

An Integrated Brief Alcohol and PTSD Intervention for Veterans in Primary Care

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Randomized Controlled Trial of PC-TIME

Specific Aim 2 is to conduct a 2-arm pilot RCT of our adapted PC-TIME compared to a PC treatment as usual (PC-TAU) (n=60). All interventions will be completed in person. All participants will complete assessments at baseline, post-treatment, 14-week follow-up and 20-week follow-up. We will test our primary hypothesis that heavy drinking veteran PC patients receiving PC-TIME will reduce their percentage of heavy drinking days and PTSD severity compared to those receiving PC-TAU.

C4.1. Description of the Sample. Veterans enrolled in PC within VA facilities in Syracuse and Binghamton, NY will be screened for eligibility. The open trial will not include Buffalo participants due to budgetary limitations, (i.e., unable to staff Buffalo in year 1 to recruit, assess and treat patients). Inclusion criteria: Patients who score a) 8-19 for men, 6-19 for women on the AUDIT and have past month drinking (i.e., have not quit drinking over the last month); and b) score ≥ 33 on the PTSD Checklist-5 (PCL-5) and report a traumatic event on the Criterion A screener. Exclusion criteria: Patients will be excluded if they 1) score a 20 or higher on the AUDIT as previous research has demonstrated the BMIs are less effective with very severe drinkers (see C2.2.a) and/or 2) demonstrate symptoms that would not allow them to actively engage in the intervention such as gross cognitive impairment and/or current symptoms of mania or psychosis. Patients will also be excluded if they have more pressing concerns that need to be addressed first: 3) in need of detox services, or 4) suicide attempt in the last two months or current intent to commit suicide. Patients with recent suicide attempts or intent may be enrolled following receipt of suicide prevention services. We will also exclude patients that 5) are already receiving psychotherapy for heavy drinking or PTSD outside of PC, 6) started or changed the dose of a psychotropic medication for heavy drinking or PTSD in the last two months that was prescribed outside of VA PC, and 7) voice a preference to be directly referred to VA specialty care for heavy drinking or PTSD. These final 3 exclusions are to allow the study to isolate the effects of the intervention and to ensure that patient preference for services is honored. In RCTs for Veterans with PTSD^{63, 64}, the effect of a psychotropic medication is typically considered to be stable after 2 months; therefore it should not confound the effect of the intervention.

C4.2. Sample Size. We will recruit a total of 60 patients to retain a minimum sample size of 51 (85% retention) at 20-week follow-up. This retention rate was observed in our previous work (See A2.1, B1).

C4.3. VA facilities. The Buffalo and Syracuse VA Medical Centers are located in urban areas and serve catchment areas that include many suburban and rural communities. Both medical centers have three PC clinics, with one in each facility dedicated to female veterans. The Binghamton VA Community Based Outpatient Clinic is located in a small city and provides PC and outpatient mental health services. According to the VA electronic medical record, over an 11-month period in 2016-2017, 782, 461, and 157 PC veterans screened positive on the AUDIT-C or PC-PTSD in Buffalo, Syracuse, and Binghamton, respectively. These three VA sites were chosen due to the affiliation of our study team to these locations and our previous success achieving strong recruitment and retention at these facilities. Recruitment at both Syracuse and Buffalo will be necessary to meet study enrollment goals and inclusion of the Binghamton clinic will allow us to investigate feasibility in a small clinic (common within the VA system). Also, running the study across three sites will provide feasibility data for the future full-scale multi-site RCT. As all three clinics are within the same VA network (VISN 2) and utilize the same model of PCMH, we do not anticipate significant site differences.

C4.4. Participant Recruitment. Recruitment will use a method already shown to be effective (see B1). Patients screening positive on the PC-PTSD screen and/or AUDIT-C, which are delivered as part of standard practice nationally in VA, will be referred by their PC or PCMH providers. Research staff will facilitate the referral process by using electronic medical record data to create monthly lists of patients screening positive and then asking their providers to refer these patients to the study. Research staff will send a letter to all referred veterans introducing the study. Study staff will then contact referred patients by phone to assess their interest in participation. Interested patients will be scheduled for a baseline research appointment within their PC clinic where study eligibility will be determined, including administering the AUDIT and PCL-5. Women will be over-sampled by devoting study resources to recruit from the Women's PC Clinics. To illustrate this recruitment method, in the Web CBT study (see B1) over a 27-month period 2,057 veterans screened positive on the AUDIT-C and/or PC-PTSD within their PC clinic. Study staff was able to contact 973 of these veterans by phone and 217 were scheduled for a baseline interview. Of the 217, 162 were determined eligible to be randomized. These numbers equate to recruiting 5 eligible participants per month. Based on the success of prior studies and our anticipated recruitment pool at Buffalo, Syracuse and Binghamton, we expect to be able to enroll 3.5 eligible participants per month. This will allow us to recruit 60 participants over 17 months.

