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2. PROJECT TITLE: Optimal Treatment of Veterans with PTSD and Comorbid Opiate Use Disorder (OUD)

3. PURPOSE:

Posttraumatic stress disorder (PTSD) is a serious psychiatric disorder affecting Veterans, particularly those from the recent conflicts.[1] PTSD is complicated by high rates of comorbidity with other disorders, notably substance use disorders.[2] Given the clinical need for the treatment of PTSD, the Veterans Administration (VA) and the Department of Defense (DoD) have invested in making access to evidenced based treatments a priority. This includes Cognitive Processing Therapy (CPT) which is an integration of psychoeducation, cognitive therapy and imaginal exposure therapy. CPT was rolled out nationally in a large dissemination project by the VA and the DoD as one of the gold standard treatments for PTSD. [Recently, the VA/DoD Practice Guidelines for The Management of Posttraumatic Stress Disorder and Acute Stress Disorder (2017)[4] have been released and *recommend behavioral interventions, specifically trauma focused manual-driven therapy, as first line of treatment.[5] However, the effectiveness of the treatments remain to be demonstrated in Veterans with comorbidities. This gap is particularly significant for those Veterans with opioid use disorder (OUD), which occurs at a particularly high rate among Veterans with PTSD.]*

Recently a national opioid epidemic has emerged as a major public health problem in the United States. This epidemic has had a significant effect on Veterans, particularly those from the recent conflicts[6], prompting a high level of public awareness. Prescription opioid use dramatically increased, in part because of the increasing emphasis on adequate management of pain, with changes in prescribing patterns of physicians and easier availability of opioids on the internet.[7] The rates of prescribed opioids increased several fold over 10 years (2001-2009) among military personnel, a factor which was found to undermine military readiness.[8] Veterans with mental health disorders, notably PTSD, are more likely to experience chronic pain, to be prescribed opioids, more likely to participate in high risk behaviors and more likely to have adverse outcomes [9] including more susceptibility to developing substance use disorders.[10] As awareness of the prescription opioid epidemic increased among health professionals, availability of prescription opioids decreased and in its wake there has been an alarming increase in heroin use. The rates of reported heroin use has doubled between 2006-2012[11] and there is a fourfold increase in heroin overdose deaths between 2000 and 2014.[12]

Buprenorphine is a partial μ-opioid agonist, that has been shown to be effective as a first line treatment for OUD.[13] Office based opioid substitution therapy is a standard of care within the VA and its utilization since FY15 is part of the mental health performance measures [14]. Unfortunately, the efficacy of treatments for comorbid conditions among those maintained on buprenorphine has not been examined. To date *no studies have demonstrated that evidence-based therapies for PTSD also work in those with comorbid OUD.* Therefore, this proposed application *will specifically address this gap in the treatment of co-morbid PTSD and OUD.*

The purpose of this study is to test whether *CPT is more effective than Individual Drug Counseling (IDC), which is standard counseling, for the treatment of PTSD among Veterans and civilians with PTSD and comorbid opioid use disorder who are also maintained on buprenorphine.* We propose to conduct a *randomized, controlled trial among Veterans and civilians (n=160) diagnosed with PTSD and comorbid OUD will be randomized to one of 2 groups: (a) buprenorphine and CPT or (b) buprenorphine and IDC (treatment as usual).*

Specific Aims:

Primary Aim 1:.To test whether CPT is more effective than *IDC in treating symptoms of PTSD* among Veterans and civilians with OUD maintained on buprenorphine. *PTSD symptoms will be measured using the PTSD Checklist – Military version (PCL-5), and confirmed by the Clinician Administered PTSD Scale using the DSM-5 criteria (CAPS-5).*

Secondary Aim 1: To test whether CPT- is more effective than *IDC* in reducing *opioid use* among Veterans and civilians with PTSD and comorbid OUD maintained on buprenorphine. *Opioid use will be measured using the* Timeline Follow-back (*TLFB) and confirmed by urine toxicology results.*

Exploratory Aims: To examine if treatment groups differ in 1) *retention*, measured by days in treatment, 2) *psychosocial functioning*, measured by the *participants RAND 12-Item Short Form Health Survey (*VR-12), 3) *sleep* as measured by the Insomnia Severity Index (ISI), since sleep disturbance is a hallmark of PTSD and during early abstinence from opioids, and 4) Because of the high comorbidity between PTSD and chronic pain we will explore this relationship and will measure *pain intensity* (measured by the Numeric Rating Scale (NRS), and *functional impairment* using the PROMIS-29 (Patient-Reported Outcomes Measurement Information System) longitudinally over the course of treatment. Follow up will be conducted 1 and 3 months after completion of the study to evaluate *durability of effect on PTSD symptoms (measured as changes in PTSD symptoms), opioid use and treatment utilization.*

4-5. BACKGROUND AND SIGNIFICANCE:

This proposal was originally developed in collaboration with the Consortium to Alleviate PTSD (CAP) (Dr. Alan Peterson Director and Dr. Terrence Keane co-Director), underwent scientific review and was proposed for funding. However, CAP was unable to fund it as buprenorphine treatment is of limited importance for active-duty personnel. The CAP leadership group encouraged our group to send this application to the VA as it has great clinical relevance for the VA and for Veterans, *although CAP is no longer involved in this proposal***.** Please see the attached letter of support.

A. Posttraumatic stress disorder (PTSD)

i) PTSD is a serious psychiatric disorder that can occur after the experience of a traumatic event. Symptoms include intrusive memories associated with the traumatic event, avoidance of stimuli related to the event, negative changes in mood and cognition and changes in arousal and reactivity. Population surveys have estimated that the prevalence of PTSD is between 4.8% (National Epidemiologic Survey on Alcohol and Related Conditions [NESARC]) and 7.8% of the general population (Epidemiologic Catchment Area [ECA]).[15] PTSD is an important issue for military personnel and Veterans, particularly those from the recent conflicts, as rates among military personnel are much higher than those in the general population. Among male and female soldiers age 18 or older returning from Iraq and Afghanistan, rates range from 9% shortly after returning from deployment to 31% a year later.[16] A review of several studies that evaluated rates of PTSD in those who served in the recent conflicts found prevalence rates of adult men and women previously deployed ranging from 5% to 20% for those who do not seek treatment, and around 50% for those who seek treatment.[17] Among those returning from the recent conflicts, those at highest risk included youngest Veterans, under 25 years of age.[18] Vietnam Veterans also report high lifetime rates of PTSD ranging from 10% to 31%.[19] It should be noted that PTSD is the third most prevalent psychiatric diagnosis among Veterans using VA services,[20] and Veterans from recent conflicts have enrolled in VA care at historically high rates, making this of high clinical importance to the VA nationally.[18]

PTSD is complicated by high rates of comorbidity with other disorders, and it has been hypothesized that comorbidity is the norm rather than the exception. Substance use disorders are among the most common to co-occur.[2] Administrative date from VA nationally, indicates that there are approximately 640,000 Veterans who have the diagnosis of PTSD; of those 70,000 Veterans (19% of those with PTSD diagnosis) have a substance use disorder (another almost 70,000 have alcohol use disorder without another substance use disorder) (personal communication, B Rosenheck). These data most likely represent lower-than-actual prevalence rates, as administrative data have been shown to underreport diagnoses in certain disorders by up to a factor of 5 (personal communication, B Rosenheck). The rates of substance use disorders may be higher among Veterans from the recent conflicts. When surveying Veterans on their "psychosocial concerns", substance abuse is reported by 25% of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) Veterans.[21] Rates of comorbidity among the recent returnees are higher in more vulnerable populations: among those who suffered from combat injuries [22] and among homeless Veterans.[23] In examining opioid use disorders (OUD) specifically, there is evidence of high comorbidity. Having a diagnosis of PTSD is associated with high rates of opioid prescription use and high-risk opioid use.[18] Among those with opioid dependence, PTSD prevalence has been as high as 33%.[24] *Comorbidity* has been shown to lead to worse outcomes than when either disorder occurs alone. For example, those with comorbid conditions have more health and social issues, have greater symptom severity, and higher utilization of services (including inpatient) than those without comorbidity.[25] Prescription opioid use is associated with PTSD symptoms severity[26] and the diagnosis of PTSD is associated with higher doses of opioid treatment among Veterans treated with opioid substitution.[27]

There are very few studies and even fewer evidence-based guidelines for treatment of comorbid PTSD and opioid use disorders.[28] Several treatments are available for these disorders when they occur without comorbidity, but there is evidence that the presence of comorbidity may alter the efficacy of the treatment.[29] Therefore testing evidence based treatments in real world clinical patients is of great importance. Further, treatment is still compartmentalized into specialty PTSD clinics and specialty substance abuse clinics and clinical staff often require sobriety for some predetermined length of time before entry into specialty PTSD clinics. This suggests that those Veterans treated primarily in substance abuse clinics may not have access to evidence based treatments for PTSD and therefore do not get adequate treatment for PTSD.

