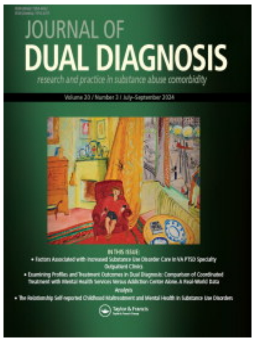

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Clusters Based on Within-Treatment Symptom Trajectories as Predictors of Dropout in Treatment for Posttraumatic Stress Disorder and Substance Use Disorder

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ABSTRACT

Objective: Dropout rates are high in treatments for co-occurring posttraumatic stress disorder (PTSD) and substance use disorders (SUDs). We examined dropout predictors in PTSD-SUD treatment. **Methods:** Participants were 183 veterans receiving integrated or phased motivational enhancement therapy and prolonged exposure. Using survival models, we examined demographics and symptom trajectories as dropout predictors. Using latent trajectory analysis, we incorporated clusters based on symptom trajectories to improve dropout prediction. **Results:** Hispanic ethnicity (integrated arm), Black or African American race (phased arm), and younger age (phased arm) predicted dropout. Clusters based on PTSD and substance use trajectories improved dropout prediction. In integrated treatment, participants with consistently-high use and low-and-improving use had the highest dropout. In phased treatment, participants with the highest and lowest PTSD symptoms had lower dropout; participants with the lowest substance use had higher dropout. **Conclusions:** Identifying within-treatment symptom trajectories associated with dropout can help clinicians intervene to maximize outcomes. ClinicalTrials.gov Identifier: NCT01211106.

KEYWORDS
Posttraumatic stress disorder; substance use disorder; therapy process; dropout; latent trajectory analysis; bayesian statistics

Posttraumatic stress disorder (PTSD) affects around 8% of people in the United States (US) during their lifetime (Kilpatrick et al., 2013). Substance use disorders (SUDs) affect 25% of the US population during their lifetime (McCabe et al., 2018). Further, PTSD and SUDs often co-occur. Individuals with PTSD are at greater risk for developing a SUD (Debell et al., 2014; Grant et al., 2015), and individuals with a SUD have a greater prevalence of lifetime PTSD (Leeies et al., 2010). In samples of patients seeking SUD treatment, observed prevalence of PTSD ranges from 25-50% (Killeen et al., 2015). PTSD and SUDs are two of the mental health problems for which US military veterans most commonly seek treatment in the Veterans Health Administration (VHA; Seal et al., 2007; Watkins & Pincus, 2011). As with the general US population, PTSD affects around 8% of US veterans during their lives (Wisco et al., 2014), and SUDs affect around 39% of US veterans (Boden & Hoggatt, 2018). The PTSD-SUD comorbidity is particularly prevalent in the veteran population (Petrakis et al., 2011; Teeters et al., 2017), with an estimated 63% of post-9/11 veterans with a SUD diagnosis having comorbid PTSD (Seal et al., 2011). This combination of conditions is associated with numerous deleterious outcomes, including additional mental health problems, physical health problems, functional impairment, and less symptom reduction during treatment (Anderson et al., 2017; Jarnecke et al., 2019; Mills et al., 2006; Ouimette et al., 2006; Young et al., 2005).

Fortunately, evidence-based treatment approaches for PTSD and SUDs are available. The clinical practice

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guidelines for the treatment of PTSD and SUDs published by the Department of Veterans Affairs (VA) and Department of Defense (Department of Veterans Affairs & Department of Defense, 2017, 2023) recommend cognitive behavioral therapies, behavioral therapies, motivational enhancement, and medication to treat PTSD and SUDs. The same clinical practice guidelines recommend concurrent delivery of evidence-based treatments for PTSD and SUDs based on research supporting the effectiveness of addressing both disorders together in the same episode of care (Back et al., 2006; Badour et al., 2017; Hien et al., 2010).

Despite the effectiveness of PTSD-SUD treatments, rates of dropout are high (Roberts et al., 2015), and many patients who discontinue treatment early do not experience clinical benefit (Berke et al., 2019; Holmes et al., 2019). A better understanding of predictors and processes of dropout in these treatments is needed to develop methods and therapy components to better retain patients in care and maximize patient benefit (Cooper et al., 2018). Many studies examining dropout in treatments for PTSD and/or SUDs have sought to identify baseline predictors of dropout, including demographic characteristics and baseline levels of symptom severity (e.g., Brady et al., 2001; Elbreder et al., 2011; Filho & Baltieri, 2012; McGovern et al., 2009). However, inconsistency in findings has been the norm (Cooper et al., 2018; Kehle-Forbes et al., 2022). Younger age has been one of the only consistent predictors of dropout in PTSD treatment (Goetter et al., 2015; Imel et al., 2013; Maguen et al., 2019), and younger age has also been found to predict dropout from SUD treatment (McKellar et al., 2006; Vuoristo-Myllys et al., 2013). Further, demographic and other baseline variables do not provide information about interdependent processes of dropout over the course of care. To gain increased understanding of treatment dropout, it is necessary to examine predictors that occur during treatment and to explore the timing of dropout over the course of treatment in relation to these within-treatment predictors (Cooper et al., 2018; Kline et al., 2021). Here, we use the term "within-treatment" to refer to processes or changes in patient status occurring during the treatment process, as opposed to pretreatment factors.

A few studies have examined within-treatment predictors of dropout that occur during integrated PTSD-SUD treatment. For example, in a study of naltrexone vs. placebo and prolonged exposure (PE) vs. medication management only, baseline PTSD symptoms interacted with rates of PTSD improvement during treatment to predict dropout (Zandberg et al., 2016). Specifically, among participants with lower baseline PTSD, faster rates of improvement predicted greater likelihood of dropout, whereas among participants with higher baseline PTSD, both faster and slower rates of improvement predicted greater likelihood of dropout compared to a more moderate rate of improvement (Zandberg et al., 2016). That study also found that among participants receiving PE, faster reductions in drinking across sessions predicted greater likelihood of dropout (Zandberg et al., 2016). In contrast, another study found that an increase in alcohol use from one session to the next in Concurrent treatment of PTSD and substance use disorders using Prolonged Exposure (COPE) predicted higher risk of dropout at the following session (Kline et al., 2021). While these studies advanced our understanding of relationships between symptom change across sessions and early dropout, they only include samples with PTSD and alcohol use disorder. More work is needed to clarify within-treatment characteristics of patients with higher likelihood of dropout to help clinicians identify those patients and intervene to retain them in treatment.

Several statistical modeling approaches can be used to advance our understanding of within-treatment processes related to dropout and our prediction of which patients may be more likely to drop out of treatment. Specifically, grouping patients by within-treatment profiles may provide insight into predictors of dropout that could help clinicians identify patients with higher within-treatment dropout risk. Latent trajectory analysis (LTA) is a type of latent class analysis or latent cluster analysis (LCA) that groups participants into latent classes (also referred to as clusters) based on trajectories of repeated assessments across time points. Sripada et al. (2017) used LTA to classify veterans receiving outpatient PTSD treatment into mild-improving, moderate-improving, and severe-stable trajectories based on PTSD symptom assessments. They then examined demographics and baseline clinical characteristics as predictors of cluster membership and found that severe-stable participants were more likely than mild-improving participants to be male, non-White, Hispanic, and have comorbid depression, and more likely than moderate-improving participants to have sleep disorders (Sripada et al., 2017). In a sample of patients with SUDs and co-occurring disorders receiving inpatient care, Vest et al. (2021) similarly used LTA to group patients based on symptom improvement and examined predictors of cluster membership. They found that younger age predicted higher likelihood of membership in the high PTSD and high drug use classes compared to the normative improvement class, and unemployment predicted membership in the high PTSD class compared to the normative improvement class.

These two studies (Sripada et al., 2017; Vest et al., 2021) used latent trajectories as outcomes. Taking a slightly different approach, patients could be clustered based on within-treatment symptom trajectories, and cluster membership could be then examined as a predictor of dropout risk, which could allow clinicians to match the characteristics of a new patient with characteristics of previously-identified groups of patients to learn about their patient's dropout risk. Clusters based on symptom trajectories have thus far not been used to predict dropout from PTSD or PTSD-SUD treatment.

Current study

The purpose of the current study was to examine and characterize dropout in integrated and phased motivational enhancement therapy and PE (MET/PE) for PTSD-SUD implemented in a completed trial (Kehle-Forbes et al., 2019). Participants were randomly assigned to receive either integrated MET/PE or phased MET/PE. In both treatment conditions, MET/PE was provided within the same treatment episode (i.e., a defined treatment period with a start and end date) with the same therapist to address both PTSD and SUD. In phased MET/PE, MET was delivered in the first four sessions, and PE was delivered starting in the fifth session. In integrated MET/PE, motivational enhancement and PE were both delivered at all sessions, and MET content was integrated into PE. For a more detailed description of the two treatment conditions, please see the Therapies section below.