C4.5. Assessment and Randomization. Baseline assessments will be conducted in person. Trained, VA-based research staff will obtain informed consent and HIPAA authorization. An interactive program (Qualtrax) on a laptop computer will administer the questionnaires. We have used computerized assessment in several previous studies to facilitate data collection and entry and to provide the input for the computer-generated feedback sheet used within the BMI. Following completion of the computerized self-report measures, participants will be randomly assigned to treatment condition. Urn randomization will be used to ensure a balanced distribution of key patient factors across treatment groups⁷². Included in the urn randomization: 1)

AUDIT score ≥ 15 , 2) PCL-5 ≥ 50 , 3) gender. Demographic and severity cut-points are informed by distributional data from previous study databases. We have used these variables in previous studies with success at obtaining similar groups in each treatment condition at baseline.

Following randomization participants will complete the Clinical Administered PTSD Scale (CAPS-5). While a CAPS-5 is not needed to determine study inclusion, it will serve as the primary PTSD outcome measure because it is a more sensitive measure of PTSD severity than the PCL-5 self-report. We carefully considered whether PTSD diagnosis with the CAPS-5 should be required for study inclusion and decided that using the established cut-point on the PCL-5 provided a more ecologically valid measure for a PC-based study. A 1-hour clinical interview such as the CAPS-5 could not feasibly be used in typical PCMH practice.

A post-treatment assessment (8 weeks) and two follow-up assessments (14 weeks; 20 weeks) will be conducted following baseline (Table 5). For a brief treatment like PC-TIME, we expect the largest treatment effects (for both alcohol use and PTSD) to be at post-treatment. The purpose of follow-ups are to examine if change is maintained and to assess engagement in additional treatment. Our four assessment points will allow for a more precise trajectory of change overtime. We chose 20 weeks for our final follow-up because this is the longest interval that our study timeline would allow. Follow-ups will be in person or by phone (based on participant preference) by study staff and were designed to reduce participant burden and minimize drop-out.

C4.6. Participant Payment. Participants will be paid for time spent completing assessments at a rate of approximately \$20/ hour (baseline session- \$40, post-treatment (week 8)- \$40, 14-week follow-up- \$20, 20-week follow-up- \$20, \$20 bonus for completing all study procedures) and can earn up to \$160. Reimbursement will be by check mailed to the veteran's home. Participants will not be reimbursed for intervention sessions.

C5. Measures

C5.1. Screening Measures

Alcohol Use Disorders Identification Test (AUDIT)⁷³. This 10-item questionnaire, developed by the WHO, identifies patients whose alcohol consumption has become harmful. Questions are scored from 0-4 with a cumulative score range of 0-40. A score of 8 or higher reflects heavy use,⁷⁴ but more recent research has identified an alternative cut point of 6 or higher for females⁷⁵. The AUDIT is used to establish eligibility.

PTSD Checklist-5 (PCL-5). This 20-item self-report measure asks respondents to rate how much they have been bothered by DSM-5 PTSD symptoms in the past month on a 0 - 4 Likert-type scale⁷⁶. The PCL-5 will be administered with the extended criterion A (traumatic event) assessment. A cut point of 33 along with meeting criterion A will be required for study inclusion⁷⁷. The total score will be used to indicate PTSD severity at post-treatment and follow-up.

Mini-Mental Status Exam (MSE). This interview determines if a patient has cognitive dysfunction and should therefore not be recruited. The MSE has sections on orientation (8 items), memory (2 items), and attention (2 items). Patients who score under 18 (highest score is 26) will not be enrolled. We have used this MSE in similar studies with good success^{15, 66}.

C5.2 Outcome Measures

Alcohol Use and Alcohol-Related Problems. Alcohol use and problems will be assessed using the 30-day Timeline Follow Back Interview (TLFB)^{78, 79} and the Short Inventory of Problems (SIP)⁸⁰. Indices from the TLFB include percentage of heavy drinking days ($\geq 4/5$ drinks in one day for women/men), percentage of drinking days, average number of drinks per drinking day, and a dichotomous variable indicating whether one's past 30-day drinking pattern would be classified as excessive drinking by the CDC; (i.e., $\geq 8/15$ drinks per week for women/men)^{81, 82}. The 15-item SIP yields a total score with high internal consistency (.98) and is a valid measure of adverse alcohol consequences.