PTSD is an important clinical issue and health care priority for the VA as Veterans from recent conflicts have enrolled in VA care at historically high rates. The high rates of comorbid disorders such as OUDs must be accounted for in designing clinical care for Veterans with PTSD.

ii) Cognitive Processing Therapy as Treatment for PTSD

Cognitive Processing Therapy (CPT)[3] was developed for the treatment of PTSD among rape victims. It is based on an information processing theory of PTSD and is an integration of psychoeducation, cognitive therapy and imaginal exposure therapy. [CPT addresses the influence of traumatic events on an individual's thoughts, and how that affects cognitive, emotional, and behavioral responses (e.g., Resick & Schnicke, 1992[3]). CPT has been found to improve PTSD symptoms as well as associated symptoms (depression, anxiety, guilt, shame), day-to-day functioning.[30] and is effective in both individual and group therapy formats[31]; improvements in PTSD symptoms appear to be sustained over time.[32] CPT has been successfully used among military Veterans,[33] [34, 35]and was rolled out nationally in a large dissemination project by the U.S. Department of Veterans Affairs and the U.S. Department of Defense as one of the gold standard treatments for PTSD. A meta-analysis of treatments for PTSD found the largest effect size for cognitive behavioral treatments (1.63), larger than for somatic therapies and for the pharmacotherapies.[36] The VA/DoD Practice Guidelines for The Management of Posttraumatic Stress Disorder and Acute Stress Disorder (2017) *recommend behavioral interventions, specifically trauma focused manual-driven therapy such as CPT, as first line of treatment* before other therapies including medication].

CPT has also been tested in individuals with comorbid conditions, notably alcohol use disorders.[CPT is a *particularly good choice* for patients with co-morbidity because there is *flexibility within the therapy during which thoughts related to drug use are addressed*. It has been hypothesized that the cognitive restructuring associated with CPT can promote *recovery from substance use*.][38] Kaysen and her colleagues [39] compared CPT outcomes among those with and without alcohol use disorders. Results suggested that CPT was safe and effective in this comorbid group because there were no differences in completion rates and both groups showed an improvement in PTSD symptoms. In this study, current alcohol use disorder was defined as having the disorder in the last 12 months. Our group piloted CPT in a small study that integrated CPT for treating PTSD symptoms with coping skills training for the treatment of alcohol dependence. This was piloted in currently drinking, alcohol dependent Veterans with PTSD and efficacy was tested using standardized scales evaluating symptoms for PTSD (Clinician Administered PTSD Symptom Scale-CAPS) and alcohol consumption (Timeline Follow-back Method - TLFB), as well as mood ratings and quality of life data (see pilot data). Findings from our preliminary studies (please see preliminary studies section) has shown that CPT is effective in reducing symptoms of PTSD (significant decrease in CAPS from 60.5, sd=9.6 at baseline to 20.3, sd=19.9 at post treatment; p=0.03). We also reported on its effective use when the comorbid condition of alcohol dependence was treated with disulfiram. There CPT was effective in treating symptoms of PTSD. Recently, we also have incorporated this therapy in an ongoing study of PTSD with comorbid alcohol dependence using CPT combined with pharmacotherapy (zonisamide vs. placebo) (clinical trials website) (see pilot data).

CPT is one of the mainstays of treatment for PTSD, with a large effect size. While this therapy has been used safely in dually diagnosed individuals who have PTSD and comorbid alcohol dependence, Our pilot data also suggests it is also safe and effective in those with comorbid opioid use disorder (OUD), supporting the rationale for a larger clinical trial.

B. Opioid use disorder (OUD) epidemic

The abuse of prescription opioids, including oxycodone, hydrocodone, hydromorphone, morphine, codeine, propoxyphene, and methadone, has emerged as a major public health problem particularly in the United States (US), which represents about 5% of the world's population but consumes 80% of the global opioid supply.[40] Prescriptions for opioid medications have increased dramatically over a 10 year period with

174 million prescriptions dispensed from retail pharmacies nationally in 2000, increasing to 257 million prescriptions by 2009. [41] Abuse or non-medical use of prescription opioids is defined as use without a prescription and/or in a manner other than intended or prescribed, and more than 12 million people reported using prescription opioids non-medically in 2010.[42] Unlike other drugs of abuse, prescription opioid medications are primarily obtained from physicians, friends or family members and/or the Internet, rather than through drug dealers.

Use of prescription opioids is associated with significant morbidity and mortality.[43] Deaths from prescription opioids have dramatically increased over the past 10 years and are now the second leading cause of accidental death in the US[44]. According to data from the Centers for Disease Control and Prevention (CDC), deaths due to prescription opioids went from 1.3 per 100,000 in 1999 to 5.0 per 100,000 in 2008, resulting in 14,800 prescription painkiller deaths in 2008.[6] As expected, exposure to opioids, including days of supply and higher doses of opioids, has been found to increase the risk of abuse and dependence.[45] A task force on prescription opioid non-medical use and abuse was convened by the College for Problems of Drug Dependence (2003). Their report confirms an increase in the incidence of prescription OUD, including survey data and from data collected regarding treatment admissions for drug abuse, based on the Treatment Episode Data Set (TEDS).[46] Many states showed an increase in incidence of 20% or more[46] over a 10 year period.

Opioid prescription drug use has been shown to be a "gateway" to use of other drugs of abuse such as heroin.[47] As awareness of the prescription opioid epidemic increased, availability of prescription opioid medications has decreased and in its wake there has been an alarming increase in heroin use, with devastating morbidity and mortality. The rate of reported heroin use has doubled between 2006-2012[11] and there is a fourfold increase in heroin overdose deaths between 2000 and 2014.[12] [Further, the spike in overdose deaths is also due to a is a proliferation of other deadly drugs such as fentanyl.[48] This has led to a national crisis and as reported in the media, (e.g. The New York Times) and the **current administration recently declared the opioid epidemic an National Emergency.]**

The recent opioid epidemic has had a significant effect on Veterans mirroring the national trends [49] This may be in part due to iatrogenic factors. For example, pain conditions, are common among young Veterans, with report of almost 50% of patients in outpatient VA settings reporting pain primarily due to musculoskeletal injuries.[50] The prevalence of these injuries may be in part due to medical advances, since more military personnel are surviving war related complex injuries, including blast injuries and this results in an increase in the number of Veterans suffering from chronic pain. Treating chronic pain is challenging, as highly addictive prescription opioids have been the mainstay of treatment.[10] The rates of prescribed opioids increased dramatically over a 10-year period (2001-2009) among military personnel, a factor which was found to undermine military readiness.[8] This issue is particularly challenging in Veterans with trauma[51] and those diagnosed with PTSD, as they are more susceptible to developing substance use disorders.[8] Veterans with mental health disorders, notably PTSD, are more likely to be prescribed opioids, more likely to participate in high risk behaviors and more likely to have adverse outcomes.[9]

After the implementation of the Opioid Safety Initiative by the VA in 2013, specifically to alert prescribers to the risk of prescription opioid use particularly in combination with sedative hypnotics, the number of Veterans prescribed opioids has dropped significantly. However, it is estimated that over 50% of Veterans continue to use them: risk factors for continuing use include diagnosis of PTSD.[52, 53] Because this is an evolving issue, good statistics are not available about how many result to heroin use.

The high prevalence of OUD and its frequent comorbidity with PTSD indicates that that treatment of OUD among Veterans is a high priority for the VA, particularly for those individuals with comorbid PTSD. By extension, it also is critical to empirically determine whether a standard PTSD treatment such as CPT will be efficacious in OUD patients.

Chronic Pain is an important clinical issue and frequently co-occurs with PTSD, with high comorbid prevalence in both directions.[54] This relationship may have several etiologies: (1) those that have experienced psychological trauma may also have had physical injuries and (2) there is a well-established link between psychological distress, mental health disorders in general and chronic pain. The link between PTSD and chronic pain is particularly relevant for military Veterans. Research suggests that psychological distress and pain perception are closely related, both cognitively and mechanistically.[55, 56] Reports have yielded high rates of comorbidity between traumatic events such as combat and motor vehicle accidents with amplified pain perceptions related to chronic headache, back pain, and fibromyalgia.[55] This link may explain in part the increased vulnerability of those with PTSD to develop OUD.[28] For example, among Veterans from recent conflicts, the diagnosis of PTSD is associated with high-risk opioid use.[9]

PTSD and chronic pain are frequently comorbid, and given the high comorbidity and the link between psychological distress and pain tolerance, the measurement of pain tolerance as related to possible improvement in symptoms of PTSD would be of clinical interest/importance. In addition, any potential relationship between PTSD symptoms and chronic pain and its functional impairment would be relevant to explore.