We first examined demographic variables and within-treatment time-varying symptom trajectories (PTSD, substance use, and consequences of use) as predictors of dropout. Time-varying symptoms are those symptoms which were assessed multiple times during treatment to examine change over time; additional details about these symptom constructs are presented in the Measures section below. We then combined survival models and LTA to identify clusters of patients, grouped by these symptom trajectories during treatment, as predictors of dropout across sessions. We extend the work of Kline et al. (2021) in identifying patterns of symptom change as treatment processes that can identify patients at higher risk of dropout across the course of treatment. This information can allow clinicians to better identify patients who may be at high risk of dropout at various points in treatment so they can potentially intervene to keep their patients in care.

The current analyses had three aims. The first aim was to characterize time-to-dropout across sessions of integrated and phased MET/PE for PTSD-SUD. The second aim was to identify demographic variables and time-varying within-treatment symptom measures that predicted time-to-dropout, as well as to compare models only including demographic predictors to models also including time-varying predictors. The third aim was to incorporate latent clusters of patients based on within-treatment symptom trajectories as predictors of dropout. To address the third aim, we first sought to examine whether there were indeed latent clusters of patients based on within-treatment symptom trajectories. If that was the case, we then sought to examine whether including those clusters in models predicting dropout improved our ability to predict time-to-dropout. If so, we sought to describe patients in clusters that conferred higher and lower risk of dropout.

We hypothesized that younger age would predict higher dropout, consistent with previous studies of PTSD (Goetter et al., 2015; Imel et al., 2013; Maguen et al., 2019) and SUD treatment (McKellar et al., 2006; Vuoristo-Myllys et al., 2013). The analyses incorporating within-treatment predictors and latent trajectories based on within-treatment symptoms were exploratory, given that past findings in PTSD and/or SUD treatment have been contradictory and dependent on factors such as baseline PTSD symptoms and treatment condition (Kline et al., 2021; Zandberg et al., 2016), and therefore do not point to clear hypotheses for these novel analytic strategies. Additionally, due to differences in the timing of treatment elements between the integrated and phased MET/PE conditions, we analyzed each condition separately.

Method

Data source

The analyses described here use data from the Substance use and TRauma Intervention for VEterans (STRIVE) study, a randomized clinical trial evaluating the effectiveness of engaging in PTSD and SUD therapy concurrently (integrated MET/PE) vs. completing SUD therapy immediately prior to PTSD therapy (phased MET/PE) in a sample of veterans with PTSD-SUD (ClinicalTrials.gov Identifier: NCT01211106; for additional details about the sample, study procedures, the rationale for inclusion/exclusion criteria, and study outcomes, see Kehle-Forbes et al., 2016, 2019). The STRIVE study was conducted in accordance with the Declaration of Helsinki and with approval from Institutional Review Boards at the Minneapolis VA Medical Center in Minneapolis, Minnesota, USA and the Corporal Michael J. Crescenz VA Medical Center in Philadelphia, Pennsylvania, USA. This secondary analysis was conducted with IRB approval from the Minneapolis VA Medical Center. All participants provided written informed consent after complete discussion of the study.

Transparency and openness

Please see Kehle-Forbes et al. (2019) for information related to determination of sample size, data exclusions, and other trial information. We report all manipulations and measures used in the present secondary analysis. This study's design and analysis were not pre-registered. Data from this study are available by emailing the corresponding author and completion of VA regulatory requirements for data sharing; analysis code is available by emailing the corresponding author.

Participants

The sample comprised 183 veterans recruited from February 2011 to June 2015 at two urban VA Medical Centers in the United States through advertisements and referrals. Participants were included if they met DSM-IV (American Psychiatric Association, 2000) criteria for PTSD and at least one SUD other than nicotine and marijuana dependence based on the Structured Clinical Interview for DSM-IV (First et al., 2002), had a PTSD Checklist (PCL; Weathers et al., 1993) score ≥50, and reported alcohol or drug use on at least 10 out of the 30 days prior to enrollment on the Timeline Follow-Back (TLFB; Sobell & Sobell, 1992). Participants were excluded for mental health problems that required immediate intervention (e.g., acute suicide or homicide risk, current bipolar affective disorder or psychotic disorder, unstable medical illness), treatment-interfering cognitive impairment, participation in PE in the prior six months, initiation of a new psychotherapy program in the prior two months, current participation in a formal addiction treatment program, change of psychotropic medication in the prior month, and benzodiazepine use greater than 40 mg of diazepam or equivalent (Kehle-Forbes et al., 2019). Descriptive statistics of baseline demographics for participants in each intervention arm are presented in Table 1. As previously reported (Kehle-Forbes et al., 2019), 85.2% of participants met criteria for alcohol dependence, 8.7% met criteria for alcohol abuse, and 18.0% were diagnosed with drug dependence. Stimulants ($n = 26$) and opioids ($n = 8$) were the most common drugs of dependence. For

Table 1. Descriptive statistics of demographic categories displayed as n (%) for categorical variables and mean (standard deviation) for continuous variables.

	Integrated ($n = 95$)	Phased ($n = 88$)	Full Sample ($n = 183$)
Gender			
Female	5 (5.3%)	9 (10.2%)	14 (7.7%)
Male	90 (94.7%)	79 (89.8%)	169 (92.3%)
Race			
White	37 (38.9%)	38 (43.2%)	75 (41.0%)
American Indian/Alaskan Native	1 (1.1%)	1 (1.1%)	2 (1.1%)
Asian	1 (1.1%)	0 (0.0%)	1 (0.5%)
Black or African American	49 (51.6%)	42 (47.7%)	91 (49.7%)
Native Hawaiian	1 (1.1%)	1 (1.1%)	2 (1.1%)
More than One Race	3 (3.2%)	3 (3.4%)	6 (3.3%)
Other	3 (3.2%)	2 (2.3%)	5 (2.7%)
Declined to Answer	0 (0.0%)	1 (1.1%)	1 (0.5%)
Ethnicity			
Not Hispanic/Latino	88 (92.6%)	85 (96.6%)	173 (94.5%)
Hispanic/Latino	7 (7.4%)	2 (2.3%)	9 (4.9%)
Declined to Answer	0 (0.0%)	1 (1.1%)	1 (0.5%)
Age	44.4 (13.1)	43.8 (13.0)	44.1 (13.0)
Marital Status			
Married	44 (46.3%)	23 (26.1%)	67 (36.6%)
Remarried	0 (0.0%)	4 (4.5%)	4 (2.2%)
Widowed	2 (2.1%)	3 (3.4%)	5 (2.7%)
Separated	7 (7.4%)	8 (9.1%)	15 (8.2%)
Divorced	27 (28.4%)	27 (30.7%)	54 (29.5%)
Never Married	15 (15.8%)	23 (26.1%)	38 (20.8%)
Experienced Combat			
Yes	58 (61.1%)	42 (47.7%)	100 (54.6%)
No	21 (22.1%)	27 (30.7%)	48 (26.2%)
Declined To Answer	16 (16.8%)	19 (21.6%)	35 (19.1%)

additional details, please see Kehle-Forbes et al. (2019).

Procedure

First, an in-person baseline screening was conducted to determine study eligibility. Study personnel administered measures including the PCL and TLFB. Within approximately a month of screening, eligible participants attended a second visit to complete baseline assessments and randomization to the integrated or phased treatment condition. Randomization used a 1:1 ratio and was stratified by site, non-alcohol drug use, PTSD severity, and service era. Participants' first therapy session occurred immediately after randomization. Doctoral-level psychologists and masters-level clinical social workers delivered both interventions. For additional information about therapist training, supervision, and treatment fidelity, see Kehle-Forbes et al. (2019).

Study personnel administered additional assessments at weeks 4, 8, 12, posttreatment, and six months posttreatment. Participants in both the integrated and phased conditions received sixteen 90-minute treatment sessions, and participants in both conditions received full courses of both MET and PE provided by the same therapist. Dropout was defined as ending treatment before session 12 in each arm; based on this definition, completers in both conditions completed at least 8 PE sessions.

Therapies

Motivational enhancement therapy (MET)

MET (Miller, 1995) is an evidence-based treatment for SUDs (Department of Veterans Affairs & Department of Defense, 2015; Project MATCH Research Group, 1998) that was adapted from motivational interviewing and encourages patients to make changes via structured monitoring and feedback related to substance use. MET has been disseminated throughout the VHA (Drapkin et al., 2016). Participants in the integrated MET/PE arm received MET integrated with PE during all treatment sessions. PTSD and SUD were linked conceptually during sessions, e.g., participants discussed and processed connections between their substance use and their trauma-related symptoms. Participants in the phased MET/PE arm received MET over the course of the first four sessions, and after they began PE in the fifth session, they continued to receive a brief substance use check-in at the beginning of each session.