Clinician Administered PTSD Scale-5 (CAPS-5). This 30-item structured interview assesses DSM-5 symptoms of PTSD⁸³. It includes assessment of traumatic events and symptom severity ratings are based on symptom frequency and intensity. CAPS-5 will be administered by study staff at baseline and post-treatment and will be the primary measure of change in PTSD symptom severity. A 10-point decrease is considered clinically significant as is associated with meaningful improvement in quality of life for veterans with PTSD⁸⁴.

C5.4. Secondary Outcomes

Post-intervention Treatment Engagement. With HIPAA authorization, information from participants' VA administrative data will be extracted to assess if treatment condition relates to engagement in specialty mental health and substance use visits. Number of visits attended and prescriptions of psychiatric and substance use medications between enrollment and 20 week follow-up will be extracted for each participant. Drs. Possemato and King have expertise in this type of data extraction. In addition, participants will be asked about non-VA treatment at each assessment point using the Treatment Services Review⁸⁶.

C6 Treatment Conditions

C6.1. Experimental Condition: PC-TIME. Participants randomized to the PC-TIME condition will participate in the intervention developed in the earlier study phases (see C1.2). Sessions will be conducted in-person and will be recorded for the purpose of monitoring protocol adherence.

C6.2. Control Condition: PC-TAU. PC-TAU consists of mandatory annual screens for all patients with the

AUDIT-C and PC-PTSD. Patients who score a 4 or higher on the AUDIT-C receive a Brief Advice intervention from their PC medical provider that is built into the electronic medical record as a mandatory response to a positive screen. In addition, patients who score positive on the AUDIT-C or PC-PTSD are offered a referral to the PCMHI provider within the PC clinic. PCMHI in VA consists of licensed, independent providers (typically psychologists or clinical social workers) providing brief assessment and interventions to veterans and consultation to other members of the PC team. Patients are often treated in PC for a few sessions then referred to specialty mental health and substance abuse care, if problems persist. On average, 4 PCMHI sessions are provided to PTSD patients typically focused on assessment, psycho-education, and supportive counseling ¹⁰. VA PC patients often decline referrals for alcohol use following the receipt of brief advice. There will be variability in the amount of provider contact PC-TAU participants receive, therefore we will closely measure the number and type of PC-TAU contacts and consider it as a covariate in our analyses.

More structured interventions were considered as comparison conditions to provide tighter control over the interventions and maximize internal validity. However, we opted not to manualize or alter PC-TAU as this would result in comparing two experimental treatments and would not answer our primary research question: Is PC-TIME superior to existing PC-based treatment? The advantages of using the PC-TAU control are that it 1) provides an efficacy evaluation in a real-world practical setting, 2) optimizes the generalizability of findings to other VAs, as the PC-TAU services at our sites are representative of most VA PC settings, 3) controls for non-specific factors such as interaction with the VA staff and receiving treatment that is problem-specific (e.g., Brief Advice for alcohol use), and 4) does not deprive veterans of receiving usual care services.

Statistical Analysis Plan

For this treatment development grant application, assessment of feasibility and acceptability of the intervention and research procedures is the primary goal. As this trial will provide us with feasibility information for a larger trial, we will describe the number of participants screened and enrolled per month, proportion of screened participants who are eligible to enroll, completion rates of follow-up assessments, retention rates in study conditions, and the rate and timing of patient drop-out. Graphs will be utilized to display rates of intervention and assessment retention at each measurement time. Confidence intervals (95%) will be calculated and used in design considerations of a larger trial. Participant retention rates in both study interventions will be described with mean, standard deviations and confidence intervals. PC-TIME therapist fidelity will be described quantitatively with the mean number of items endorsed on fidelity checklists. Items with lower fidelity will be described to inform future PC-TIME training curriculums. For client satisfaction total CSQ scores and scores on individual CSQ items will be described with means, standard deviations and confidence intervals to understand the satisfaction and acceptability in each condition.