Buprenorphine, a derivative of the opiate alkaloid thebaine, is a partial μ-opioid agonist and a weak k-opioid antagonist.[57] In clinically used doses, buprenorphine effects are similar to low doses of the full μ-opioid agonist like morphine or methadone. However, the effects of buprenorphine plateau, and it acts like an opioid antagonist of higher dose effects. This "ceiling" effect of buprenorphine blocks the effects of higher opioids and decreases the risk of overdose even at high intravenous doses and limits the abuse liability of buprenorphine itself.[57] In addition, its slow dissociation from the opioid receptors allows flexible dosing ranging from several times a day to three times per week. It should be noted that agonist properties of buprenorphine result in full analgesic efficacy as shown in multiple clinical trials (reviewed in Raffa et al, 2014).[58]

Buprenorphine, formulated as a sublingual tablet or film, is available alone or in a combination tablet containing buprenorphine and naloxone (**BUP/NLX**) in a ratio of 4:1. Since naloxone is poorly absorbed when taken orally or sublingually, naloxone effects are negligible when the medication is taken as directed. However, injection of this combination in dependent individuals would precipitate opioid withdrawal symptoms due to naloxone effects, and thereby deters the diversion of this product to injection drug use. A large number of studies have demonstrated the efficacy of buprenorphine as an agonist treatment in opioid dependent individuals and those who are addicted to prescription opioids.[59, 60] Office based opioid substitution therapy is standard of care within the VA.[14] In recognition of the importance of using opioid substitution therapy in Veterans with OUD, the Fiscal Year (FY) 15 VA performance measures include utilization of opioid substitution therapy (percent of patients with OUD receiving opioid substitution therapy) as a measure within the population coverage composite. *As more Veterans are prescribed buprenorphine in the VA nationally, the efficacy of treatments in this population will be of increasing clinical importance.*

C. Significance

Conducting studies in populations with "multi-morbidities" is increasingly recognized as an important area of study within the field of medicine in general and psychiatry in particular. This concept challenges the single disease framework used throughout medicine in education, reimbursement, and research [61]. The co-occurrence of comorbid conditions is not simply additive, as the presence of one disorder can complicate the other. Rather, the influence of each disorder is bi-directional creating a loop that leads to worsening of symptoms in both conditions over time. For example, symptoms of PTSD can lead to ongoing opioid use and relapse, while opioid withdrawal symptoms can precipitate and mimic symptoms of PTSD; more severe symptoms of PTSD are associated with higher risk for opioid dependence. (reviewed in Fareed et al)[28]

Although there is recognition that individuals with comorbidity have special treatment needs, several aspects of treatment remain controversial. For example, are trauma- focused treatments effective for individuals in early recovery? Does[62] treatment of PTSD lead to improvements in substance use outcomes? Is substance abuse treatment alone adequate in early recovery and does it lead to improvement in PTSD symptoms?

The growing literature on treatments of comorbidity suggests that trauma-focused interventions can be safely administered in individuals with comorbidity and, in general, are associated with better PTSD outcomes than the comparison conditions.[63] Improvement in symptoms of PTSD is associated with improvement in substance use outcomes, while the opposite relationship is not always true [64], From laboratory studies, it has been shown that substance use can be cued by strong emotions and trauma cues are more potent than other stressors in inducing craving in the laboratory[65]-suggesting that inadequate treatment of PTSD can lead to relapse. Our own pilot data shows that among those with OUD, trauma-focused interventions lead to better substance abuse outcomes that substance abuse treatment alone.]

Despite this growing literature, there is a gap in the published research regarding opioid use disorder and comorbid PTSD.[28] There is some evidence that treatment with buprenorphine among those with PTSD leads to an overall improvement in treatment outcomes[28] and an observational study suggests buprenorphine treatment is associated with improvement in PTSD symptoms compared to a control group prescribed high dose opioid therapy.[66] Despite these advances, there are no studies evaluating the combination of opioid substitution therapy with a PTSD evidence-based treatment. This has been identified as an important area of study[28] that the proposed research is intended to address.

Studying an evidence based psychotherapy for co-occurring PTSD among those with comorbid OUD has substantial significance and great clinical relevance. To apply an intervention to a new vulnerable clinical population has a potential to change clinical practice. Most importantly, this study has the potential to fill knowledge gaps and challenge the VA to improve healthcare delivery based on scientific evidence.

We would like to underscore that while we hypothesize that CPT will be safe and effective for Veterans with PTSD and OUD, we believe that we cannot assume this to be true. There is a body of literature that suggests that treatments developed for a single condition, such as PTSD, are not equally effective when used in individuals with comorbidity. For example, medications to treat PTSD including the FDA-approved antidepressant, sertraline and the alpha adrenergic medication prazosin [which are recommended by the VA/DoD practice guidelines [67] for sleep disturbances associated with PTSD] are *not equally effective* when used among individuals with comorbid alcohol use disorders.[68-71] Without well-designed clinical trials conducted in comorbid groups, assumptions about efficacy would have been mistaken. *Particularly with behavioral therapies,* there is controversy regarding the use of evidence-based psychotherapy in individuals with comorbid substance use disorders for fear of precipitating relapse.[62] Studies among those with opioid use disorders maintained on buprenorphine are therefore important. *Clinical trials are needed to show efficacy and safety*.

1. ***Potential benefits of research to subjects and others****:* Potential benefits of participation in this study may include a reduction in PTSD symptoms. However, there is no guarantee or promise that participants will receive any benefit from participation in this study.
2. ***Importance of knowledge to be gained****:* Since 11 September 2001, more than 1.5 million Service Members have deployed more than 2 million times in support of combat operations in Afghanistan and Iraq. One of the signature injuries from these operations is PTSD. Various reports of the post-deployment health-related needs estimated that 20% of Veterans returning from deployment will have symptoms of PTSD or related behavioral health conditions. In addition, the prescription opioid epidemic has seriously affected Veterans, and Veterans with PTSD are more likely to abuse opioids and to have high-risk behaviors. Nevertheless, treating comorbid PTSD and OUD has not been systematically tested. This study proposes to test an evidence based psychotherapy for PTSD vs. individual drug counseling in Veterans with PTSD OUD, working towards characterizing effective, evidence-based interventions for this at-risk group. The plans for monitoring risk as described above warrant the conduct of this study for the knowledge that may reasonably be expected to result.

D. Preliminary studies

(1) Clinical Trials in Veterans with PTSD and Comorbid Alcohol Dependence: Our group has conducted several clinical trials in Veterans with PTSD and comorbid alcohol dependence. These studies are randomized, multi-site, outpatient clinical trials evaluating (a) medications to treat alcoholism in a comorbid group of patients [72]; (b) a comparison of 2 different antidepressants in patients with PTSD and comorbid alcohol dependence [69] and (c) a recently completed study of prazosin for dually diagnosed Veterans with PTSD [71].

(2) Use of CPT for Veterans with PTSD and comorbid alcohol dependence:

(a) Pilot study of CPT in Veterans with PTSD and comorbid alcohol dependence.[73]

CPT is a mainstay of treatment for PTSD, but Veterans with comorbid alcohol dependence are excluded from participation. Our group piloted CPT treatment, incorporating sessions addressing alcohol consumption as a symptom of PTSD (eg. challenging beliefs, patterns of problematic thinking worksheets to be completed on alcohol use) and role of drinking throughout treatment. CPT was tested in a pilot study of (n=5) male Veterans diagnosed with PTSD and comorbid alcohol dependence. CPT was administered by a trained psychologist for 12 weeks and PTSD symptoms were assessed using the CAPS (Clinician Administered PTSD Scale) every 2 weeks while daily drinking data was assessed using the TLFB (Timeline Follow-back Method).

Results: Therapy participation was excellent, with an average of 9.4 (out of 12) sessions attended. PTSD symptoms (see Figure 1) significantly decreased with treatment. Alcohol use (see Figure 2 and Figure 3) measured as total number of standard drinks and percent of heavy drinking days also decreased during treatment.

Figure 1: Total CAPS scores over time across participants

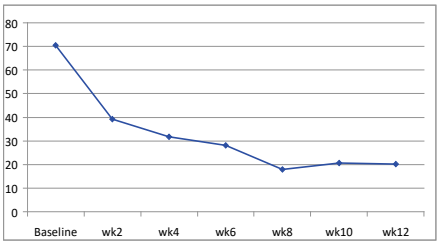


Figure 2: Total number of standard drinks before and after treatment

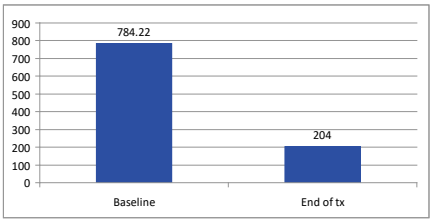
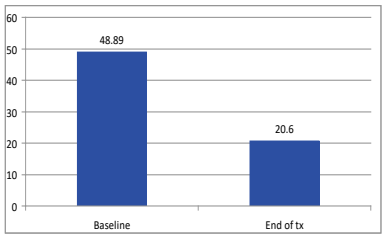


Figure 3: Percent heavy drinking days before and after treatment

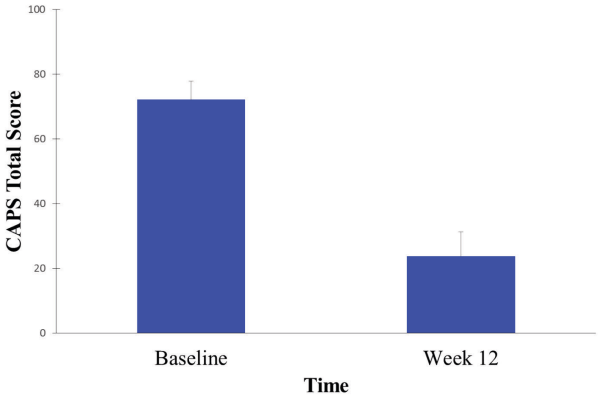


(b.) Report on the Use of Cognitive Processing Therapy, Enhanced to Address Alcohol Use. [74]

This case report described the 12-week course of CPT treatment which also addressed heavy alcohol use in a Veteran with PTSD and comorbid alcohol dependence. During the therapy sessions, he became more aware of the negative consequences of his heavy alcohol use. In week 9 of the therapy, the patient requested and began disulfiram therapy to help him abstain from alcohol use. His alcohol use dramatically decreased, and his symptoms of PTSD continued to abate with the therapy. This study supports an integrated treatment model for PTSD and heavy alcohol use and suggests the combination of CPT and pharmacotherapy can be used effectively.

