the potential to improve quit rates in smokers with pain.

Our study was limited to older, predominantly white male Veterans who reside in New England and therefore may not generalize to other areas of the U.S. or more diverse groups of Veterans. We required participants to be willing to quit smoking in the next 30 days, and our findings may not generalize to pre-contemplators. We were also unable to collect information on non-participants and cannot extrapolate our results to smokers who may not wish to participate in studies like this one. Finally, our study was limited to Veterans using VHA care and may not generalize to all Veterans or non-Veterans.

In previous trials, combining behavioral therapy with smoking cessation medication has increased the likelihood of successful quitting [91]. Varenicline, a partial nicotine receptor agonist used for smoking

cessation, was shown to reverse nicotine-induced hyperalgesia in a rodent model [92]. This may impact patient perception of pain while working as a smoking cessation treatment. Future research should also address the juxtaposition of smoking, pain, and mental health. Per the Surgeon General's 2020 report on smoking cession, 40% of the cigarettes consumed in the United States are by people with mental health or substance use disorders [93]. Trials that can tailor therapy and medication to consider the complexities of mental health and pain treatment with smoking cessation would hopefully further increase quit rates and overall wellbeing.

Although the rate of evidence-based smoking cessation usage has increased since 2000 [93], more than two-thirds of adults who tried to quit smoking in the last year did not use these methods [93]. Unfortunately, most smoking quit attempts fail, and relapse to smoking after aided or unaided cessation is common [94]. Furthermore, smoking prevalence has become increasingly concentrated in populations including those with low socioeconomic status, individuals who identify as LGBT, American Indians/Alaskan natives, recent immigrants from countries with high prevalence of smoking, residents of the South and Midwest, and people with disabilities [93]. Thus, expanding clinical and health systems-level access to smoking cessation treatment becomes critical, which could include ensuring insurance for treatments and using health information technology to recommend treatments to all smokers [93]. While telephone-based interventions can increase access to smoking cessation, newer delivery methods such as web-based interventions, text messaging, and smart-phone applications have been shown to increase smoking cessation rates as well [95–97]. More research is needed to look at the most effective methods of communicating smoking cessation treatment with the broadest outreach in smokers with pain.

Given the widespread prevalence of smoking among Veterans, efforts to improve the reach of smoking cessation efforts while simultaneously removing barriers that limit access to and participation in effective interventions is critical to improving cessation rates at the population level. PASS is focused on reaching Veterans with chronic pain to deliver a smoking cessation intervention that also involves a cognitive behavioral component in order to improve cessation rates, improve pain, and decrease pain-related anxiety.

Authors' contributions

Bastian, Driscoll, Goulet, Kerns, Brandt, Ditre, and Becker were all involved in the study conception and design. All authors were involved in drafting the manuscript and approved the final manuscript.

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Authors declare that they have no conflicting interests.

Disclaimer

The opinions expressed here are those of the authors and do not represent the official policy or position of the United States Department of Veterans Affairs or the United States government.

Author declaration

1) We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

2) We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

3) We confirm that neither the entire paper nor any of its content has been submitted, published, or accepted by another journal. The paper will not be submitted elsewhere if accepted for publication in the Journal.

4) We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

5) We confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

6) We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

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