The Effect of Sleep Disorders, Sedating Medications and Depression on Cognitive Processing Therapy Outcomes: A Fuzzy Set Qualitative Comparative Analysis

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Abstract

Cognitive processing therapy (CPT) for posttraumatic stress disorder (PTSD) is an effortful process requiring engagement in cognitive restructuring. Sleep disorders may lead to avoidance of effortful tasks and cognitive performance deficits. We explored whether sleep disorders, as assessed by polysomnography, were consistently associated with treatment response in combination with other factors. Thirty-two U.S. Veterans were examined before and after CPT for combat-related PTSD. We employed a novel, case comparative technique, fuzzy-set qualitative comparative analysis (fsQCA), to identify combinations of fuzzy and crisp factors (recipes) achieving a clinically significant outcome. Approximately one-quarter of cases experiencing clinically significant change were either: 1) Vietnam era veterans without sedating medications, moderate sleep disordered breathing, and severe depression, or 2) Non-Vietnam era Veterans with sedating medications and without severe periodic limb movements (or significant periodic limb movement arousals). Recipes involving the absence of the relevant sleep disorder were associated with the highest coverage values. These results using fsQCA (a) provide valuable information about the heterogeneity of CPT response and (b) suggest that sleep disorders are important factors to consider in theoretical discussions of who responds to CPT for PTSD.

Keywords: PTSD, sleep disorders, cognitive-behavioral therapy, sedating medications, veterans

The Effect of Sleep Disorders, Sedating Medications and Depression on Cognitive Processing Therapy Outcomes: A Fuzzy Set Qualitative Comparative Analysis

Cognitive Processing Therapy (CPT) is a highly efficacious, first-line treatment for posttraumatic stress disorder (PTSD) (Galovski, Monson, Bruce, & Resick, 2009; Resick, Nishith, Weaver, Astin, & Feuer, 2002). Although the attrition rate is comparable to other forms of psychotherapies, approximately 20-27% of patients who start CPT do not finish the treatment (Resick et al., 2002). Also, approximately 50-60% of patients who start CPT continue to meet PTSD criteria at the end of treatment (Monson et al., 2006; Resick et al., 2002).

A number of studies have examined predictors of PTSD psychotherapy response and yielded mixed and ambiguous results. For instance, baseline depression has been associated with positive (Elliott, Biddle, Hawthorne, Forbes, & Creamer, 2005; Rizvi, Vogt, & Resick, 2009) and negative (Stein, Dickstein, Schuster, Litz, & Resick; Taylor et al., 2001) PTSD outcomes. Also, several studies suggest that depression has no effect on PTSD outcomes (Lloyd et al., 2014; van Minnen, Arntz, & Keijsers, 2002). van Minnen and colleagues (2002) found that benzodiazepine use leads to poor outcomes. In contrast, Rosen and colleagues (2014) found that benzodiazepine use leads to no difference in treatment outcome but may contribute to worse maintenance of gains. Combat veterans (especially Vietnam Era veterans) may be overall less responsive to psychotherapy (Bisson, Roberts, Andrew, Cooper, & Lewis, 2013). Data are mixed as to whether more combat exposure is associated with positive (Elliott et al., 2005) or negative outcomes (Price, Gros, Strachan, Ruggiero, & Acierno, 2013).

No studies to our knowledge have examined sleep disturbances as a potential predictor of treatment response, despite the fact that sleep disturbances caused by disorders such as sleep apnea and periodic leg movements are highly prevalent in patients with PTSD (Krakow et al.,

2001, 2004; Williams, Collen, Orr, Holley, & Lettieri, 2015) and depression (Ong, Gress, San Pedro-Salcedo, & Manber, 2009), and especially outpatient veterans (Mustafa, Erokwu, Ebose, & Strohl, 2005; Williams et al., 2015). Left untreated, these sleep disorders may lead to sleep fragmentation and complaints of non-restorative sleep (Scalise et al., 2014; Stone, Taylor, McCrae, Kalsekar, & Lichstein, 2008). Both sleep fragmentation and non-restorative sleep complaints have been shown to exhibit daytime impairments (Bonnet & Arand, 2003; Ohayon, 2005; Roth et al., 2010). The daytime effects of sleep fragmentation may mimic the effects of chronic partial sleep deprivation. Sleep deprivation is associated with: increases in subjective sleepiness (Howard et al., 2014), problems with constructive thinking skills (Killgore et al., 2008), avoidance of effortful tasks (Engle-Friedman et al., 2003), dysregulation of response inhibition, which may interfere with goal-driven behavior (Drummond, Paulus, & Tapert, 2006), emotional dysregulation (Yoo, Gujar, Hu, Jolesz, & Walker, 2007), decreased psychomotor performance (Bonnet & Arand, 2003; Howard et al., 2014) impaired decision making (Killgore, Balkin, & Wesensten, 2006), and cognitive performance deficits (Durmer & Dinges, 2005). Under these conditions, patients may be limited in their ability to attend to new information, apply this information in a new or flexible manner, or remember new skills. They may also only partially adhere to treatment, limiting the efficacy of treatment and likely leading to fewer therapeutic gains overall.