(c.) Zonisamide in Addition to Cognitive Processing Therapy (CPT) for Veterans with PTSD and Comorbid Alcohol Dependence (pilot study)

In this pilot study, the anticonvulsant zonisamide was tested as an augmentation of CPT therapy, in Veterans with PTSD and comorbid alcohol dependence. Veterans with current PTSD and current alcohol dependence were recruited. All participants (n=24) received CPT; participants were also randomized to receive zonisamide or placebo (3:1 ratio). Overall, CPT was very well tolerated among these dually diagnosed subjects and subjects showed a decrease in symptoms of PTSD from baseline to end of treatment (see figure below). Zonisamide treatment was associated with reduced number of drinking days compared to placebo (see below), increased rates of abstinence (78% vs 50%) and a greater reduction in craving.



These studies demonstrate our group's extensive experience in: a) the methodology proposed, b) our ability to recruit, and c) safely and effectively conducting studies in Veterans with PTSD and comorbid substance use disorders. Further, it demonstrates our experience in conducting studies using standardized psychotherapy, notably CPT in individuals with comorbid disorders *and* in conjunction with pharmacotherapy. Finally, these studies highlight the importance and feasibility of conducting clinical trials in "real world" patients, as treatment efficacy may vary based on comorbid conditions.

(3) Experience with Buprenorphine:

(a) Setting up a Buprenorphine Clinic: One year Later: The Principal Investigator (PI) developed and set up the buprenorphine clinic as a Mental Illness Research, Education, and Clinical Center (MIRECC) clinical project in 2004; [the clinic is now well developed and has 166 Veterans. VA Connecticut, at Newington, also has a robust clinical program, with another 115 Veterans. MD investigators involved in this project (Petrakis, Arias, and Yoon) and other study physicians (Dr. Belinda LeBlanc) have the ability (DEA X-license) to prescribe buprenorphine, as well as extensive experience with this patient population.] The PI has authored several articles considering clinical issues that have arisen since the inception of the clinic.

(b) Buprenorphine/Naloxone treatment for prescription opiate dependence (not currently recruiting): A study was initiated to evaluate whether low vs. high dose of buprenorphine was more effective in treating Veterans with prescription opioid dependence entering buprenorphine treatment. Following seven days of buprenorphine induction, n=10 Veterans with OUD were randomized in an open label fashion to low dose (LD)

(<8mg) vs high dose (HD) (>16 mg) of buprenorphine. There was a higher dropout rate in the LD group (3/5, 60%) vs the HD group (1/4, 25%) (one participant was never randomized). Three of the drop-outs (2 in the LD group and 1 in the HD group) were lost to follow up, and one dropped out because the low dose was not effective. It is important to note that 4 out of 10 participants (40%) also had a diagnosis of PTSD in this sample. Results suggest patients prefer higher doses of buprenorphine.

Investigators in this study have had extensive clinical experience with buprenorphine (Petrakis, Arias, Yoon) and Dr. Sofuolgu have had research experience in conducting clinical trials in individuals maintained on buprenorphine.

(4) Use of CPT for Veterans with PTSD and comorbid Opioid Use Disorder (OUD):

This retrospective chart review evaluated the feasibility and outcome of Veterans admitted to the examined all Buprenorphine Clinic at VA CT in West Haven to evaluate feasibility and outcomes for those with comorbid PTSD. In this study, all new buprenorphine clinic admissions between January 2016-December 2016 were identified via the electronic consult (n=103) Of those, 4 were not examined (n= 2 had a restricted record, n=2 were deceased). The remaining 99 records were evaluated for rates of comorbid PTSD, rates of referral to trauma focused treatment and retention in buprenorphine clinic after 3 months. PTSD diagnosis was evaluated using the problem list in the electronic medical record or service connection status.

Results: Of the 99 records examined, 46 (46.5%) had the diagnosis of PTSD. Most of the Veterans were male (94.9%), with an average age of 45.3 years and majority were Caucasian (78.8%); approximately half (52.5% were single/never married. Of those with PTSD, 10 (21.5%) were referred to trauma focused treatment: of those 4 were referred to CPT, 1 was referred to Prolonged Exposure (PE), and the rest received unspecified trauma-focused therapy. Of those who received trauma-focused treatment, 4/5 (80%) completed 12 sessions. Retention at 3 months was ***significantly different*** *between groups*: of those referred to trauma focused therapy *10/10 (100%) were retained in treatment compared to 11/36 (30.5%)* (p<.05) of those without referral to trauma focused therapy (See Fig 1). As a comparator, among those without PTSD (n=53) 28 were retained in treatment (52.8%). While PCL scores are not available in all cases, the *n*=5 who participated in the EBP had PCL scores documented in the record. *The average PCL score= 61.4 (range 53-68) at the beginning of therapy* ***was significantly reduced*** *to PCL= 29.2 (range 10-48) (p<.05) at the end of the 12-session intervention*. (See Fig 2)]

Figure 1

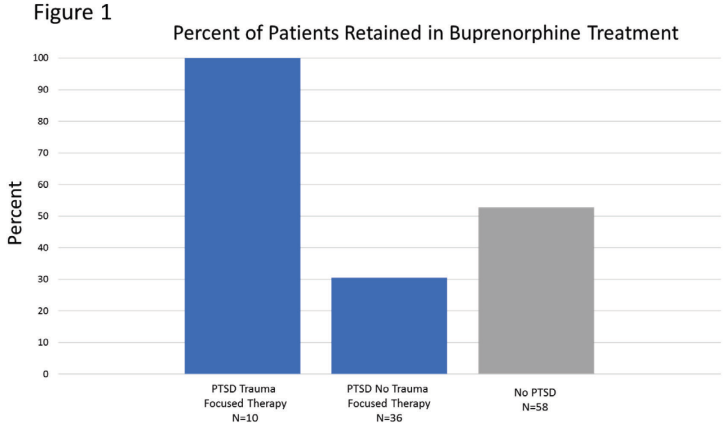
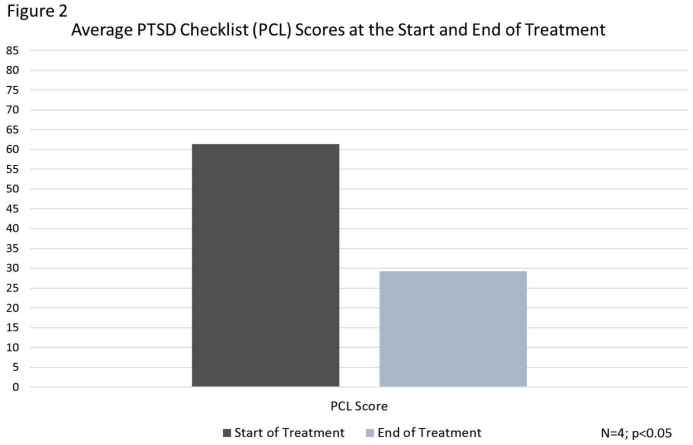


Figure 2



These studies demonstrate our group's extensive experience in the methodology proposed and our ability to recruit and safely and effectively conduct pharmacologic studies in Veterans with PTSD and comorbid substance use disorders. Further, it demonstrates our experience in conducting studies using standardized psychotherapy, notably CPT in individuals with comorbid disorders <u>and</u> in conjunction with pharmacotherapy.

6. RESEARCH PLAN

Research design and methods

Overview: We propose to conduct a randomized, controlled trial with 160 (assuming a 30% drop out rate, for 120 participants) Veterans and civilians diagnosed with PTSD and comorbid OUD. This study will use *open*

randomization to 2 groups: (a) buprenorphine + CPT vs. (b) *buprenorphine + IDC*. All subjects will be maintained on buprenorphine and the standard clinical treatment. Participants will be recruited primarily through the clinical facilities at the VA and from other collaborators.

The Bedford VAMC has been added as an additional enrollment site for this study. The principal investigator for the Bedford site is Megan Kelly, PhD and the study will be overseen by the Bedford VA IRB has gained local IRB approval.

Experimental subjects: Veterans and civilians (n=160) aged 18- 65 years old, with a current diagnosis of PTSD and opioid use disorder (OUD) will be enrolled at 2 sites (VA Connecticut Healthcare System, Bedford VAMC) for a study with 12-weeks of active treatment. Participants will be recruited from four main sources: 1) from the PTSD clinic patients at the local VAs , 2) from the group of Veterans entering treatment for opioid use disorders at the local VA Substance Abuse Treatment Programs and 3) advertisement (flyers, posters, Craigslist) 4. Community clinics. Under a HIPAA waiver, IRB-approved letters of invitation can be mailed to prospective participants with a past diagnosis of OUD or PTSD who otherwise might meet eligibility criteria. Outreach will also be conducted at local Veteran Centers, where staff from both VAs consult. The PTSD staff has also been involved in outreach to the community for returning OIF/OEF Veterans. Each participant will be carefully screened and assessed using the following inclusion and exclusion criteria:

Inclusion Criteria:
1) Male and female Veterans and civilians between the ages of 18-70 years old.
2) Current diagnosis of PTSD as determined by an independent evaluator assessment using CAPS-5.
3) Opioid Use Disorder diagnosed by Mini International Neuropsychiatric Interview for DSM-5 (MINI). To meet entry criteria for buprenorphine treatment, will also have documented prior treatment for opioid use disorder, history of opioid withdrawal or signs of opiate withdrawal as evidenced by a Clinical Opiate Withdrawal Scale (COWS) score of 7 or greater, and a positive urine toxicology for opioids.
4) For women, negative pregnancy test and use of acceptable method of contraception.