Prolonged exposure (PE)

PE (Foa et al., 2019) is one of the treatments for PTSD with the most empirical support (Gallagher et al., 2015; Steenkamp et al., 2015) and has been disseminated throughout the VHA (Karlin et al., 2010), where it is considered a best practice. PE is comprised of three primary components: in vivo exposure (approaching previously avoided yet safe trauma-related people, objects, situations, and reminders, completed as homework between sessions), imaginal exposure (repeatedly revisiting and recounting the memory of the most distressing traumatic event, completed during sessions), and processing the trauma with the therapist (completed in session following imaginal exposure). In the integrated MET/PE condition, PE was provided in all treatment sessions, and the processing portion of sessions included discussion of substance use as it related to participants' experiences of trauma and PTSD symptoms. In the phased MET/PE condition, PE began in the fifth treatment session and was provided for the rest of treatment. Aside from a brief check-in at the start of the session, substance use was only discussed during PE as related to trauma triggers or to participants' difficulty engaging in the procedures of PE.

Measures

PTSD checklist (PCL)

The PCL (Weathers et al., 1993) is an established self-report measure of PTSD severity and was used to assess PTSD symptoms at each session. Each of the 17 items asks participants to rate the severity of a DSM-IV PTSD symptom on a scale from 1 (*Not at all*) to 5 (*Extremely*), and higher total scores reflect greater symptom severity. The PCL has demonstrated strong internal consistency, test-retest reliability, and concurrent validity (Blanchard et al., 1996). The PCL served as the primary measure of PTSD in the parent trial (Kehle-Forbes et al., 2019), as it was the current version at the time of the study.

Timeline follow-back (TLFB)

The TLFB (Sobell & Sobell, 1992) is an interview measure assessing daily substance use. The TLFB has demonstrated good psychometric properties for assessing substance use (Fals-Stewart et al., 2000). In the current study, participants reported on their use of alcohol and drugs each day over the prior assessment period, including 60 days prior to baseline. The outcome of interest was the percentage of days in the past month with either drug use or heavy drinking (five or more standard drinks in a day for men or four or more drinks in a day for women). The TLFB was the primary measure of substance use in the parent trial (Kehle-Forbes et al., 2019).

Short inventory of problems—revised (SIP-R)

The SIP-R (Bender et al., 2007) is a 15-item self-report measure of consequences of substance use. Each item assesses a specific use-related consequence and is scored on a scale from 0 (*never*) to 3 (*daily or almost daily*). Items are summed to create a total score ranging from 0-45, where higher scores reflect greater negative impacts of substance use. The SIP-R assesses interpersonal, physical, social, impulsive, and intrapersonal consequences of substance use. The SIP-R was administered as a secondary outcome in the parent trial (Kehle-Forbes et al., 2019). The SIP-R has demonstrated good internal reliability and convergent validity (Kiluk et al., 2013).

Data analytic approach

In the present analyses, to match therapy session numbers with measures administered only at study assessment visits (weeks 4, 8, 12, posttreatment, six-months posttreatment), scores for assessment visit measures were repeated for each weekly session until the next assessment. To account for missing data, missing entries were imputed by carrying forward the most recent value (i.e., last observation carried forward). Data were not imputed past the time of dropout.

Statistical analyses were conducted separately for each intervention arm due to differences in the structure and duration of MET/PE in each condition, and particularly the differences across conditions in content presented at each session. For example, session 4 in integrated MET/PE was the fourth session of PE and the second session of imaginal exposure, whereas session 4 in phased MET/PE was the final session of MET before starting PE. Additionally, as reported by Kehle-Forbes et al. (2019), the difference between dropout in the integrated (76.8%) and phased conditions (63.6%) did not reach statistical significance, but it warranted additional probing to examine differences in time-to-dropout. To evaluate Aim 1, to characterize time-to-dropout over the sessions in integrated and phased treatment arms, Kaplan-Meier curves were graphed depicting survival (i.e., continuing in treatment vs. dropping out) at each session up to session 12 in the integrated and phased MET/PE conditions.

Aim 2 was to identify baseline variables and within-treatment symptom trajectory measures that predict time-to-dropout, as well as to compare models only including demographic predictors to models also including time-varying predictors. To examine this aim, we first prefiltered the demographic variables that were associated with dropout via Cox proportional hazards regression by identifying demographic variables with p-values <0.15. To avoid adjusting for too many variables, it is common practice to conduct an initial screening of potentially informative variables using a loose p-value threshold such as 0.15, and then to retain variables with p-values <0.15 in the multivariable analyses that use a more stringent threshold. For categorical variables (e.g., combat experience), a reference category was identified (e.g., experienced combat), and when a non-reference category (e.g., did not experience combat) demonstrated no statistical difference in hazard from the reference category, that category was merged with the reference category (e.g., yes and no were combined, and declined to answer was kept as a non-reference variable).

For the multivariable survival models in Aim 2, we used a Bayesian formulation of a discrete-time survival model (Cox, 1972; Sparapani et al., 2016) wherein a logistic regression was fit for each session where the outcome indicator was 1 if dropout occurred in the subsequent session, and 0 if the participant continued to the next session. The four models we considered for predicting dropout used either preidentified demographic variables only or the demographic variables with one of the within-treatment measures (PCL, TLFB, SIP-R) as a time-varying predictor using the most recent assessment measure at a given session. We refer to these models as "demographics-only models" and "time-varying predictor models," respectively. Consistent with studies by Gmeinwieser et al. (2020) and Kline et al. (2021), each within-treatment measure was given one treatment-wide effect on dropout. In a Bayesian model, all parameters are assumed to be random unless otherwise specified. However, we used fully vague prior distribution specifications for the time-varying effects, and theoretically the resulting estimates closely resemble those a frequentist analysis assuming they are fixed effects. We elaborate on these prior distributions in the Supplemental Materials. In the logistic regression models, we assessed the demographic and within-treatment measures' associations with dropout via 95% credible intervals.

The analysis for Aim 3 used latent clusters based on symptom trajectories to predict dropout; we refer to these as "cluster models." These analyses were comprised of two components. We first employed a Bayesian formulation of latent trajectory analysis to identify clusters of patients that exhibited similar trajectories of within-treatment measures (PCL, TLFB, SIP-R). We assumed that trajectories were quadratic over time and that each participant's trajectory arose from a pool of latent trajectories to allow for flexibility (Dunson & Herring, 2006; Paddock & Savitsky, 2013; Pitman, 2002). Specifically, the model included an intercept, linear slope, and quadratic slope, which were all assumed to be centered around 0 *a priori*; this assumption encourages shrinkage of group parameters if warranted. If the quadratic term is shrunk to 0 and the linear term is not, then this suggests a linear fit is better for that group and outcome. This method further encouraged clustering of the trajectories as evidenced by the data. For the Bayesian LTA, the latent mixture components are auxiliary parameters that assist in estimating which participants should be assigned to which latent cluster. These latent clusters are not the final groups participants are assigned to; rather, they are unobserved parameters that aid in finding posterior probabilities of each participant being grouped with another participant. After fitting the latent trajectory model, an additional post-processing step was completed to calculate the optimal groupings of participants based on the posterior probabilities of participants being grouped with each other (Binder, 1978; Lau & Green, 2007). We grouped patients together in three ways, where each within-treatment measure (PCL, TLFB, SIP-R) was used independently of the others to cluster patients into groups based on their similarity in trajectories. We expected that some patients would not group into the estimated clusters with modest to high membership, so we visualized results for clusters with at least 6 members; in the figures, cluster numbers refer to the assigned post-processed groups of participants based on symptom patterns.

To address the second component of Aim 3, examining predictors of dropout in models including latent clusters, we re-ran the Bayesian discrete-time survival models adding the cluster assignments of participants based on symptom trajectories. We assumed that the effects of demographic measures on dropout were time-static while the effect of the cluster assignments on dropout were allowed to differ at each session. We used clusters that were fit based on each of the three within-treatment measures independently: PCL, TLFB, and SIP-R. We summarized results with 95% credible intervals (CrI) and posterior means of odds ratios (aOR for adjusted odds ratio) as the measures of uncertainty and parameter estimates, respectively. We ran the Bayesian latent trajectory analysis assuming 20 latent mixture components and concentration parameter equal to 3/log(N), where $N = 95$ and 88, the sample sizes of the integrated and phased arms respectively, to enforce clustering, and collected 40,000 iterations while discarding the first 10,000 (Dunson & Herring, 2006). The discrete-time survival model collected 40,000 posterior samples while discarding the first 10,000. Both samplers used two chains. We collected measures of model deviance (lower values reflect better model fit to the data) and pD (effective number of parameters, lower values reflect a more parsimonious model), and the sum known as DIC (lower values reflect a better-quality model overall) to compare the evaluated models in Aims 2 and 3 (Spiegelhalter et al., 2002). Additional details regarding the clustering and survival models are discussed in the Supplement.