The purpose of this study was to examine whether Veterans with fewer disturbances in sleep, in combination with other patient characteristics (e.g., depression status, Vietnam War era status, medication status), were more likely to have clinically significant improvements after Cognitive Processing Therapy. Sleep disturbance was assessed by polysomnography using the apnea hypopnea index and the periodic limb movement index, two indices associated with

chronic sleep fragmentation and sleep loss. These indices are also required for the diagnosis of sleep disordered breathing and periodic limb movement disorder.

To systematically examine sleep disturbance in combination with other factors, we employed fuzzy set Qualitative Comparative Analysis (FsQCA), a set theoretic analytic method originating in comparative sociology that uses Boolean algebra to compare within-case combinations of causal and outcome conditions (Ragin, 2008). In fsQCA, all combinations of causal and outcome conditions are presented in a data matrix reformulated as a "truth table," that is subject to paired comparisons and logically simplified through a process that parallels circuit minimization (Ragin, 2014).

Fuzzy set QCA is an analytic approach that is novel and highly suitable to the in-depth examination of PTSD psychotherapy success. Currently, the majority of PTSD outcome studies examine questions of moderation using generalized least squares (GLS) techniques. These techniques are employed to test hypotheses derived from well-defined theories. However, theory is not well-articulated in the psychotherapy research to guide choices about who responds to psychotherapy and under what conditions. Also, GLS techniques are designed to test the relative importance of competing independent variables to arrive at a single causal model applied across all cases. However, available data suggest that psychotherapy success is unlikely to result from any one single moderator but rather the combination of multiple patient and contextual features. In addition, psychotherapy clinical trials are plagued by low enrollment numbers and insufficient power often exists to analyze the complexity that would be involved-in multiple moderation and moderated mediation pathways.

Set theoretic analysis is highly compatible with the analysis of causal complexity for psychotherapy outcomes. In fsQCA, researchers explore multiple pathways, or recipes, for an

outcome by examining configurations of relevant case characteristics. Within-case analysis is used to strengthen and deepen cross-case analysis (and vice-versa) in order to inform theory. FsQCA is ideal for the exploration of these questions because it is not limited by degrees of freedom and is frequently employed in small samples. Although application of fsQCA to intervention research is novel, the conceptual approach upon which it is based is highly consistent with the aims of the National Institutes of Health (NIH) Precision Medicine Initiative, "an innovative approach for disease prevention and treatment that takes into account individual differences in people's genes, environments, and lifestyles" ("Fact Sheet: President Obama's Precision Medicine Initiative," 2015).

Methods

All procedures were reviewed and approved by the U.S. Army Human Research Protection Office, the University of X Human Subjects Protection Program, the X VA Health Care System and the X VA Health Care System Institutional Review Boards and Research and Development committees**.** Research participation consisted of two major study-related visits. The first visit was timed at least one week before CPT start date. At this visit, participants received a demographic and medical history form, the Clinician-Administered PTSD Scale (CAPS), and the PTSD Checklist (PCL) to verify inclusion criteria and assess PTSD symptom severity.

Participants then received a natural course of CPT with a VA provider, who was designated by VA Central Office as having successfully received a certificate of training in CPT (Karlin et al., 2010). To receive a certificate of training, providers were required to: (a) be independently licensed, (b) attend an approved CPT workshop, (c) participate in 12 weekly phone consultation calls with a CPT expert, and (d) complete 4 individual or 2 group cases with treatment summaries.

One month after therapy ended, (or one month after their estimated completion date for those who discontinued treatment) participants met with study staff again for the second study-related visit, where they completed the CAPS, PCL, and in-home ambulatory polysomnography (PSG) to assess for sleep apnea and periodic limb movements. In order to study the effect of undetected sleep disorders on psychotherapy response, ambulatory PSG was administered after the psychotherapy. The detection of moderate sleep disordered breathing prior to CPT would ethically require immediate treatment that would not allow delay for the examination of CPT response. All participants in the study received ambulatory PSG, a procedure they otherwise would not have received as part of standard care for PTSD. All participants prescribed a Positive Airway Pressure machine were encouraged to follow usual practice for the sleep study.

Participants

Participants were recruited from flyers and clinician referrals at the X VA Health Care System and the X VA Health Care System. To be included in the study, participants had to be between the ages of 18 and 75 and designated by VA clinicians for individual or group Cognitive Processing Therapy (CPT) (or Prolonged Exposure (PE) therapy for PTSD, see below) with Criterion A trauma sustained during deployment in a combat zone. Participants were required to have PTSD as assessed by the CAPS using the F1/I2 scoring rule (Weathers, Keane, & Davidson, 2001). Patients designated for therapy were excluded for issues that would interfere with their ability to engage in therapy, such as: active suicidality, active alcohol/substance abuse, psychotic disorders, uncontrolled serious medical conditions, or overt cognitive problems. Additionally, participants were required to have no previous courses of PE or CPT and no alterations in their psychoactive medication and mental health treatment regimens 6 weeks prior to the baseline visit and during the course of the study.