Please note, because of the high incidence of depression that co-occurs with PTSD, those individuals with comorbid depressive disorders will be allowed into the study. This is in keeping with the purpose of this study to evaluate the effectiveness of a CPT in a "real world" clinical population. It also is anticipated that a significant proportion of Veterans and civilians will likely be treated with concurrent antidepressant pharmacotherapy [and/or with other medications (eg. prazosin).]However, again this enhances the "real world" application of treatments within the VA system, and secondly it is common to allow antidepressant medication in psychotherapy trials and still be able to show benefit with CPT.[37] For those who are already prescribed antidepressant medication, they will be continued on their current pharmacologic treatment Please note that since not all subjects will be on psychotropic medications, randomization will be stratified by presence of concurrent medications-a strategy we have used successfully in other comorbidity studies with PTSD[71]

Exclusion Criteria:
1) Females who are pregnant or lactating.
2) Veterans and civilians with a current unstable medical condition such as neurological, cardiovascular, endocrine, renal, liver, or thyroid pathology (e.g. abnormal BUN and creatinine, and unmanaged hypertension with BP > 200/120) which in the opinion of the physician would preclude the patient from fully cooperating or be of potential harm during the course of the study.
3) Veterans and civilians who meet current criteria for the following diagnoses (schizophrenia and schizophrenia spectrum and psychotic disorders) as determined by the MINI.
4) Veterans and civilians who have significant current suicidal or homicidal risks necessitating a higher level of care.
5) Those with known allergy or intolerance to buprenorphine.

Methods:
Overview: This study is a 14-week, RCT with open-label randomization to 2 groups (described in detail below): (a) buprenorphine (BUP) + CPT vs. (b) BUP + IDC. This study will be conducted in 3 Phases: Phase I:

buprenorphine induction and stablization for all participants (x1 week). Participants will be started at a dose of 2mg/0.5 mg BUP/NLX and this dose will be increased as needed for stabilization of opioid withdrawal symptoms up to 32 mg per day, which is standard practice. Phase II: randomization to CPT vs. *IDC* (x12 weeks). *CPT will be provided by one of our licensed therapists trained and who has been trained and certified in the standard VA rollout.* The therapists will have weekly case consultation from a qualified CPT consultant. *IDC will be provided by research staff under the supervision of Dr. Martino. All of the sessions will be recorded for supervision purposes and for the independent fidelity raters to assess 20% of the sessions for adherence and competence.* [*Phase III: Subjects wil be referred to one of the buprenorphine clinics (West Haven or Newington) and will be referred for ongoing treatment for PTSD if they choose, including the option for CPT for those who did not receive this during the study.]

Participants will be seen on a daily basis (excluding weekends) for the initial 5-7 day induction. Once subjects are on maintenance dose of BUP/NLX (goal is within 5 days), they will be seen weekly by study RN for the first 4 weeks, biweekly for a month then monthly for symptom evaluation, and medication refill.

[At study end, participants will be referred to a buprenorphine clinic. *Buprenorphine treatment is the standard treatment for OUD, and subjects who discontinue are at high risk for relapse.*]

** Due to COVID-19 precautions it may not be possible to record CPT/IDC sessions especially those conducted via telephone or telemedicine.*

Main Outcome Measures: Symptoms of PTSD using the CAPS-5 and PCL-5. Frequency of opioid use using the TLFB and confirmed by urine toxicology. Other outcomes will include treatment retention measured by days in treatment and functioning using the VR-12. Functional impairment related to pain will be measured during the trial. Follow-up will be conducted at 1 and 3 months after end of the study to evaluate the durability of treatment effects on drug use and psychosocial outcomes.

To fully assess and appreciate complex symptomatology in this patient population, assessments were selected to have both relevance to our study of PTSD and comorbid OUD. Assessments will be done by an Independent Evaluator (IE) blind to treatment group.

Screening: After signing informed consent*, participants will undergo screening. Screening will be done by members of the research team (i.e., research assistant, nurse, clinician) and will take about 3-4 hours. In order to qualify for participation, individuals will complete the following: (1) Subjects will be personally interviewed with the CAPS-5 (diagnosis of PTSD) and MINI. The MINI is a widely used structured psychiatric diagnostic instrument. (2) Frequency of opioid use will be assessed using the TLFB method[75] and confirmed with urine toxicology results. (3) PTSD symptoms will be assessed using the CAPS-5 and PCL-5.

Non-veterans who do not already have a medical record at the VA will have a medical record created for them, following VA guidelines, in order to order study relevant laboratory assessments, medications, and to document consent and study procedures. Non-veterans will be provided with a copy of the VHA Notice of Privacy Practices and asked to sign the corresponding acknowledgement form.

***In order to reduce face-to-face interactions during COVID-19 potential participants will be given the option to complete a portion of the screening procedures remotely using a VA approved video platform (or by telephone when video is not feasible). If the psychological screening is conducted remotely, the participant will be mailed/emailed a blank consent form and an informed consent process with study staff will then take place either over the phone or via VA-approved video platform. We will go over the consent form in detail with the participants. We will obtain their verbal consent, which we will record in CPRS. Consents that are mailed will be sent using US Mail (USPS/UPS/FedEx). Consents that are e-mailed will be encrypted using a VA approved encryption platform (e.g. Azure Rights Management, My HealtheVet).**

<u>A fully signed consent and HIPAA will then be obtained prior to randomization should they still be interested and eligible to continue in the study.</u> We will accept the following forms of signed consent and HIPAA: a) signed in person; b) signed at home and mailed back to the research team using a pre-addressed envelope; c) signed at home and the patient will take a photo of the consent and HIPAA pages and email the images to a member of the research team (or use My HealtheVet); or d) signed at home during a video visit where we will ask the patient to hold

each consent and HIPAA page up to the camera and we will take a screenshot of the pages (ensuring the patient's face is not in view) and print and file the screenshots in the patient's research record.

Standard Treatment for all Participants:

Buprenorphine*:* Buprenorphine will be prescribed for *all subjects*. Buprenorphine is available alone or in combination tablet containing buprenorphine and naloxone in a ratio of 4:1 or in an injectable form. In this study, a combination tablet is preferred, since it is less likely to be diverted than the buprenorphine only formulation, however if an injectable formulation of buprenorphine is prescribed, the participant can continue on that medication. Consistent with the clinical guidelines, before BUP/NLX is administered, participants will be instructed not to use any prescription opioids for 24 hours and be prepared to stay in the clinic for at least 2 hours following the first dose of BUP/NLX. [During induction into buprenorphine, all participants will be started at a dose of 2mg, and this dose will be increased as needed (up to 32mg per day) for stabilization of opioid withdrawal symptoms *within about a 5-7-day period, which is standard practice.* Participants will be seen on a daily basis (excluding weekends) for the initial 5-7-day induction. Once subjects are on maintenance dose of BUP/NLX, they will be seen weekly by study RN for the first 4 weeks, biweekly for a month then monthly for *Medical Management*, symptom evaluation, and medication refill. *+ At the end of the active study, participants will be referred to a buprenorphine clinic.]

** Due to COVID-19 we are reducing the frequency of in-person visits. During this time, patients will be seen in the research clinic by the study RN on a monthly basis. All other regularly scheduled visits will still occur (as outlined in Table 1) but they will be telemedicine visits using VA approved platforms (e.g. VA Video Connect or VVC) or telephone if a video platform is not feasible. In order to maintain continuity of care, patients may opt to have their BUP/NLX prescribed by their regular provider (instead of the study physicians) and dispensed via the VA Pharmacy rather than the VA Research Pharmacy. This decision will be communicated with the patient's provider by the research team.*

+ Subjects will be allowed to receive their medications according to their clinic dosing schedule (weekly, monthly, daily) and can change based on the clinical judgement of the provider.

Any participants already taking Buprenorphine will skip the induction phase and continue with their prescribed dose dispensed through the research pharmacy while enrolled in this study. For participants receiving daily Buprenorphine through the Methadone clinic, they will continue to receive their medication from there. Any participants who cannot tolerate BUP/NLX and are on standalone Buprenorphine will continue to receive their medication directly from their VA provider.

Buprenorphine is a Schedule III drug that, in community settings, is often prescribed for up to a one month's supply at a time. Patients are generally seen on a weekly or monthly basis like those treated with other psychiatric medications. Buprenorphine will be delivered by the research pharmacy on the day of the participant's weekly, biweekly, or monthly appointment, and will be returned to the research pharmacy should the subject fail to present for the appointment. Buprenorphine treatment is generally well tolerated. Its side effects, such as abdominal pain, constipation, nausea, vomiting, headache and sweating, are similar to other opioids. Increases in liver enzymes and hepatitis are rarely reported. Participants will be educated to keep their medication in a safe place to prevent unintentional exposure to others, especially children.