For other outcomes, we are well aware that effect size estimates with small samples have large standard errors and therefore wide confidence intervals ⁹² and believe that the most important factor in determining sample size for a Stage II clinical trial is have adequate power to detect a clinically relevant difference between conditions if one truly exists. Nonetheless, pilot data can be used to demonstrate whether the effects of treatment looks promising across a set of outcome variables, to begin to examine distribution of outcome variables to inform future analytic strategies, and to suggest, in concert with results from larger scale clinical trials in related fields, the range of effect sizes that would be reasonable to expect in a future trial. As a result, we will obtain the between treatment condition effect size estimates (with 95% confidence intervals) at each assessment (e.g., Cohen's *d* or *h*) as well as the correlation between the same dependent variable at adjacent assessments. These parameters will provide one source of information that will be used to help determine necessary sample size for a future clinical trial. We will have complete data on approximately 51 participants (the minimum expected after participant loss due to attrition), within the recommended sample size for treatment development of 15 to 30 participants per cell ⁹³. Primary analyses will be intent-to-treat (using data from all treatment enrollees). Secondary completer analyses (including only subjects who attend at least 4 of the 5 scheduled sessions) will also be conducted. In examining our draft treatment manual, we determined that at least 4 sessions are necessary to receive an adequate does of the essential elements of treatment. We will also report attendance and treatment satisfaction to assess intervention feasibility and acceptability.

D1. RCT Primary Analyses: Alcohol Use, PTSD, and Negative Consequences (Aim 2)

Preliminary analyses will examine distributional properties of variables and correlations among DVs. For highly collinear DVs, we will consider data reduction methods such as principal components analyses to create composite scores (this reduces the total number of tests conducted). Because we use in-person (or phone) assessments, missing data for specific questions and measures are expected to be minimal (see D3 for missing data). We will conduct multilevel growth curve modeling permitting us to estimate the between- and within-person change trajectories over time (Time: baseline, week 8 [post-tx], week 14 [F/U 1], week 20 [F/U 2]) and intervention impact (Group: PC-TIME, PC-TAU) on a given outcome variable. Time will serve as the Level 1 predictor and treatment condition on Level 2 to yield the following fixed effect equation: DV (percent of heavy drinking days or PTSD severity) = $\beta_{00} + \beta_{10}\text{Time}_{ti} + \beta_{01}\text{Treatment}_i + \beta_{11}\text{Time}_{ti} * \text{Treatment}_i + e_{ti}$. Raw data will be plotted and model fit indices will be used to determine whether change is optimally modeled linearly or

curvilinearly. Growth modeling is a powerful and flexible method well-suited for handling longitudinal data particularly in cases with missing data, nonlinear trajectories, and time-varying covariates.

We do expect to observe a linear or curvilinear decrease in heavy drinking and PTSD severity with a significant treatment effect such that the aggregate trajectory for the PC-TIME condition will demonstrate the greatest reduction (steepest slope) of drinking behaviors and PTSD severity. We also anticipate observing a significant interaction effect where we expect no differences in the mean intercept between the groups at baseline but group differences in the mean slope or trajectory of change over time. In preliminary analyses, we will examine the equivalence of the random assignment of groups with regards to key baseline characteristics. This will involve comparison of treatment groups on sociodemographic characteristics and alcohol-related variables. In the unlikely event that groups differ significantly on any characteristics we will run analyses with indicated covariates to control for baseline differences on outcomes. Attrition effects will be evaluated by testing whether systematic differences exist between participants who complete the research and those who drop out to determine the nature of the potential bias introduced by attrition. Based on prior trials, we anticipate the level of attrition will be low (<15%) and equal across groups (see D3 for missing data). Data analysis will follow a sequence designed to answer the primary outcome question: "Does PC-TIME reduce heavy drinking and PTSD severity relative to PC-TAU?" All analyses assume two-tailed alpha = .05.

We will test the effects of PC-TIME, compared to PC-TAU, on primary variables (percentage of heavy drinking days, average number of drinks per drinking day, a dichotomous variable indicating whether one's past 30-day drinking pattern would be classified as excessive (see C5.2), PTSD severity, and drinking-related problems at post-treatment. Depending on the nature of the variable, the analyses will use either a normal distribution (e.g., for the SIP and PCL-5) or a Poisson or negative binomial model for count data (e.g., number of drinks). The intervention condition will be dummy-coded using PC-TAU as the reference group and will be included as a time-invariant covariate on Level 2 of the multilevel growth model ⁹⁴. If any covariates are identified as necessary during preliminary analyses, these will also be included in the model.

D3. Missing Data

Missing data can complicate interpretation of clinical trial outcomes. Although our follow-up rates in similar clinical trials are high (87 to 93%), some data will inevitably be missing. We will explore patterns of missing data to determine possible mechanisms of missingness (e.g., if missingness is associated with baseline measures). If data are determined to be missing at random, missing data will be modeled using Full Information Maximum Likelihood (FIML) methods which produces unbiased estimates by using a likelihood function based on existing data to estimate missing values ⁹⁶.