Fifty-three combat veterans were screened, 14 participants were excluded, and 33 participants attended follow-up visits. Technical failure resulted in the loss of PSG data for one participant, and the data from another participant was excluded because this represented the only participant enrolled in Prolonged Exposure therapy (N = 32 final sample size; see Figure 1 for flow diagram). Participants ranged in age from 26 to 69 years old (M = 55.47 years, SD = 13.49 years). See Table 1 for demographic and clinical characteristics.

Measures

Participants were administered a demographic and medical history form to assess exclusion criteria and military status. Data were extracted from medical charts to assess number of therapy sessions completed, duration of therapy, and medication regimen. All interviewers completed a structured training program and established ongoing interrater reliability with an intraclass correlation coefficient, ICC ≥ .80 with a licensed clinical psychologist.

Clinician Administered PTSD Scale. The Clinician Administered PTSD Scale, DSM-IV version (CAPS) (Blake et al., 1990) was the primary measure of PTSD symptom severity. The CAPS is a widely used, reliable, and valid measure of PTSD symptoms (Weathers, Keane, & Davidson, 2001). The scale consists of 17-items, rating the frequency and intensity of PTSD symptoms with a possible score of 0 to 136; with higher scores indicating more severe PTSD symptoms.

Hamilton Rating Scale for Depression. The Hamilton Rating Scale for Depression – 17 Item version (HAMD-17) (Hamilton, 1960) was the primary measure of depressive symptomatology. Symptom severity can be calculated by summing the scores of the 17 items, with higher scores indicating more severe depressive symptoms. Internal consistency reliability coefficients range from .83-.94, and inter-rater reliability was above .85 in 7 of 8 studies (Rabkin

& Klein., 1987).

Ambulatory Polysomnography. To assess sleep disordered breathing and periodic limb movements, one-night ambulatory polysomnography (PSG) was administered in the participants' homes. All physiological measurements were recorded and scored using the 25-channel Grass Polysomnograph, AURA with TWin PSG Record and Review Software (Grass Instrument Division, Astro-Med, Inc.). Scalp electrodes were applied according to the International 10-20 system, with central and mastoid references, and standard electrooculogram (EOG), and electromyogram (EMG) placements, including bilateral anterior tibialis EMG measurements to assess periodic leg movements. Oronasal airflow was measured using a pressure transducer, pulse oximetry for detection of oxygen desaturation events, and two channels of respiratory effort using strain gauges to measure chest and abdominal movement during breathing. Maximal electrical impedance was set at 5 K Ohms.

All records were scored by a registered polysomnographic sleep technician (RPSGT) using AASM sleep scoring criteria (Iber, 2007) who had no knowledge of study purpose or design. The results were used to generate the (a) Apnea Hypopnea Index (AHI), representing the number of apnea and hypopnea events per hour of sleep, (b) Periodic Limb Movements of Sleep (PLMS) Index, representing the number of periodic limb movements per hour of sleep, and (c) Periodic Limb Movement Arousal (PLMA) Index, representing the number of arousals associated with periodic limb movements per hour of sleep.

Data Analysis

We employed fuzzy set Qualitative Comparative Analysis (fsQCA) to investigate set theoretical relationships between various patient conditions and the proposed outcome, clinically significant change in PTSD symptoms. Qualitative Comparative Analysis is an analytic

technique that uses Boolean algebra to compare combinations of causal and outcome conditions (Ragin, 2008). With QCA, it is possible to assess different combinations of causal conditions capable of generating the same outcome, which can be differentiated from the "net effects" approach in conventional GLS techniques. Fuzzy set QCA balances in-depth case knowledge with the identification of cross-case patterns, which is one reason it is recommended for use in small to intermediate-size samples (5-50); samples of this size are often too small for inferential statistical techniques but too large for researchers to conduct in-depth case analysis.

In fsQCA, two sets of analyses are conducted: necessity analyses and sufficiency analyses. A condition is defined as necessary if it must be present for an outcome to occur. Necessity analyses investigate the presence of conditions shared by all instances of the outcome; a necessary condition is a superset of the outcome. Necessity analysis is performed by examining consistency scores of the calibrated outcome against each of the causal conditions. Consistency is a parameter of fit that refers to the degree to which the conditions (X) display the outcome of interest (Y), or is a subset of that outcome $\sum[\min(X_i, Y_i)] / \sum (X_i)$ (Ragin, 2008). The higher the consistency, the stronger the set relationship. Consistency scores range from 0 to 1 with 0 indicating no consistency and 1 indicating perfect consistency. A consistency threshold of .90 or greater was employed for necessity analysis, and a Proportional Reduction of Inconsistency (PRI) threshold of greater than .70 was employed for sufficiency analysis (C. Ragin, personal communication, 2016). Consistency is the key index to examine in fsQCA in the same way that p-values (or confidence intervals) are the key index to examine in GLS techniques.