Medical Management*:* Medical Management (MM) will be provided for all patients in the study. It is a behavioral intervention designed for patients with substance dependence, and is particularly well suited to a medication clinical trial [76]. The objective of MM is to focus on medication compliance and symptom reduction. In this study MM will be provided by a trained registered nurse and will be conducted at each visit. The initial visit will be 40-60 minutes and the focus will be on educating the patient on medication regiment and compliance; other health issue such as negative consequences of drug use, may also be discussed. Consecutive sessions will be 15-20 minutes and will be focused on monitoring of compliance with the medication and psychoeducation. This intervention was chosen because of MM's focus on medical issues which

makes it highly compatible with a pharmacologic intervention. Our group has extensive experience with MM in a comorbid group of patients.

Medication Compliance: We employ a number of strategies to ensure maximum compliance with the medication regimen. All medications will be dispensed in clearly labeled prescription vials. Before each visit each patient will receive a reminder phone call about his/her appointment and is also reminded to return the bottle with the study medication regardless of whether any medication is left over. At the beginning of each study visit the left-over medication will be counted, and the patient will be prompted to report any doubling of dose or missing days of study medication. If the visit is completed via video, the patient will be asked to count the medication "in front" of the research staff member. If the visit is completed by telephone (without a video option), the patient will be asked to count the remaining study medication and report this to the staff member conducting the visit; accountability will be conducted during the monthly in-person visits. Since BUP/NLX is a controlled substance, study staff will instruct the participant on how to properly dispose of any leftover medication, in a manner that is compliant with VA policy (e.g. take back envelopes, flushing down the sink/toilet, or by placing in CS waste disposal bins while being observed by VA staff). The session will also provide an opportunity for subjects to review critical issues and problem areas, the subjects' involvement in any ancillary treatments, and other clinically significant events. Other formal treatment concurrent with their study treatment (including self-help meetings) will be monitored.

All medications (buprenorphine) will be prescribed by the study physicians or individuals' current physician. Participants will be seen weekly by research staff for the first four weeks then biweekly for 1 month, and then monthly. There will be close monitoring for psychiatric symptoms in the study, as well as safety monitoring through Adverse Events (AE) reporting (see Human Subjects section), we believe this will provide a reasonable level of protection for a control group for this trial.

Experimental Treatments: Subjects will be randomized to (1) CPT or (2) IDC.

Cognitive Processing Therapy (CPT): CPT is a manualized, 12-session 1:1 cognitive therapy that has been designed for patients with PTSD [76]. In this study the sessions will be conducted weekly. The stated goal of CPT is "to assist the client in refraining from assimilating (distorting the event to fit prior beliefs) and in accommodating schemas to the new information without over-accommodating".[77] CPT uses Socratic questioning targeting distorted cognitions such as self-blame, hindsight bias, and other guilt cognitions. CPT is focused on the cognitive components of the therapy without exposure. Therapy will be provided by psychologists who either have been or will be trained in conventional CPT through the VA rollout initiative. [Dr. Meshberg-Cohen will be responsible for coordinating therapy and therapists will have weekly case consultation/supervision from a qualified CPT consultant (Dr. Greer Richardson, who is a national CPT trainer and supervisor).]

Individual Drug Counseling (IDC): IDC will serve as the control group. The current standard of treatment for individuals entering buprenorphine maintenance is to do drug counseling. In most VA settings, including VA Connecticut Healthcare System, psychiatric symptoms (such as PTSD) are evaluated but psychiatric treatment is often deferred until the individual demonstrates a commitment to treatment and demonstrates abstinence. Standard counseling is the primary means to achieve these goals. IDC uses a semi-structured, time-limited addictions-counseling model in a 1:1 setting. The main focus is on helping individuals achieve and maintain abstinence by encouraging behavioral changes, such as avoiding triggers, structuring one's life, and engaging in healthy behaviors (e.g., exercise). The IDC manual provides an organized, concise version of what is currently practiced by most addiction counselors. In operationalizing this approach, the developers drew from their own clinical experience and that of expert drug counselors in the field The approach is consistent with the 12-step approach that regards recovery as a gradual process, and participation in self-help groups such as Alcoholics Anonymous or Narcotics Anonymous is strongly encouraged. IDC will be conducted by study personnel and supervised by Dr. Martino on a weekly basis.[78]

Initial certification for CPT and IDC will be defined as at least adequate or average adherence and competence ratings on the respective CPT and IDC consistent techniques on six consecutive practice sessions. After certification, the therapists will begin seeing participants in the trial. The CPT and IDC supervisors will rate one audio recorded session each week, rotating among study therapists, and discuss feedback in weekly supervision. If this ongoing review determines that a therapist drifts below the initial certification level, then the therapist will be provided additional supervision and training to assure adequate delivery of their assigned treatment.

Fidelity to ratings:

To assure the study therapies are delivered in a manner consistent with manual guidelines, all CPT and IDC sessions will be audio recorded* and selected sessions (3 randomly selected sessions from each participant) will be evaluated by raters, who are blind to type of treatment received, using the Yale Adherence and Competence Scale (YACS) rating system developed for assessing therapist adherence and competence in previous trials.[79-81] The YACS consists of a series of Likert-type items utilizing key unique components of specific therapies (e.g., Cognitive Behavioral Therapy, Motivational Interviewing, CPT, Twelve Step Facilitation, contingency management, clinical management) as well as a series of scales utilizing common factors in general drug counseling (e.g., assessment of substance use and functioning, facilitative conditions). For each item, raters are asked to rate the degree to which the therapist used that particular intervention in the session (adherence), as well as how skillfully the therapist implemented the intervention (skillfulness). The YACS measure used in our proposed study will focus on items specific to CPT and IDC, allowing for a test of discrimination between the delivery of the two distinct treatments. The YACS has very good psychometric properties, with coefficient alpha for the treatment scales in the .80-.95 range, indicating a high degree of internal consistency, and ICC's (intraclass correlation coefficients) for the adherence and competence scales ranging from .75 to .90. Dr. Martino has extensive experience training YACS raters to perform very reliable session process ratings.

** Due to COVID-19 precautions it may not be possible to record CPT/IDC sessions especially those conducted via telephone or telemedicine.*

Study Assessments:

Table 1: Summary of Study Assessments

Assessments	Baseline	1	2*	3*	4	5	6*	7	8	9	10	11	12	Follow Up 1 and 3 months*
CAPS	X								X				X	X
PCL-5	X	X	X	X	X		X		X				X	X
MINI	X													
TLFB	X	X	X	X	X		X		X				X	X
DRRI-2	X													
Demographics	X													
COWS	X													
Blood Pressure/Pulse**	X	X	X	X	X		X		X				X	X
Urine Toxicology**	X	X	X	X	X		X		X				X	X
Pregnancy test (females)	X				X				X				X	
PHQ-9	X	X	X	X	X		X		X				X	X
ISI	X		X	X	X		X		X				X	X
VR-12	X												X	X
C-SSRS	X	X	X	X	X		X		X				X	X
AE (SAFTEE)	X	X	X	X	X		X		X				X	X
NRS for pain intensity	X				X				X				X	
PROMIS–29	X				X				X				X	
LEC-5	X													
CTQ	X													
Cannabis Use History	X													
Synthetic Cannabinoids Use History	X													

Note: Study visits occur weekly for 4 weeks, then biweekly, then monthly. Study assessments collected weekly are self-assessments and can be distributed and collected by the therapist conducting the therapy.

* In order to reduce the number of in-person visits weeks 2, 3, 6, and the two follow-ups (months 1 and 3) will be conducted via telephone or telemedicine.

** Due to COVID-19, blood pressure/pulse and urine toxicology will not be collected unless the visit is done in person.

COVID-19 Safety Precautions:

1. Adhere to local VA policies or mandates (ie., wearing cloth face coverings, COVID-19 screening at the main entrance, temperature checks, etc).
2. A study staff member will call participants the day before their scheduled visit and ask the COVID-19 screening questions; anyone who screens positive for COVID-19 (exposure or symptoms) will be rescheduled.
3. Staff members will sanitize high-touch surfaces before and after each in-person visit with approved disinfectant.
4. Staff members will wear protective facial masks, participate in frequent handwashing, and/or use alcohol-based hand sanitizer, and practice social distancing.
5. Only one participant will be scheduled for an in person visit at a time and visits will take place in a large enough space so that study staff and the participant can practice social distancing.
6. Contact information will be updated at each visit in the event that contact tracing needs to occur.
7. We will minimize the frequency and duration of study visits in the following ways:
    a. Attempt to schedule study visits on the same day as another clinic visit the patient has scheduled.
    b. As much as possible, self-assessment forms should be completed via telephone or telemedicine and can be given directly or mailed to the participant in advance of any appointment. If the patient desires to complete in-person visit forms on site, staff will honor that request while maintaining social distancing.
    c. Study therapy sessions (CPT or IDC) will be allowed to be conducted as telemedicine visits using VA approved platforms (e.g. VA Video Connect or VVC). If a video option is not possible, therapy can be conducted over the phone or in person (patient's choice).
    d. Scheduled in-person visits at weeks 2, 3, 6, and the two follow-up visits (months 1 and 3) will now be conducted by telephone or telemedicine.