To address the third component of Aim 3, describing clusters that conferred risk for higher dropout, we first visually inspected cluster-specific dropout patterns. If any pairs of clusters appeared to have a strong difference in average dropout rates over the sessions, we tested their differences in therapy retention probabilities by using 85% CrIs at each session. If at any session a CrI for these differences did not contain 0, we determined at 85% credibility that these two clusters statistically differed in therapy retention probability. Using an 85% credible level effectively reduces the instability in 95% CrI estimates due to anticipated low sample sizes in each cluster (i.e., $n < 30$) by narrowing these intervals around estimate values of higher probability. We label these as 85% credible (as opposed to 95%) because we are "less sure" that the true difference in therapy retention probability lies in this estimated interval.

All analyses were conducted in the R-Studio Version 4.1.2. All Bayesian models were computed using the Just Another Gibbs Sampler (JAGS) software within R-Studio with packages *haven*, *tidyr*, *dplyr*, *ggplot2*, *Matrix*, *survival*, *survminer*, *Rcpp*, *runjags*, *mcclust*, *mvtnorm*, and *readr*.

Results

Aim 1: Characterizing time-to-dropout in integrated and phased MET/PE

Visual examination of the Kaplan-Meier curve depicting dropout across sessions of integrated and phased MET/PE (Figure 1) suggests that dropout remained

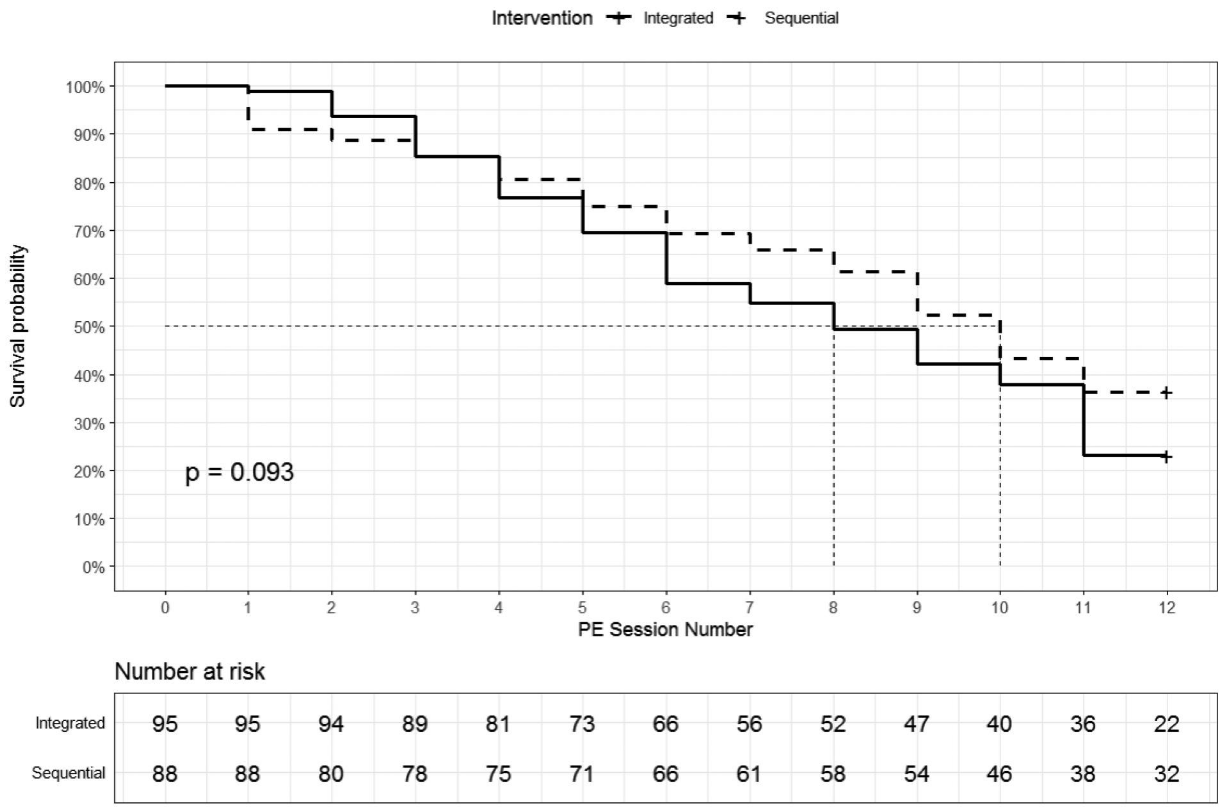

Figure 1. Kaplan-Meier curves depicting survival probabilities (opposite of dropout) as a function of intervention with attached table denoting number of participants at risk at each time point for integrated (solid) and phased (dashed) intervention arms.

fairly steady over the course of treatment. Rates of therapy retention in the integrated arm were only larger than the phased arm in sessions 1-3, then for the remainder of therapy the phased arm retained more participants after each session (see Figure 1). The rates of completing 12 sessions were 23.2% (95% CI [16.1%, 33.4%]) for the integrated arm and 36.4% (95% CI [27.6%, 47.9%]) for the phased arm. The unadjusted hazard ratio between the intervention arms was 0.74 (95% CI [0.52, 1.04], $p = 0.09$), indicating that participation in phased MET/PE corresponded to a roughly 25% reduced risk of dropout compared to integrated MET/PE, although as reported previously (Kehle-Forbes et al., 2019), this difference was not statistically significant (see Figure 1).

Aim 2: Demographic variables and within-treatment symptom trajectories as predictors of time-to-dropout

When examining each demographic variable as a predictor of dropout risk using a p-value threshold of <0.15, the two arms yielded different variables with associations with dropout risk that were statistically significant using this relaxed threshold. In the integrated arm, demographic variables that were significant at a threshold of $p < 0.15$ were gender (female vs. male), race (Native Hawaiian vs. all other races), ethnicity (Hispanic vs. not Hispanic and declined to answer), age, and combat during service (declined to answer vs. yes or no). In the phased arm, gender (female vs. male), age, race (Black or African American vs. all other races), and marital status (never married vs. all other options) were significant. The adjusted demographics-only models including these demographic variables together indicated that in the integrated arm, participants with Hispanic ethnicity had more than double the risk of dropout compared to their non-Hispanic counterparts (aOR = 2.985, 95% CrI = [1.003, 8.411]); in the phased arm, race (Black or African American vs. all other races) predicted almost a twofold dropout risk (aOR = 1.932, 95% CrI = [1.058, 3.592]; see Tables 2 and 3 "Demographics Only" columns).

To follow up on the significant relationship between race and dropout in the phased arm, we examined whether differences in the racial compositions of participants at the two study sites may have contributed to this association, given that most participants at the Philadelphia site were Black or African American ($n = 83$, 69%), and most participants at the Minneapolis site were White ($n = 49$, 77.8%).

Table 2. Odds ratio estimates of effects on dropout in the integrated arm for each model.

	Demographics Only	+ PCL Time Varying	+ TLFB Time Varying	+ SIP-R Time Varying	PCL Clusters	TLFB Clusters	SIP-R Clusters
Female Gender	0.238 (0.040, 1.001)	0.258 (0.045, 1.141)	0.261 (0.047, 1.109)	0.261 (0.044, 1.133)	**0.218 (0.036, 0.942)**	0.271 (0.041, 1.400)	**0.231 (0.038, 0.952)**
Native Hawaiian vs. Other Racial Categories	2.497 (0.079, 63.10)	3.245 (0.098, 83.743)	3.26 (0.096, 84.01)	3.089 (0.084, 78.321)	3.606 (0.124, 100.975)	1.497 (0.001, NA)	3.145 (0.094, 91.716)
Hispanic vs. Not Hispanic or Declined to Answer	**2.985 (1.003, 8.411)**	2.414 (0.808, 6.783)	2.444 (0.813, 6.956)	2.563 (0.882, 7.467)	2.105 (0.723, 6.052)	1.131 (0.312, 4.042)	2.540 (0.887, 7.198)
Age	0.997 (0.977, 1.018)	0.993 (0.973, 1.014)	0.993 (0.974, 1.015)	0.995 (0.974, 1.016)	**0.975 (0.957, 0.994)**	**0.944 (0.929, 0.957)**	0.986 (0.966, 1.007)
Experienced Combat: Declined to Answer vs. Yes or No	1.724 (0.852, 3.443)	1.500 (0.717, 3.066)	1.456 (0.713, 2.968)	1.486 (0.696, 3.190)	1.286 (0.623, 2.616)	1.012 (0.427, 2.257)	1.377 (0.660, 2.819)
Time Varying Effect	NA	0.997 (0.979, 1.015)	1.000 (0.991, 1.008)	0.990 (0.968, 1.013)	NA	NA	NA

Note. PCL: PTSD Checklist (a measure of posttraumatic stress disorder symptoms); TLFB: Timeline Follow-Back (a measure of substance use); SIR-R: Short Inventory of Problems – Revised (a measure of consequences of use); NA: not applicable. Estimates are posterior means (95% Credible Intervals) and model measures are averages over the posterior samples. Model names relate to what variables are in each model: "demographics only" contains only demographic variables while time-varying effect and cluster models retain the demographic variables and adjusts for the time-varying covariate and clusters. Bolded estimates are significant at 95% credible level (i.e., the 95% credible intervals for the effects did not contain 1).