A condition is defined as sufficient if by itself it can produce a certain outcome. Sufficiency analyses investigate the agreement between the causal condition and outcome; a sufficient condition is a subset of the outcome. We conducted the core sufficiency analyses by

identifying the combination of conditions (recipes) that were associated with clinically significant clinical change in PTSD symptoms. These combinations are compared with each other and then logically simplified through a bottom-up process of paired comparison. The simplification process begins with the development of a "truth table" that reports all the different logical combinations of conditions (2^4 or 16 for this study). Next, combinations with the outcome (minimum PRI consistency threshold of .70) are paired, and logically redundant recipes are reduced via the use of Boolean algebra. This process of simplification incorporates the use of simplifying assumptions, or truth table rows without observations (i.e., remainders). The complex solution does not use any remainders. The parsimonious solution uses all remainders to yield fewer recipes or a logically simpler solution. The intermediate solution uses remainders that are consistent with theory and/or substantive knowledge. For this reason, the intermediate solution best represents a balance of complexity and parsimony that can both inform theory and facilitate a meaningful interpretation of results.

Finally, recipe and solution consistency scores, raw and unique coverage scores are evaluated. High consistency scores mean that almost all the patients that followed the recipes (or all the recipes in the case of solution consistency) exhibited positive outcomes. Coverage scores indicate the degree to which the recipe explains all cases of positive outcomes (how much a consistent subset 'covers' the superset). In sufficiency analysis, coverage can provide an estimate of the empirical importance of each recipe; the higher the coverage, the more patients the recipe describes. A significant number of resources are available for researchers interested in learning more about QCA (e.g., "Compasss," 2016; Ragin, 2008; 2014; Schneider & Wagemann, 2010).

We chose to examine patient-related factors and included the following variables in each of our recipes: (1) prescription of a sedating medication (benzodiazepine, narcotic, or hypnotic

medication, M, medication), (2) severe depression as determined by a Hamilton Depression Rating Score – 17 item version of 24 or above (D, depression), (3) Vietnam era veterans (V, Vietnam era). For each hypothesis, we examined the combination of these factors with the sleep index of interest. Unless otherwise specified, we calculated fuzzy sets using three values: (1) full membership into the set of interest, (2) a cross-over point reflecting maximum ambiguity in membership in the set of interest, and (3) full nonmembership in the set of interest. The benefits of variable definition by fuzzy sets has been previously described in medicine (Vineis, 2008) and sleep (Gehrman et al., 2002). Clinical cut-offs are frequently required for diagnosis and reimbursement, yet these cut-offs often represent artificial dichotomies in continuous health-related phenomenon.

We computed fuzzy sets based on the direct method of calibration, rescaling variables by using the cross-over point as an anchor to calculate deviation scores, with the full membership and nonmembership values as the upper and lower bounds respectively (Ragin, 2008). For severe depression, we used psychometrically-derived severity values on the Hamilton Depression Rating Scale (Zimmerman, Martinez, Young, Chelminski, & Dalrymple, 2013) to inform the criteria of 24 (severe), 17.1 (moderate), 7 (none). Medication and Vietnam Era were dichotomous or “crisp” sets. The outcome was defined as a clinically significant reduction on the Clinician Administered PTSD Scale (CAPS) (Weathers et al., 2001), 15 points (clinically significant improvement), 7.5 (partial improvement), 0 (no change). For moderate sleep disordered breathing, we calibrated a fuzzy set for the apnea hypopnea index using values of 15, 5, 0, which were based on the Medicare-derived criterion for reimbursement. We calibrated a fuzzy set for severe Periodic Limb Movements using the Periodic Limb Movements Index (PLMI) of 30, 15, 0, and Periodic Limb Movement Arousal Index (PLMAI) of 5, 2.5, 0, based on

International Classification of Sleep Disorders-2 criterion (American Academy of Sleep Medicine, 2005).

Results

Necessity Analysis

Individual condition consistency scores for clinically significant change in PTSD symptoms were as follows: presence of severe depression (.48), absence of severe depression (.66), Vietnam Era (.56), other military era (.44), absence of sedating medication prescription (.50), absence of moderate SDB (.49), and absence of severe PLMI (.67). No one condition was a superset of the outcome, clinically significant change in PTSD symptoms. Next, we analyzed necessary conditions for all two x two union relations and found a 15-point drop in CAPS score had the following necessary conditions: (a) Vietnam era veteran or the absence of severe PLMI (.98 consistency, .46 coverage), and (b) the absence of severe depression or the absence of severe PLMI (.91 consistency, .52 coverage).

Sufficiency Analysis

Sleep disordered breathing. First, we examined the combination of sedating medication prescription, severe depression, Vietnam Era and at least moderate sleep disordered breathing (S, Sleep disordered Breathing). Table S1 in the Supplementary Material available online lists all 16 logically possible combinations of the individuals examined in this study including the number of patients that exhibited each combination. Four combinations met both the minimum frequency threshold of one case and the minimum PRI consistency threshold of .70.