(a) **Clinician Administered PTSD Scale (CAPS-5)** will be used to diagnose PTSD and to obtain data [(pre and post treatment, follow-up)] on the frequency and severity of PTSD symptoms. The CAPS-5 is a structured diagnostic interview for DSM-5 diagnosis and the gold standard for assessing PTSD. It has excellent psychometric properties and diagnostic efficiency.[82] The CAPS for DSM-5[83] uses only a single 5-point ordinal rating scale to measure symptom severity. CAPS-5 scores range from 0 to 80 with higher scores indicating greater PTSD symptom severity. The CAPS-5 was revised with an eye towards maintaining backwards compatibility with the DSM-IV version of the instrument.

(b) **PCL-5** will be used to collect information on PTSD symptoms. The PTSD Checklist for DSM-5 [83] is similar in form to the PTSD Checklist (PCL) based on the DSM-IV.[84] The PCL-IV has excellent psychometric characteristics. The PCL-5 is a 20-item self-report measure, selected for its dimensional sensitivity, with higher scores reflecting greater PTSD severity. Scoring is based on how much the patient has been bothered by the symptoms on a scale from "0 = not at all" to "4 = extremely." PCL scores will be collected based upon symptoms experienced in the past month at baseline, but since the last visit, during the weekly assessments.

(c) The **MINI International Neuropsychiatric Interview for DSM-5 (MINI)** will be used for diagnosing other possible psychiatric disorders. The MINI is a widely used structured diagnostic instrument designed for evaluating major AXIS I disorders and is a standard assessment in OUD clinical trials. Our group has extensive experience using the MINI with high degree of inter-rater agreement. Note: Sections B, L, M, and MB will be omitted as these are assessed by other measures (section B: Suicidality assessed by the C-SSRS) or do not impact study inclusion/exclusion (sections L, M, and MB which assess eating disorders).

(d) Calendar-based interviews using the **Timeline Follow-Back (TLFB)** method [75] will document the frequency of opioid use for the month prior to and during the 12 weeks of treatment. The TLFB will also be used to document the frequency of use of other substances (i.e.; alcohol).

(e) The **Deployment Risk and Resiliency Inventory-2 (DRRI-2)** will be used to determine war zone exposure. The DRRI-2[86] is a suite of 17 individual scales that assess key deployment-related risk and resilience factors with demonstrated implications for Veterans' long-term health. The following subscales will be used to assess deployment factors: Combat Experiences, Aftermath of Battle, and Unit Social Support. We will use the post-deployment stressors and social support scales to evaluate post-deployment factors (for service members and Veterans).

(f) Basic demographic characteristics will be collected using the **Demographics and Military Service Characteristics Form**. The Demographics and Military Service Characteristics Form measures standard demographics (race, gender, age) and military service information (e.g., rank).

(g) **Clinical Opiate Withdrawal Scale (COWS)** will be used to determine if an individual has opioid withdrawal symptoms prior to treatment with buprenorphine.[87]

(h) The **Patient Health Questionnaire-9 (PHQ-9)** will be used to measure depressive symptoms; [these will be collected weekly.] The PHQ-9 is a widely used and well-validated instrument for measuring the severity of depressive symptoms.[88] It consists of 9 items that assess both affective and somatic symptoms related to depression and depressive disorders; these 9 items correspond to the diagnostic criteria for DSM Major Depressive Disorder (MDD). Respondents rate the frequency with which they have been bothered by depressive symptoms within the past two weeks on a scale ranging from 0 ("not at all") to 3 ("nearly every day"). Scores on all items are summed to obtain a total severity score. Scores reflect no significant depressive symptoms (0-4), mild depressive symptoms (5-9), moderate depressive symptoms (10-14), moderately severe depressive symptoms (15-19), and severe depressive symptoms (>19). Respondents also indicate the degree to which their depressive symptoms have made it difficult for them to do their work, take care of things at home, or get along with other people, from "not difficult at all" to "extremely difficult." The PHQ-9 has high internal consistency (e.g., alpha ranging from .83 to .92), and correlates strongly with other measures of depression.[88]

(i) Sleep will be measured by the **Insomnia Severity Index (ISI)**[89] which is a 7-item self-report measure that assesses perceived severity of insomnia. Each item uses a 4-point Likert type scale from 0 (not at all satisfied) to 4 (very much satisfied). The items sum to produce a total score (range 0 – 28). The ISI has an internal consistency alpha coefficient of 0.74, and has shown convergent validity with other measures such as the Pittsburgh Sleep Quality Index (r = 0.67), the Dysfunctional Beliefs and Attitudes about Sleep (r = 0.55), and sleep diaries (r ranges from 0.32-0.91)[90].

(j) **Columbia-Suicide Severity Rating Scale (C-SSRS)**: The C-SSRS has both lifetime/recent and since last visit versions. The "Lifetime/Recent" version gathers information on lifetime history of suicidality and recent suicidal ideation/self-injurious behavior. The "Since Last Visit" version of the C-SSRS asks about any suicidal thoughts or behaviors the subject has exhibited since the last time administered the C-SSRS[91]

(k) Adverse Events (AE) will be assessed by the RN at each weekly assessment using Food and Drug Administration (FDA) standards for AE reporting. Serious Adverse Events (SAE) and Unanticipated Problems Involving Risk to Subjects or Others (UPIRSO) will be reported to the local IRB as well as to the DSMB and other authorities according to their standard reporting requirements.

(l) Pain will be measured during the clinical trial using recommendations from the consensus group that has published a large number of papers with recommendations for pain clinical trials called the Initiative of Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT)[92]. IMMPACT recommends an assessment of several key domains including pain intensity and functional interference. For pain intensity, a simple 11-point ***Numeric Rating Scale*** **(NRS)** has been recommended by IMMPACT and remains the gold standard in clinical trials. It is the VA's "5th vital sign" so participants will be familiar with it. Functional impairment due to pain will be measured using the ***PROMIS–29*** **scale**.[93]

(m) Additional baseline characteristics will be assessed using the Life Events Checklist for DSM-5 (LEC-5), Child Trauma Questionnaire (CTQ), Cannabis Use History Questionnaire, and the Synthetic Cannabinoids Use History Questionnaire.

Confirmation of self-reported drug use: Urine toxicology screening will be done at every in-person MM visit and urine will be tested using Abbott Diagnostics CI8200 screen done at the VA Facility. The standard urine toxicology includes testing for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and oxycodone. Methadone and buprenorphine are ordered separately, but all will be including in the weekly

screening. *Fentanyl is a separate test and will be ordered if a participant has a history of use/abuse.* Testing for each of these substances uses immunoassays; if there is a question about accuracy, testing is confirmed using gas chromatography/mass spectroscopy. Urine drug testing is a routine part of buprenorphine maintenance treatment.

Subject Payment. All participants will be compensated for their participation. Participants will be paid $30 for the initial screening/baseline assessment. They will be compensated $30 for each medication visit (x7), and $45 for follow up visits. There will be no payment for therapy sessions. Individuals can receive up to a total of $330 if attending all scheduled treatment and visits. Payment will be made through electronic funds transfer (EFT). Participants will need to provide us with your banking information by completing a special payment form. Alternatively, if participants do not have a bank account, a check will be mailed to them instead. This check(s) will be mailed to the address they provide us with. Patients may choose to receive gift certificates issued to them for use at the VCS canteen (retail store) or VCS cafeteria here at the VACHS in lieu of EFT/check payment. If a patient chooses to receive payment by gift certificate they will be paid for the telemedicine/telehealth visits they participated in at their next in-person visit (e.g. if they complete weeks 2 and 3 by telephone they will receive gift certificates for weeks 2, 3, and 4 at the week 4 visit). Study payments are subject to withholding for outstanding federal debts (i.e., defaulted student loans, interstate child support, back taxes etc) without notification.

Power analysis: The sample size calculation for our primary hypothesis (change in PTSD symptoms) was based on findings from one of the largest and most comprehensive meta-analysis reports on PTSD treatment to date.[36] The report evaluated N=112 studies and reported on 137 comparisons, using validated PTSD symptom measures. The meta-analysis reported that the *effect sizes* for psychotherapy when contrasted with a control group were consistently large and averaged g=1.14. Three studies administered CPT specifically and the overall effect size for those was large and averaged g=1.69. For this study we conservatively are basing our calculations on a moderate effect size by Cohen's definition.[95] For the First and Second Primary aim we estimate that with 60 subjects randomized to each group we have 80% power to detect a medium effect size (f=0.25) at two-sided alpha level of 0.05, and assuming 25% dropout we will recruit a total of N=160.]