Table 3. Odds ratio estimates of effects on dropout in the phased arm for each model.

	Demographics Only	+ PCL Time Varying	+ TLFB Time Varying	+ SIP-R Time Varying	PCL Clusters	TLFB Clusters	SIP-R Clusters
Female Gender	2.306 (0.958, 5.496)	2.126 (0.886, 5.073)	2.144 (0.890, 4.874)	2.109 (0.876, 4.931)	2.415 (0.927, 6.002)	1.541 (0.425, 4.988)	2.195 (0.882, 5.033)
Age	0.977 (0.953, 1.002)	**0.972 (0.948, 0.996)**	**0.971 (0.946, 0.995)**	**0.973 (0.948, 0.996)**	**0.945 (0.926, 0.964)**	**0.925 (0.905, 0.944)**	**0.965 (0.943, 0.988)**
Black vs. Other Racial Categories	**1.932 (1.058, 3.592)**	**2.132 (1.140, 4.005)**	**2.189 (1.137, 4.126)**	**2.099 (1.115, 3.930)**	**1.905 (1.011, 3.724)**	**2.441 (1.124, 5.402)**	**1.954 (1.057, 3.606)**
Never Married vs. Other Marital Statuses	1.238 (0.618, 2.311)	1.175 (0.603, 2.304)	1.171 (0.590, 2.277)	1.204 (0.605, 2.334)	0.898 (0.459, 1.718)	**0.464 (0.208, 0.969)**	1.056 (0.544, 1.979)
Time Varying Effect	NA	0.999 (0.977, 1.020)	0.998 (0.988, 1.009)	0.987 (0.962, 1.013)	NA	NA	NA

Note. PCL: PTSD Checklist (a measure of posttraumatic stress disorder symptoms); TLFB: Timeline Follow-Back (a measure of substance use); SIR-R: Short Inventory of Problems – Revised (a measure of consequences of use); NA: not applicable. Estimates are posterior means (95% Credible Intervals) and model measures are averages over the posterior samples. Model names relate to what variables are in each model: "demographics only" contains only demographic variables while time-varying effect and cluster models retain the demographic variables and adjusts for the time-varying covariate and clusters. Bolded estimates are significant at 95% credible level (i.e., the 95% credible intervals for the effects did not contain 1).

However, participant site did not associate with treatment completion (Unadjusted Hazard Ratio = 0.84, 95% CI = [0.58, 1.22], $p = 0.37$), reflecting that site differences do not seem to account for this relationship.

Next, time-varying predictor models were fit that included within-treatment symptoms (PCL, TLFB, and SIP-R) as time-varying covariates of dropout (see Tables 2 and 3 "Time Varying" columns). In the integrated arm, the model including demographics and time-varying symptoms did not yield any significant predictors of dropout. In the phased arm, younger age (aORs = 0.971-0.973) and race (Black or African American vs. other races; aORs = $1.932-2.099$) continued to significantly relate with higher dropout risk, but none of the time-varying covariates significantly predicted dropout risk. However, including these variables in the model increased precision for some of the demographic variable estimates compared to the models including only demographic variables. For both arms, all of the time-varying effect estimates were near 1 (aORs = $0.987-1.000$, all 95% CrIs contained 1).

Aim 3: Using LTA to model clusters based on within-treatment symptom trajectories as predictors of time-to-dropout

Generally, the cluster-based survival analyses improved model fit which strengthened precision in estimating fixed effects. Using the PCL, we estimated two clusters for the integrated arm ($n = 57$ and 38) and 6 clusters for the phased arm, where 3 clusters had membership of greater than 5 participants. Using the TLFB, the integrated and phased arms had 24 and 22 clusters, with 4 and 3 clusters having membership of 5 participants or more, respectively. Using SIP-R scores yielded one cluster for each arm that included all participants in that arm. We performed a sensitivity analysis for each intervention arm where we altered the SIP-R clustering method's concentration parameter to larger values which associates with increasing the chances of more groups. As expected, the number of post-processed groups increased, but their differences in dropout rates were negligible, so these analyses were not retained.

In the integrated arm, models including clusters based on PCL and SIP-R trajectories showed that female gender was associated with reduced dropout risk (aOR = 0.218 PCL and 0.231 SIP-R, 95% CrI = [0.036, 0.942] PCL and [0.038, 0.952] SIP-R; see Tables 2 and 3 "Cluster" columns). The PCL and TLFB cluster models showed that younger age corresponded with increased dropout odds (aOR = 0.975 PCL and 0.944 TLFB, 95% CrI = [0.957, 0.994] PCL and [0.929, 0.957] TLFB). In the phased arm, all cluster models suggested that younger participants had higher dropout risk (aORs = $0.925-0.965$). Black or African American participants had double the risk of dropout (aORs = $1.905-2.441$). The TLFB cluster model detected that never being married corresponded to 50% reduced dropout risk (aOR = 0.464, 95% CrI = [0.208, 0.969]).

Model fit comparisons

Model fit results are displayed in Table 4 for both the integrated and phased arms. The TLFB cluster models for each treatment arm produced substantially better fit to the data as compared to the time-varying models without clusters (i.e., lower model deviance). This suggests that including clustering based on TLFB trajectories added meaningful information in predicting dropout. In fact, all the cluster models had better model fit than the demographics-only models, except for the SIP-R cluster model in the phased condition. However, cluster models were heavily penalized in pD calculations due to the higher number of parameters, which increased model complexity and reduced parsimony. For this reason, the TLFB cluster models had the worst pD values. Using the DIC as an overall measure of model quality, of all the models that were fit, the SIP-R cluster model (which was comparable to the demographics-only model) provided the best overall model quality for the integrated condition, and the PCL cluster model provided the best overall model quality for the phased condition.

Describing clusters that confer risk for higher dropout

Clusters based on PCL scores. In both integrated and phased arms, PCL trajectories classified participants into high (cluster 2, $n = 38$ integrated; cluster 1, $n = 51$ phased) and low symptom trajectories (cluster 1, $n = 57$ integrated; cluster 2, $n = 24$ phased), where the lower group experienced marginal improvement on average (Figure 2). Based on visual examination, in the integrated condition, dropout looked similar between the two clusters across the sessions. In the phased condition, there was an additional group with noticeably higher dropout: cluster 4 ($n = 10$), with PCL trajectories between the high and low groups. Cluster 4 had lower retention rates than cluster 1 consistently from session 4 (difference in probability = 28.8%, 85% CrI = [8.58%, 51.64%]) to session 12

(44.6%, [26.36%, 60.83%]; see Figure S1). Similarly, cluster 4 yielded consistently lower retention rates than cluster 2 from session 2 onwards (12.93%, [2.22%, 28.23%]), except for session 10 (13.14%, [-10.82%, 36.64%]; Figure S1). In this sense, the lowest dropout rates were observed in the phased condition among participants with higher or lower PCL score trajectories.

Clusters based on TLFB scores. Visual examination revealed that TLFB trajectories were split into consistently high percent use across sessions and varying initial percent use but decreasing across sessions (i.e., substance use responders); this partitioning occurred for both treatment conditions (Figure 3). These TLFB responder clusters for the integrated arm were initially high use and improving (cluster 6, $n = 12$, >75% use), initially in the middle use and improving (cluster 3, $n = 17$, ∼50%), and initially low use and improving (cluster 2, $n = 27$, ∼25%). TLFB responder clusters 6 and 3 (high and middle initial use before improving, respectively) appeared to have lower dropout risk, whereas participants in cluster 2 (low initial use) had increased dropout early on (sessions 1-4) and then rebounded in dropout rates. We noted that participants with consistently high use without improvement in cluster 9 ($n = 13$) appeared to have a steep increase in dropout between sessions 4-6, and then they had the highest dropout rates compared to all other groups from session 6 onward.