Using Boolean algebra, these four combinations were logically simplified into an intermediate solution that incorporated simplifying assumptions based on substantive knowledge that sleep disordered breathing and use of sedating medication (van Minnen et al., 2002) may

lead to worse PTSD outcomes and that severe depression and military era may or may not lead to worse PTSD outcomes (See Table 2). In this analysis, the intermediate solution was the same as both the complex and parsimonious solutions, yielding 3 recipes for clinically significant improvement. Vietnam era veterans who did not have moderate sleep disordered breathing, did not have severe depression, and were not prescribed a sedating medication almost always experienced a clinically significant improvement (recipe 2). Veterans from other military conflicts experienced positive, clinically significant outcomes when they did not have severe depression and were prescribed a sedating medication (recipe 1) or when they had severe depression and moderate sleep disordered breathing and were not prescribing a sedating medication (recipe 3). The presence and absence of each of these conditions in different combinations highlights that there are different pathways to clinical improvement.

Consistency scores were high for each individual recipe and for the three recipes together. In terms of solution coverage, the set of recipes accounts for .45 of fuzzy membership into the set of clinically significant outcome. The second recipe was the more empirically relevant recipe in absolute terms (raw coverage) and in relative terms (unique coverage). Similar raw and unique coverage values indicate that these recipes do not overlap.

Alternative tests. We conducted a number of alternative fsQCA models to assess the sensitivity of our results. First, we changed criteria of clinically significant outcome from 15 point to a 10-point drop in CAPS scores (Schnurr et al., 2003). The intermediate solution yielded three recipes similar to the previous analysis; the only differences was that recipe 3 no longer included the presence of sedating medications (consistency = .77, raw coverage = .21, unique coverage = .19). The solution consistency for this alternative test was .83 and solution coverage was .51. These findings suggest few differences using this less stringent cutoff suggesting that

psychotherapy changes in PTSD may operate on a continuum. They also support the use of fuzzy sets in evaluating CPT improvement.

Next, we examined recipes using a set negation of the outcome. In other words, we examined recipes for individuals who did not experience a 15-point drop on CAPS scores. We conducted these analyses because set theoretic analysis is not symmetrical; the recipes that led to clinically significant improvement may be quite different from the ones that lead to a lack of improvement. We found that Veterans did not have clinically significant outcomes when they were (1) Vietnam Era without severe depression and prescribed sedating medications (consistency = .86, raw coverage = .33, unique coverage = .33), (2) Vietnam Era with severe depression and moderate sleep disordered breathing and not prescribed sedating medications, (consistency = .93, raw coverage = .17, unique coverage = .17), and (3) from military conflicts other than the Vietnam War Era with severe depression but no moderate sleep disordered breathing (consistency = .75, raw coverage = .08, unique coverage = .08). Solution consistency was high (.86) indicating that a significant proportion of patients who followed these recipes did not exhibit a positive outcome; coverage score for these recipes was .59.

Periodic limb movements. Table S2 in the Supplemental Material available online lists all 16 logically possible combinations of the individuals examined in this study including the number of participants that exhibited each combination. Three combinations met both the minimum frequency threshold of one case and the minimum PRI consistency threshold of .70.

Using Boolean algebra, these combinations were logically simplified into an intermediate solution incorporating simplifying assumptions based on substantive knowledge that sleep disturbance and sedative use may lead to worse PTSD outcomes and that severe depression and military era may or may not lead to worse PTSD outcomes (See Table 3).

Vietnam Era Veterans were most likely to experience a clinically significant outcome when they were not prescribed a sedating medication, did not have severe depression, and when they had severe periodic limb movements (recipe 1). Veterans from other military conflicts experienced positive, clinically significant outcomes when they did not have severe periodic limb movements and when they were prescribed a sedating medication (recipe 2). A final recipe emerged indicating that, regardless of era, Veterans experience clinically significant improvements when they have severe depression, are prescribed sedating medications, and do not have severe PLMS index (recipe 3). The same three recipes emerged for the complex solution. For the parsimonious solution, recipe 1 no longer included Veteran Era (unique and raw coverage = .22; consistency = .84); there were negligible differences in overall solution consistency and coverage.

Alternative tests. Next, we examined recipes using a set negation of the outcome. The three-recipe intermediate solution had good solution consistency (.84) and coverage (.65). Recipe 1 indicated that veterans from Vietnam Era do <u>not</u> experience clinically significant outcomes when they are prescribed a sedating medication and do not have severe depression (raw coverage = .33, unique coverage = .27, consistency = .86), or they have severe depression and are not prescribed a sedating medication (Recipe 2, raw coverage = .23, unique coverage = .23, consistency = .86). Recipe 3 indicated that veterans do not experience clinically significant outcomes when they are prescribed a sedating medication, have severe depression, and have severe periodic limb movement index (raw coverage = .15, unique coverage = .09, consistency = .84).

Next, we substituted PLMS Index with a fuzzy set variable defined as present with a Periodic Limb Movement Arousal Index (PLMAI) of 5 or more per hour. All recipes from the

main analyses were consistent with results reported for PLMI with negligible differences in consistency and coverage values. Solution consistency was high at .85 with a solution coverage of .57 indicating a relatively high fuzzy membership into the set of clinically significant outcome. These findings indicate that PLMAI and PLMI are similar indices in the way they combine with other variables and relate to CPT outcome.

Discussion

The purpose of this study was to identify combinations of patient factors that led to clinically significant CPT outcomes. The most empirically relevant recipes (i.e., those with the highest coverage) included the absence of moderate Sleep Disordered Breathing and severe Periodic Limb Movements. Approximately one-quarter of cases that experienced clinically significant change were either: (1) Vietnam era veterans without moderate sleep disordered breathing, without sedating medications, and without severe depression; and (2) Non-Vietnam era Veterans with sedating medications and without severe periodic limb movements (or significant periodic limb movement arousals). Moreover, the absence of periodic limb movements may be a necessary condition for clinically significant improvement, in combination with Vietnam era status or severe depression.

However, other recipes existed in both conditions unrelated to sleep disorders. Necessity analyses indicated that the absence of sleep disordered breathing was not a necessary condition for clinically significant improvement alone or in combination with another condition. Non-Vietnam Era Veterans who experienced a positive outcome were most likely to be prescribed a sedating medication and not experiencing severe depression. Neither the absence nor the presence of moderate sleep disordered breathing played a role in this recipe, suggesting that other factors related to arousal or motivation may hold greater importance for this subset of

patients representing a younger age group. Also, a small number of veterans from eras other than Vietnam experienced clinically significant change in the *presence* of moderate sleep disordered breathing, severe depression, and the absence of a prescription of a sedating medication. One possible explanation for this recipe may be representation of a more severe subset of patients with higher levels of pathology and therefore an increased likelihood of exhibiting improvement, often associated with regression-towards-the-mean phenomena.

Also, the presence of severe periodic limb movements was associated with clinically significant change at a .20 coverage level in the sample; this pathway represented Vietnam Era veterans, who did not have severe depression and were not prescribed a sedating medication. These findings did not differ substantially with the substitution of PLMAI. Periodic limb movements are associated with the use of antidepressants (Yang, White, & Winkelman, 2005). The significance (or lack thereof) of periodic limb movements in the absence of associated arousals remains controversial (Mahowald, 2007).

Finally, set negation analyses indicated that sleep disorders may play a minor role in explaining the lack of clinical improvement. In both sets of analyses, the recipes with the most coverage (.33 raw coverage for each) were those in which the cases had no severe depression and a prescription for a sedating medications. These findings are consistent with the results from a large-scale examination of PTSD psychotherapy response that used Latent Growth Mixture Modeling to empirically divide individuals into latent subgroups (‘mixtures’) on pre-treatment severity (Elliott, Biddle, Hawthorne, Forbes, & Creamer, 2005). PTSD scores were linked with other symptoms (anxiety, anger, depression, alcohol use, trauma exposure), and individuals with the lowest levels of pre-treatment PTSD had worse outcomes over a 24-month period. Pre-treatment sedative or benzodiazepine use was not a variable analyzed in their subgroups but may

be one potential explanation for these findings. While benzodiazepines may be partially efficacious in lowering PTSD symptoms, they are not recommended due to untoward side effects including worse PTSD psychotherapy response (Guina, Rossetter, DeRhodes, Nahhas, & Welton, 2015; van Minnen et al., 2002).

Overall, the results in this report provide valuable information about which patients might be the best candidates for the receipt of PTSD psychotherapy. These findings suggest that there could be an important role for the screening and treatment of sleep disorders in PTSD clinics. These data support a recommendation to treat comorbid sleep apnea and disorders involving periodic limb movements prior to the initiation of PTSD psychotherapy. Data also suggest that the treatment of sleep disorders alone is neither necessary nor sufficient to ensure positive treatment response.

Further work must be conducted to validate these findings. The use of QCA with fuzzy sets allowed an exploration of the heterogeneity in treatment response. Our findings suggest that both the absence and presence of a serious sleep disturbance are important factors in PTSD psychotherapy outcome; the importance of one versus the other in treatment outcome depends upon the presence and absence of other factors, including benzodiazepine, narcotic, or hypnotic prescription, severe depression, and also era of military participation. Use of generalized least squares techniques would have averaged these sleep results highlighting the value of employing a configurational comparative approach that explores heterogeneity in response. Set theoretic analysis is much more compatible with the analysis of causal complexity than traditional methods, especially given the paucity of articulated theory guiding CPT moderation variable choices. To our knowledge, this is the first psychotherapy study employing fsQCA, a well-established methodology in the social sciences that is highly suitable for addressing

psychotherapy moderation questions with small sample sizes ($n < 50$).