Probing these patterns for statistical significance, cluster 9 (consistently high use) had statistically greater dropout than cluster 3 (middle use and improving) from session 5 onward (23.3%, 85% CrI = [2.96%, 46.1%]; Figure S2). Likewise, at session 7 onward, cluster 9 had greater dropout than cluster 6 (high use and improving; 31.8%, [4.68%, 57.2%]). From sessions 1-10, cluster 2 (low use and improving) did not differ from cluster 9 in therapy retention (30.2%, [11.1%, 48.0%]; Figure S2). This suggests participants in the highest- and lowest-use groups in the integrated condition had the highest dropout rates compared to the other groups and had similar dropout rates to each other for most of the therapy course. Cluster 2 (low-and-improving use), had greater dropout than clusters 3 and 6 in sessions 4 and 5, but this difference was not significant for most sessions from session 6 (cluster 6) or 7 (cluster 3) onward (Figure S3). This pattern suggests membership in the low-use cluster was associated with dropout in the sessions just after starting imaginal exposure in the integrated arm, but later in treatment, membership in the low-

Table 4. Model fit and complexity measures for integrated and phased arm data with best model performance values for each measure in each condition bolded.

	Integrated Condition			Phased Condition		
	Model Deviance	Model Complexity (pD)	Overall Quality (DIC)	Model Deviance	Model Complexity (pD)	Overall Quality (DIC)
Demographics Only	436.68	**16.57**	453.25	380.22	15.62	395.84
+ PCL Time Varying	440.20	17.54	457.75	380.01	16.67	396.68
+ TLFB Time Varying	440.20	17.59	457.79	379.96	16.57	396.53
+ SIP-R Time Varying	434.80	17.60	452.40	379.18	16.56	395.74
PCL Clusters	434.51	27.09	461.60	357.31	37.95	**395.26**
TLFB Clusters	**378.82**	92.99	471.81	**322.98**	80.36	403.34
SIP-R Clusters	433.27	16.64	**449.91**	381.30	**15.53**	396.83

Note. PCL: PTSD Checklist (a measure of posttraumatic stress disorder symptoms); TLFB: Timeline Follow-Back (a measure of substance use); SIP-R: Short Inventory of Problems – Revised (a measure of consequences of use); pD: the effective number of parameters (lower values reflect a more parsimonious model); DIC: deviance information criterion (lower values reflect a better-quality model overall).

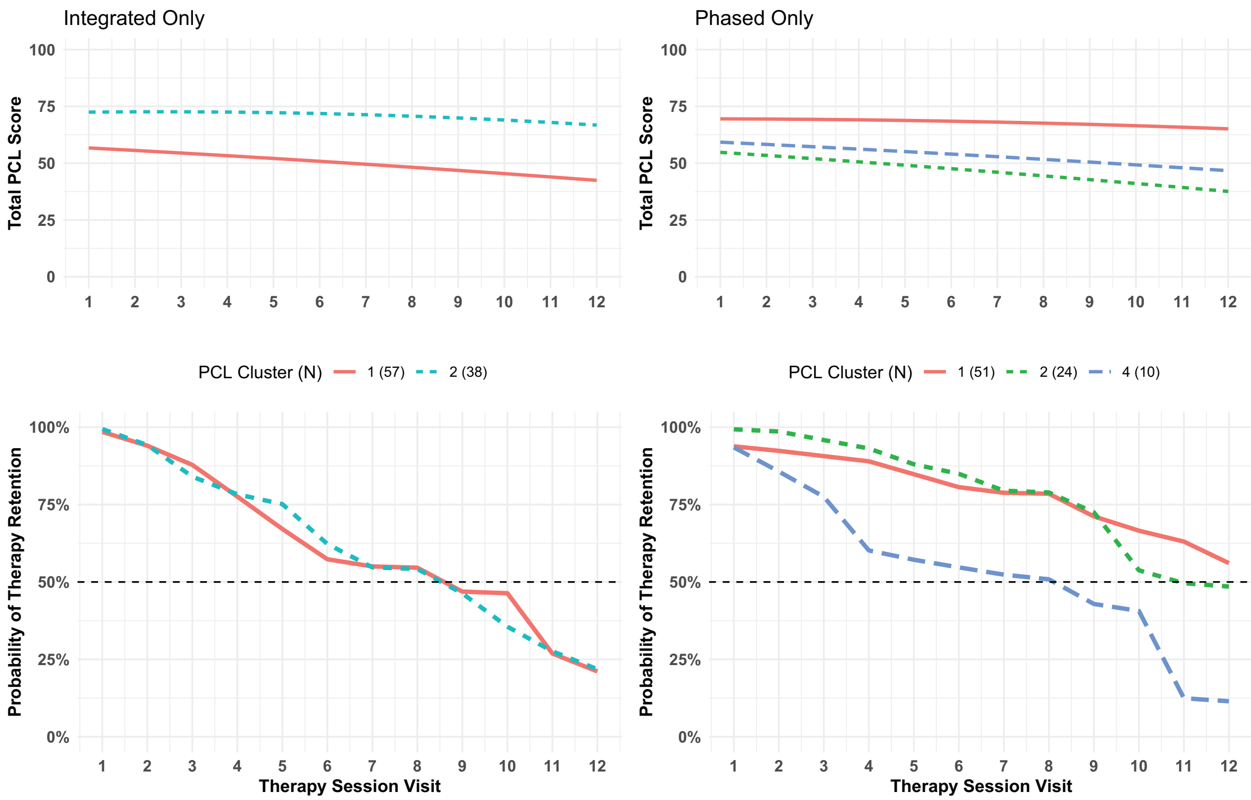

Figure 2. PTSD checklist (PCL) cluster model results and corresponding dropout rate.
Note. PTSD = posttraumatic stress disorder. Top row shows quadratic fits to PCL trajectories stratified by post-processed cluster labels for integrated (left) and phased (right) arms. Bottom row shows corresponding survival from dropout curves for each post-processed cluster for integrated (left) and phased (right) arms. Dash style and color correspond to cluster ID and only correspond from top to bottom row (do not correspond from left to right column of figures). Legends contain sample size per cluster in parentheses for each intervention arm.

use cluster corresponded to similar attrition patterns as clusters with moderate to high and improving use.

In contrast, in the phased condition, the consistently high use cluster (cluster 1, $n = 7$), the initially high use and then improving cluster (cluster 3, $n = 22$), and the initially low use and then improving cluster (cluster 2, $n = 32$) all exhibited relatively similar dropout rates. The only noticeable difference among clusters in the phased arm was that the low-use cluster (cluster 2) appeared to have greater dropout than the other two groups from the beginning of treatment through session 9. While cluster 2 did not significantly differ from cluster 1 over the course of therapy, cluster 2 had greater dropout than cluster 3 at sessions 1 (8.81%, [2.83%, 16.82%]) through 5 (15.23%, [4.56%, 27.18%]), but not at later sessions (not shown). In the phased condition, participants with low initial substance use were more likely to leave therapy during the MET phase of treatment (sessions 1-4) compared to their higher-use counterparts.

Clusters based on SIP-R scores. LTA using SIP-R scores yielded one cluster for each arm that included all participants in that arm, suggesting the demographic adjusted model is comparable to one including clustering based on SIP-R. As expected, the overall model complexity (pD) was comparable to the demographics-only model; these models only differed in prior specifications on session-by-session hazards of dropout (see Tables 2 and 3; for prior specification comparison see Supplement). Thus, using SIP-R scores to cluster participants did not provide meaningful information.

Discussion

The present study examined within-treatment predictors of dropout in integrated and phased MET/PE for PTSD-SUD. We modeled dropout over the course of treatment in both conditions and examined demographic variables and time-varying symptoms (PTSD, substance use, and consequences of use) as predictors of dropout. This study added to the literature by combining survival models and LTA to identify clusters of participants based on trajectories of PTSD symptoms, substance use (operationalized as percent of days with drug use or heavy drinking), and consequences of