Results in this study must be qualified by causal conditions chosen for analysis. We had access to medical record information verifying prescription of benzodiazepines, sedatives, and hypnotics but not actual information about whether/how much participants were taking these medications. Also, a number of other factors (e.g., IQ, alcohol/drug use, therapy type) were not represented in the current models because of limited variability among participants. In general, the field of sleep medicine has not arrived at a solution of how to combine or prioritize sleep indices to calculate a global measure of sleep disturbance. Future studies might benefit from an exploration of combinations of comorbid sleep indices. Polysomnography was administered after the therapy to allow for the study of sleep disordered breathing on treatment outcomes; although unlikely, it is possible that AHI and PLMS Index could have been impacted by psychotherapy response. Last, all participant data analyzed in this study were based on enrollment in CPT. At these chosen VAs, CPT was the predominant therapist preference and availability. Although studies have demonstrated that CPT and PE have analogous outcomes on PTSD symptoms, no conclusions may be drawn for Veterans engaged in PE.

Despite these limitations, the results from this study provide valuable information about complex causal conditions that predict positive treatment response in a naturalistic VA environment. To our knowledge, this is the first study to date examining sleep disorders as a potential factor in CPT for PTSD in combat veterans.

Acknowledgments

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Table 1

Demographic and Clinical Characteristics of Study Completers, n = 32

Demographic and Clinical Variables	*N*	%
Male	31	97
Female	1	3
Military Era		
Vietnam	21	66
Operation Enduring Freedom/Operation Iraqi Freedom	6	19
Desert Storm/Gulf War	4	12
Other	1	3
Ethnicity		
Caucasian	20	63
Hispanic	7	22
African American	3	9
American Indian	2	6
Medication, Prescription		
Benzodiazepine	6	19
Narcotic	12	38
Trazodone	4	13
Prazosin	9	28
Zolpidem	3	9
Benzodiazepine, Narcotic, or Hypnotic (Zolpidem)	16	50
Prescribed Continuous Positive Airway Pressure machine	6	19

Documented adherent, ≥4h per night ≥70% of nights at follow-up	4	67[a]
CPT responders (15 point drop)	10	31
Completed 8+ sessions CPT for PTSD	27	84
	M	*SD*
Baseline CAPS Score	75.48	16.63
Baseline, Hamilton Depression Scale-17	14.06	7.05
Ambulatory Polysomnography Indices		
Apnea Hypopnea Index	13.98	17.72
Periodic Limb Movements Index	19.77	25.07
Periodic Limb Movement Arousal Index	6.11	9.47

Note. CPT = Cognitive Processing Therapy. PTSD = Posttraumatic Stress Disorder. CAPS = Clinician Administered PTSD Scale.

[a]n = 6 Veterans prescribed CPAP.

Table 2

Simplified Recipes for Achieving Clinically Significant PTSD Outcome with Moderate Sleep Disordered Breathing

	Recipe		
Condition	1	2	3
Benzodiazepine, Narcotic, or Hypnotic	●	⊗	⊗
Moderate Sleep Disordered Breathing		⊗	●
Severe Depression	⊗	⊗	●
Vietnam Era	⊗	●	⊗
Consistency	0.77	0.97	0.83
Raw Coverage	0.15	0.22	0.08
Unique Coverage	0.15	0.22	0.08
Overall Solution Consistency		0.87	
Overall Solution Coverage		0.45	

Note. ● indicate the presence of a condition. ⊗ indicate the absence of a condition. Blank spaces in a solution indicate that the causal condition may be either present or absent.

Table 3

Simplified Recipes for Achieving Clinically Significant PTSD Outcome with Periodic Limb Movements Index

	Recipe		
Condition	1	2	3
Benzodiazepine, Narcotic, or Hypnotic	⊗	●	●
Severe Periodic Limb Movements Index	●	⊗	⊗
Severe Depression	⊗		●
Vietnam Era	●	⊗	
Consistency	0.83	0.82	0.95
Raw Coverage	0.20	0.28	0.26
Unique Coverage	0.20	0.13	0.10
Overall Solution Consistency		.85	
Overall Solution Coverage		.59	

Note. ● indicate the presence of a condition. ⊗ indicate the absence of a condition. Blank spaces in a solution indicate that the causal condition may be either present or absent.

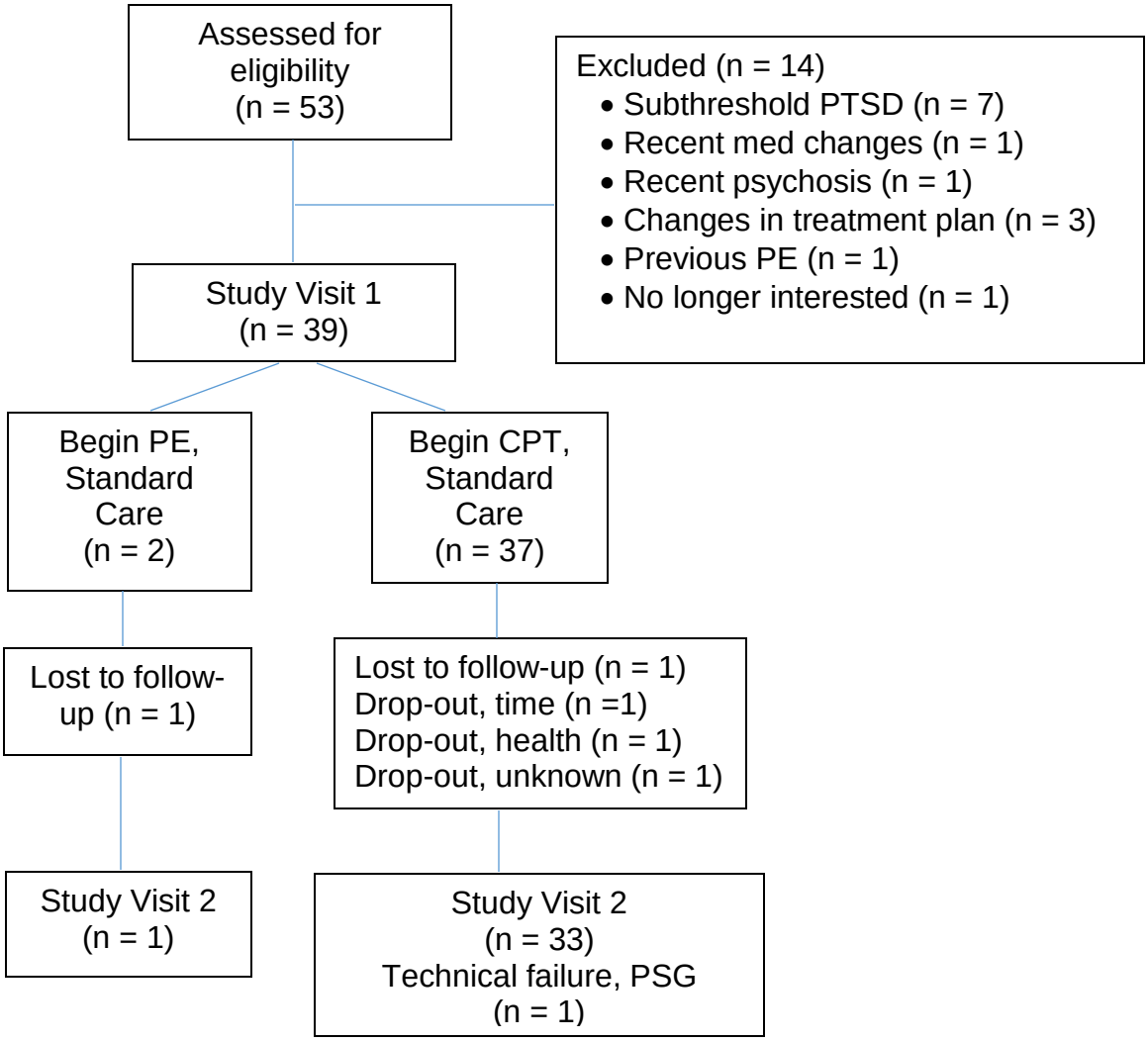

Figure 1. Participant flow diagram.

Table S1. Truth Table Summarizing the Recipes for Clinically Significant Outcome (with Moderate Sleep Disordered Breathing)

Solution	N	PRI Consistency
VMdS	**2**	0.10
VMds	**5**	0.00
VmDS	4	0.08
Vmds	**4**	**0.96**
VMDS	3	0.49
VmDs	1	0.33
VmdS	2	0.41
VMDs	0	--
vMds	**1**	**0.73**
vmds	2	0.33
vmDs	1	0.26
vMDS	**3**	0.69
vMDs	0	--
vMdS	**2**	**0.74**
vmDS	**1**	**0.79**
vmdS	1	0.33

Note. Bold font indicates recipes meeting both the minimum frequency threshold of one case and the minimum PRI consistency threshold of .70. Upper-case letters indicate presence of the participant characteristic; lower-case letters indicate absence of the characteristic.
Abbreviations. V, Vietnam era veteran; M, prescription of sedating medication (benzodiazepine, narcotic, or hypnotic); D, Severe depression as determined by a Hamilton Depression Rating Score of 24 or above; S, Moderate sleep disordered breathing as determined by Apnea-Hypopnea Index (AHI) of 15 or above on polysomnography at post-treatment

Table S2. Truth Table Summarizing the Recipes for Clinically Significant Outcome (with Severe Periodic Limb Movements Index)

Solution	N	PRI Consistency
VMdP	4	0.02
VMdp	3	0.10
VmDP	3	0.19
Vmdp	3	0.57
VMDP	2	0.12
VmDp	2	0.11
VmdP	**3**	**0.79**
VMDp	**1**	**0.95**
vMdp	**3**	**0.75**
vmdp	3	0.30
vmDp	2	0.55
vMDP	1	0.16
vMDp	**2**	**0.93**
vMdP	0	--
vmDP	0	--
vmdP	0	--

Note. Bold font indicates recipes meeting both the minimum frequency threshold of one case and the minimum PRI consistency threshold of .70. Upper-case letters indicate presence of the proposed patient characteristic; lower-case letters indicate absence of the patient characteristic. Abbreviations. V, Vietnam era veteran, M, Chart-reviewed prescription of sedating medication (benzodiazepine, narcotic, or hypnotic); D, Severe depression as determined by a Hamilton Depression Rating Score of 24 or above; P, Periodic limb movement index of 30 or greater