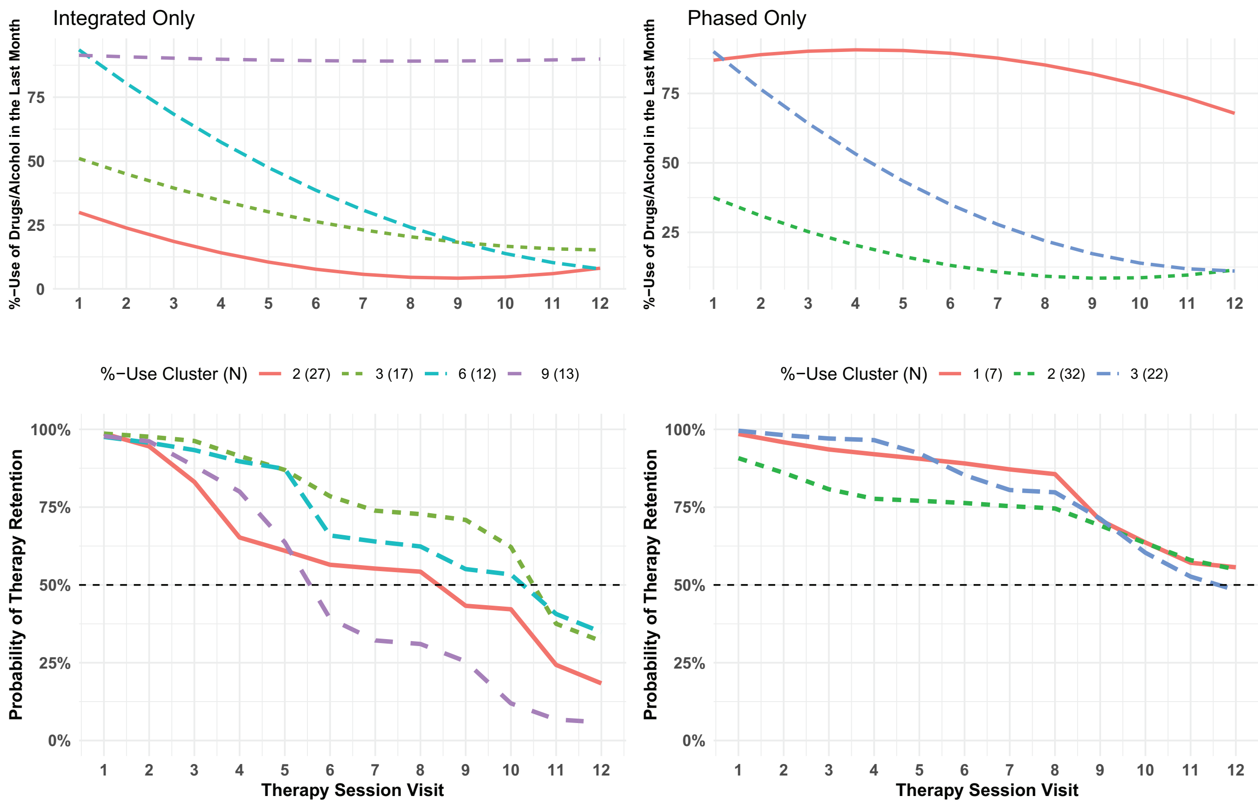

Figure 3. Timeline follow-back (TLFB) cluster model results and corresponding dropout rate.
Note. Top row shows quadratic fits to percent-use of substances in past month trajectories stratified by post-processed cluster labels for integrated (left) and phased (right) arms. Bottom row shows corresponding survival from dropout curves for each post-processed cluster for integrated (left) and phased (right) arms. Dash style and color correspond to cluster ID and only correspond from top to bottom row (do not correspond from left to right column of figures). Legends contain sample size per cluster in parentheses for each intervention arm.

substance use, and then using cluster membership to predict dropout over the course of treatment. The addition of clusters based on trajectories of PTSD and substance use increased model complexity but improved the fit of the survival model to the data, and significant differences in dropout emerged among clusters. Inclusion of clustering based on consequences of substance use did not improve the model based on model fit, and only one cluster was identified in each treatment arm, which was not useful for predicting dropout.

The demographics-only models and time-varying predictor models, which did not include latent clusters, identified some predictors of dropout. In the integrated arm, Hispanic ethnicity emerged as a predictor of greater dropout risk in the demographics-only model, though neither Hispanic ethnicity nor any other demographic variable predicted dropout when including time-varying effects of symptoms. In the phased arm, Black or African American race conferred higher risk of dropout across all models, and younger age conferred higher risk of dropout in all models that included time-varying symptoms.

These findings are consistent with prior studies that found younger age to predict greater dropout risk in studies of PTSD treatment (Goetter et al., 2015; Imel et al., 2013; Maguen et al., 2019) and SUD treatment (Vuoristo-Myllys et al., 2013). Regarding findings related to race and ethnicity predicting dropout, these findings are likely proxies for unmeasured factors rather than race and ethnicity themselves, such as stress during treatment or perhaps increased stigma toward psychotherapy (Lester et al., 2010). These findings warrant further study. Our findings are consistent with a study that found Black or African American race to predict greater dropout in cognitive behavioral therapy for PTSD (Lester et al., 2010) and a study that found membership in a minoritized racial or ethnic group to predict greater dropout in PE and virtual reality exposure (Reger et al., 2016). Our findings are inconsistent with other studies that have not found relationships between race/ethnicity and dropout in

PE and other PTSD and PTSD-SUD treatments (Goodson et al., 2013; Tuerk et al., 2011; Zandberg et al., 2016; Zoellner et al., 1999). Notwithstanding, our findings support calls to attend to racial trauma, discrimination, stigma, and culture when implementing treatments with patients of color to optimize their outcomes (Asnaani & Hall-Clark, 2017; Bryant-Davis, 2019; McClendon et al., 2020; Williams et al., 2014).

Some of the more meaningful and potentially clinically applicable findings emerged from the cluster models that estimated latent clusters based on substance use (percent of days with drug use or heavy drinking). In the integrated condition, the consistently-high use and low-and-improving use clusters had higher rates of dropout than participants with high-and-improving and moderate-and-improving use. The low-and-improving use cluster had particularly higher dropout in the two sessions after starting imaginal exposure. In the phased condition, the lowest-use cluster had greater dropout for most of treatment. These findings could reflect that participants experiencing less difficulty with substance use may not have perceived engaging in treatment, and specifically imaginal exposure in the phased condition, to be useful to them or worth the distress.

The finding that the highest-use cluster had higher dropout is consistent with Kline et al.' (2021) findings that greater alcohol use between PTSD-SUD treatment sessions predicted greater dropout at the following session. This suggests patients who maintain a pattern of high use throughout PTSD-SUD treatment are at greater risk of dropout. On the other hand, our finding that the lowest-use cluster also had higher dropout risk is inconsistent with Kline et al. (2021) findings that lower use between sessions predicted lower dropout. However, this finding is consistent with Zandberg et al. (2016) finding that fast rates of improvement in alcohol use predicted greater dropout risk in PTSD-SUD treatment. These findings suggest patients who are at the other end of the spectrum and engaging in low levels of use may perceive that their treatment goals are met and they no longer need care.

The differences in findings across studies may be due to differences in how change in substance use was operationalized. The present study estimated latent clusters based on intercepts and slopes of use across the treatment period. Kline et al. (2021) examined changes in use from one individual session to the next session. Zandberg et al. (2016) modeled trajectories of use across all sessions without estimating clusters of participants based on those trajectories. Taken together, findings across these studies point to a pattern in which consistently high use and low or fast-improving use both seem to confer dropout risk. The present findings are also consistent with research showing that some participants who drop out of care are doing well (Szafranski et al., 2017), as well as research that many who drop out are still experiencing high symptom levels (Berke et al., 2019; Holmes et al., 2019). Ultimately, both of these patterns may be accurate to some patients' experiences. In light of this, clinicians might initiate discussions with patients at either end of the spectrum of substance use during PTSD-SUD treatment to engage in shared decision-making and agreement related to potential early termination due to low continued need for treatment, as well as motivation building related to patients' treatment goals when they do still need care.

Cluster models that estimated latent clusters based on PTSD symptom trajectories revealed that in the phased treatment arm, participants with the highest and lowest PCL scores across treatment had the lowest dropout rates, whereas a smaller group of participants with moderate PCL scores across treatment had higher dropout rates. In the integrated arm, only two clusters emerged, and participants with high and low PCL scores did not differ in dropout rates. These findings are counter to Zandberg et al. (2016) findings in a sample receiving medication management and PE that fast and slow rates of PTSD improvement conferred *higher* dropout risk. However, those findings applied specifically to participants with higher baseline PTSD, whereas the current study did not include baseline PTSD symptoms as a moderator of effects. Further, there were fewer participants in the phased condition's moderate PCL trajectory cluster than the high or low PCL clusters. The moderate PCL cluster's trajectory was visually like the low PCL cluster's trajectory, making it difficult to decipher what about membership in the moderate vs. the low PCL trajectory contributed to dropout risk. Future research is needed to clarify the nature of relationships between both fast and slow PTSD symptom improvement and dropout risk, including whether these relationships differ depending on participants' baseline PTSD severity and the PTSD-SUD treatment they receive.

Cluster models that estimated latent clusters based on trajectories of consequences of substance use assessed via the SIP-R resulted in one cluster including all participants in each treatment arm, so they were not useful for improving dropout prediction. Visually, there appeared to be high variability across participants' SIP-R intercepts and slopes, yet there was low consistency across participants, such that participants did not cluster into distinct groups. Future research might focus on more complex models that may be able to better account for the variability across participants in consequences of use during treatment.

Strengths, limitations, and Future directions

A strength of the present study is that our statistical approach allowed us to identify symptom change processes during treatment that predict dropout risk, in line with calls to move beyond studying demographics and baseline clinical characteristics to examine within-treatment dropout predictors that can point to processes of dropout (Cooper et al., 2018). By analyzing treatment conditions and symptoms separately, we were able to detect different relationships with dropout across integrated and phased MET/PE as well as across PTSD, substance use, and consequences of use symptomatology. Further, using LTA to cluster participants based on symptom trajectories improved model fit—albeit while increasing complexity—and allowed for identifying clusters with distinct characteristics that predicted higher or lower likelihood of dropout. We chose to interpret models that had high complexity and pD values because the model complexity seemed to accurately fit the complex data, thus providing appropriately nuanced results. We also examined patterns of dropout at each treatment session, allowing for the exploration of dropout patterns at different stages of integrated and phased PTSD-SUD treatment, such as the sessions after beginning imaginal exposure.

Analyzing the integrated and phased conditions separately created the limitation of yielding differences in patterns of findings that were surprising and difficult to interpret. We analyzed the two arms separately because of their differing treatment structures and patterns of dropout, and while this approach allowed for confidence in the findings for each treatment arm, our approach did not allow for the statistical comparison of relationships between the treatment arms. In other words, our approach did not allow us to determine whether the relationships observed in the integrated and phased arms were statistically significantly different from each other. Future research can help elucidate which patterns of findings replicate across different PTSD-SUD treatment approaches and which findings are specific to a particular treatment protocol or sequence of procedures.

Another limitation is that the present trial had higher dropout rates (77% integrated arm, 64% phased arm) than other trials of PTSD-SUD treatment. For example, dropout rates in other PTSD-SUD trials were 43% in the relapse prevention arm and 45% in the COPE arm in Lancaster et al. (2020) study, 37% in the seeking safety arm and 67% in the COPE arm in Kline et al. (2021) study, and 32% combined across PE or medication management with naltrexone or placebo in Zandberg et al. (2016) study. The higher dropout rate observed in the present study may be in part explained by aspects of the study design (e.g., all participants received trauma-focused treatment) and the study setting (i.e., VA medical centers). Dropout rates from PTSD treatment tend to be higher in VA care than in clinical trials of PTSD that take place outside the VA (Maguen et al., 2019; Sayer et al., 2022). In support of this interpretation, the present study's dropout rate is most comparable to the 67% rate observed in the COPE arm of Kline et al.' (2021) study; COPE and MET/PE are both trauma-focused PTSD-SUD treatments that include PE, and Kline et al.' study also took place in the VA. Zandberg et al. (2016) observed a lower dropout rate than in the present study, which may be in part because not all participants in their study received trauma-focused treatment, and part of their sample received treatment in a university clinic setting rather than a VA setting. Given the present study's higher dropout rate than others, it may be the case that the present findings do not generalize to samples of patients receiving PTSD-SUD treatment in trials or settings that tend to have lower dropout rates.

Another strength is that our approach of using LTA along with a discrete-time survival model allowed us to address assumptions built into the standard time-varying survival model that may contribute to null findings. By example, time-varying estimates for within-treatment measures collected by Kline et al. (2021) and Gmeinwieser et al. (2020) approached insignificance for the hazard ratio and had noticeably short uncertainty intervals near or containing the null value of 1. The present study's time-varying predictor models (i.e., those not incorporating latent clusters based on symptom trajectories) also produced estimates with uncertainty intervals that contained the null value. We surmise that these null findings may be in part due to the large amount of variability between patient trajectories and the modeling assumption that time-varying effects are shared across patients and sessions, which may be an oversimplification of relationships that are more complex. To address this potentially problematic assumption of time-varying survival models, we summarized the variability in symptom changes into cluster labels and measured the per-session dropout for each cluster. In future research, it would further be beneficial to estimate models that assume each study participant can have their own effect of the within-treatment measure on dropout and assume that these effects arise from the same distribution with a shared variance.

Another limitation is that as an initial step, we analyzed trajectories of PTSD, substance use, and consequences of use separately, instead of forming clusters on all three within-treatment measures simultaneously. When clusters were estimated using all three within-treatment measures together, the results were too complex to interpret in a way that could be useful to clinicians providing treatment for PTSD-SUD. The present models, while more interpretable and therefore more clinically useful, are limited in that they do not provide information about likelihood of dropout for patients with consistently-high use and consistently-high PTSD scores vs. consistently-high use and rapidly-improving PTSD scores, for example. These types of symptoms are likely not independent but rather interact dynamically over time, and the present analyses did not account for interactive or transactional relationships among PTSD symptoms, substance use, and dropout. Future studies might attempt to clarify these complex relationships.

The clustering approach can also be improved. We did not constrain the number of post-processed clusters and, for example, more than ten TLFB groups had fewer than six members, with most having one participant. This contributed to high model complexity in the subsequent survival models, as each cluster was modeled to have 12 dropout effects, one for each session. While we sought to capture the sizeable variability across participant trajectories by modeling as many clusters as contained participants with reasonably similar TLFB trajectories, future analyses may constrain the number of clusters to circumvent this issue.

A second limitation of the clustering approach is the preclusion of group sizes of five or fewer participants in the subsequent inferences of the time-to-dropout models. Data from participants in clusters with fewer than six members were excluded from the results of cluster analyses, but included in the survival models. This constraint lowers the extent to which we can generalize our findings to these excluded participants' dropout patterns or generalize our findings to patients outside this sample whose symptom patterns may be similar to the excluded participants'. However, this strategy avoided forcing individuals with trajectories into a cluster where their comparative trajectories were not similar, and so this resulted in clusters that only included one participant. Our data-driven approach for evaluating who is in what cluster emphasized who is "similar enough" to be labeled as a cluster, whereas non-Bayesian methods force those individuals with dissimilar trajectories to others to be in one of the pre-specified clusters despite the dissimilarity. Additionally, we did not model a symptom-change effect per cluster per session, so we could not determine for a specific cluster at a specific session the extent to which a higher or lower score on a symptom measure predicted a higher or lower dropout likelihood. This is a possible modeling extension in future studies. Even in light of these limitations, we successfully identified different behavior patterns across groups, and collapsing the within-treatment measures into cluster assignments provided stronger model fit as compared to the time-varying methods alone.

An additional limitation is that the current approach only examined demographic variables and symptom trajectories as predictors of dropout. Reasons for dropout are multi-faceted (Kehle-Forbes et al., 2022; Meis et al., 2023), and important within-treatment reasons for dropout are not captured by examining symptom trajectories alone. Future research can incorporate more predictors (e.g., symptom change, self-report measures or observational coding of treatment processes, qualitative interviews) to account for a broader range of potential contributors to dropout vs. completion. Finally, the current sample, while demographically diverse, was a veteran sample nearly entirely comprised of men. Future research is needed to determine the generalizability of the present findings to broader samples, as it is unclear the degree to which the present findings generalize to non-veteran samples, samples with greater gender diversity than the present sample, and samples receiving PTSD-SUD therapies other than MET/PE. Future research is also needed to examine whether the present findings may differ for participants with different substance use disorders (e.g., cannabis use disorder vs. opioid use disorder).

Clinical implications

Together with a growing body of literature examining within-treatment dropout predictors, the current study may help clinicians identify patients at higher risk of dropout so they can intervene. Dropout is complex and multidimensional, yet together with other findings (e.g., Kline et al., 2021; Zandberg et al., 2016), the present results suggest clinicians might attend to both high and not improving PTSD and SUD symptoms and low and fast-improving symptoms as potential markers of poor prognosis for treatment completion. Once high dropout risk has been identified, the question as to how to best intervene remains a critical one. Particularly in the sessions after beginning imaginal exposure in PE, patients whose substance use is low may benefit from discussion of their treatment goals and factors motivating them to continue in PTSD treatment to help them remain engaged, or alternatively, whether their treatment goals have been met and agreed-on early termination may be warranted. More generally, some research suggests engagement interventions such as problem-solving barriers to treatment participation (Shulman et al., 2019) and directly addressing patients' concerns about high symptom levels and functional impairment during treatment (Kehle-Forbes et al., 2022) may be promising. However, additional research is needed to identify effective strategies clinicians can use to intervene to retain patients in care when patients seem to be at high risk of dropout. Further, the conflicting findings among studies conducted to date and differing findings between the integrated and phased arms in this study necessitate caution when considering clinical implications. The present analyses also do not provide benchmarks as to what levels of symptomatology or rates of improvement confer the highest dropout risk in new patients, and they do not necessarily generalize to non-veteran samples or to PTSD-SUD treatments other than MET/PE. Future studies can aim to quantify such benchmarks in the context of complex symptom trajectories in broader samples to help clinicians use information about new patients to "hedge the hazard" and prevent dropout before it occurs.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

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Data availability statement

Data from this study are available by emailing the secondary corresponding author and completion of VA regulatory requirements for data sharing; analysis code is available by emailing the primary or secondary corresponding author.

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