Data Analysis:
Study data will be collected and managed using REDCap electronic data capture tools hosted at VA CT Healthcare System. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Descriptive statistics and graphs will be used to summarize the data on all randomized subjects. All continuous variables will be examined for adherence to the normal distribution using normal probability plots and Shapiro-Wilk tests. Transformations will be applied if needed. If normality is not satisfied and transformations do not help with achieving normality alternative analytic strategies will be considered such as generalized estimating equations (GEE) or nonparametric methods for repeated measures analysis. Baseline demographic and clinical characteristics for the two randomized groups (e.g., age, gender, severity of PTSD, and opiate use) will be compared using chi-square tests for categorical variables and t-tests or nonparametric tests for continuous variables. If there are baseline differences between study treatment groups, these variables will be used as covariates in the mixed-effects models analyses described below. Drop outs and completers will also be compared on baseline characteristics using the same approach. Between group differences in treatment retention, medication compliance and frequency of the occurrence of side effect symptoms across the treatment period will also be assessed. Residual plots and other diagnostics will be used to assess model assumptions.

The primary analyses will be intent-to-treat but sensitivity analyses on completers and non-completers will also be performed. All statistical testing will be at a two-tailed alpha level of 0.05. *Adjustments for multiple comparisons will be conducted among measures in specific domains. In the case of PTSD symptoms (use of 2 measures, PCL-5 and CAPS-5) and opiate use (use of TLFB and urine toxicology) the level of significance will be adjusted to 0.025.*

Primary and Secondary Hypotheses:
For the primary and secondary hypotheses, we will use mixed effects models to assess changes in PTSD symptoms and opiate use over time. Treatments will be used as between-subject factors and time (in weeks) will be used as a within-subject factor. The primary outcome variables will be PTSD symptoms as measured by generated from the PCL-5 and CAPS scales. The secondary outcome variables will be frequency of opiate use generated from the TLFB and confirmed with urine toxicology results each medication visit (weeks 1-4, 6,8, 12) and follow-up. The use of the mixed-effects models approach for the analysis of our longitudinal data has several specific advantages. Unlike traditional repeated measures analyses, mixed effects models allow for different numbers of observations per subject, use all available data on each subject and are unaffected by randomly missing data. They also provide flexibility in modeling the correlation structure of the data.[96]
Primary Aim 1. We hypothesize that CPT will significantly reduce PTSD symptoms compared IDC in Veterans and civilians with PTSD and comorbid OUD maintained on buprenorphine. This hypothesis will be tested by the interaction of treatment (CPT vs. *IDC*), and time in the mixed model specified above. Significantly greater decrease in PTSD symptoms in the CPT group will be considered supportive of the hypothesis.

Secondary Aim 1. We hypothesize that CPT will significantly reduce opioid use compared to IDC in Veterans and civilians with PTSD and comorbid OUD maintained on buprenorphine. This hypothesis will be tested by the same approach as described in primary aim 1 but with frequency of opioid use as the dependent measure.

Exploratory Hypothesis:
We hypothesize that CPT will significantly improve retention (days in treatment) compared to IDC in Veterans and civilians with PTSD and comorbid OUD maintained on buprenorphine. This hypothesis will be tested using ANOVA or nonparametric equivalent comparing the two treatment groups (CPT vs. *IDC*).

We hypothesize that CPT will significantly improve psychosocial functioning (measured by the VR-12 survey) compared to standard counseling in Veterans and civilians with PTSD and comorbid OUD maintained on buprenorphine. This hypothesis will be tested by the interaction of treatment (CPT vs. *IDC*) and time.

We hypothesize that CPT will significantly improve sleep (measured by the ISI) compared to standard counseling in Veterans and civilians with PTSD and comorbid OUD maintained on buprenorphine. This hypothesis will be tested by the interaction of treatment (CPT vs. *IDC*) and time.

We hypothesize that CPT will significantly reduce pain intensity (measured by the NRS) and improve functional impairment due to pain (measured by the PROMIS-29) when compared to standard counseling during 12 weeks of treatment in Veterans and civilians with PTSD and comorbid OUD maintained on buprenorphine. These hypotheses will be tested by the interaction of treatment (CPT vs. *IDC*), and time (four time points during treatment) in the mixed model. ***We propose to follow up Veterans and civilians 1 and 3 months after completion of the study to evaluate changes in PTSD symptoms, opioid use and treatment utilization.*** This analysis is exploratory and will assess change over time in symptoms and treatment using mixed-effects models with two factors (study treatments [CPT vs. *IDC*], and time (end of treatment, 1 month, and 3 months follow up).

Potential Risks and Adequacy of Protection from Risks

Potential Risks: There are potential risks, discomforts and inconveniences associated with participation in this study. These may be due to buprenorphine maintenance, Cognitive Processing Therapy (CPT), standard (drug) counseling, and nonspecific risks such as loss of confidentiality.

a) All subjects will be treated with buprenorphine maintenance. Buprenorphine is a partial μ-opioid agonist and a weak k-opioid antagonist available alone or in combination tablet containing buprenorphine and naloxone in a ratio of 4:1. In this study, a combination tablet will be used, since it is less likely to be diverted than the buprenorphine only formulation. The doses of buprenorphine/naloxone used here are within the recommended guidelines of the manufacturer. Consistent with the clinical guidelines, before BUP/NLX is administered, participants will be instructed not to use any prescription opioids for 24 hours and be prepared to stay in the clinic for at least 2 hours following the first dose of BUP/NLX. [During induction into buprenorphine, all participants will be started at a dose of 2mg, and this dose will be increased up to 32 mg per

day as needed for stabilization of opioid withdrawal symptoms, within a 5-7-day period, which is standard practice. At the end of the active study, participants will be referred to a buprenorphine clinic.].

Common side effects of buprenorphine/naloxone, which are similar to other opioids, include: abdominal pain, constipation, nausea, vomiting, headache, sweating, sedation, and allergic reaction. Uncommon but more serious adverse effects of BUP/NLX include liver enzyme and/or hepatic abnormalities, orthostatic hypotension, and respiratory depression. There is also a risk of unintentional exposure, especially with children, so for that reason participants will be educated to keep their medication in a safe place to prevent unintentional exposure to others. Buprenorphine is a Schedule III drug and is generally well tolerated, although it does cause a physiologic addiction and may lead to withdrawal effects if discontinued abruptly. *Buprenorphine/Naloxone detoxification:* detoxification from BUP/NLX can produce signs and symptoms of opiate withdrawal including: nasal congestion, abdominal symptoms, anxiety, myalgia, insomnia, sweating, and diarrhea.

b) Subjects who are randomized to *Cognitive Processing Therapy (CPT)* will receive 12 weeks of therapy by a licensed provider. CPT may produce some discomfort and/or emotional upset including an initial increase of PTSD symptoms due to the discussion of traumatic events. This is likely to happen during the early sessions of therapy as the participant begins to describe his/her experiences, thoughts, images and feelings to the therapist as well as during the evaluations. However, these experiences are believed to be an important part of the treatment and recovery process. Dealing effectively with emotional upset means experiencing the negative emotion in order to learn to handle it in future instances. Concerns have been expressed about the safety of CPT, particularly the concern that some individuals may find the treatment overwhelming and cause an increase in symptoms or further deterioration in functioning. These concerns are based primarily on unsystematic clinical impression and research does not support such concerns.

c) Subjects who are randomized to Individual Drug Counseling (IDC) will receive 12 weeks of therapy by a licensed provider. IDC uses a semi-structured, time-limited addictions-counseling model. The main focus is on helping individuals achieve and maintain abstinence by encouraging behavioral changes, such as avoiding triggers, structuring one's life, and engaging in healthy behaviors (e.g., exercise). The current standard of treatment for individuals entering buprenorphine maintenance is to do drug counseling. In most VA settings, including VA Connecticut Healthcare System, psychiatric symptoms (such as PTSD) are evaluated but psychiatric treatment is often deferred until the individual demonstrates a commitment to treatment and demonstrates abstinence. Standard counseling is the primary means to achieve these goals. PTSD symptoms are not addressed and this may lead to worsening of PTSD symptoms. In cases where worsening of PTSD symptoms necessitates a change in case, the same strategies (outlined later in this document) will be used across treatment conditions.

d) Nonspecific Risks: Other risks from the counseling, rating scales and urine collections are not beyond usual clinical procedures in a substance abuse treatment program. Confidentiality of study results are specifically protected by Federal laws, and all records will be identified by code number only, with the master file kept under lock by the Principal Investigator or Data Manager. With the handling of medical and research records, there is always the possibility of a breach of confidentiality.

- ***Sources of Materials:*** Sources of research material include interview assessments conducted by trained Independent Evaluators, self-reported questionnaires, medical record review, urine samples, activity patterns, sleep patterns, etc. that will be obtained specifically for research purposes.
- ***Therapeutic risk:*** All subjects will be inducted into buprenorphine maintenance, the risks of which are described above.
- ***Research risk:*** The research risks include the risks of the interventions into which subjects will be randomized, and include CPT and standard counseling, all of which are described above. In addition, there are risks associated with gathering of assessments, and a potential breach of confidentiality. These have also been described above.

Adequacy of Protection from Risk

- **Recruitment and Informed Consent:** Potential participants may be identified through referrals from various health care providers at hospital clinics. Providers may forward contact information of interested individuals directly to the study team. Or, potential participants may self-refer in response to

the recruitment flyer approved by the IRB. Flyers will be distributed to various health care providers and will be posted in locations in the hospital and surrounding community frequented by Service Members. Interested persons may call or walk in to the research offices. Research staff will field incoming phone calls and walk-ins.

We will also conduct chart reviews for patients enrolled in VA clinics (e.g., Mental Health Clinic; Buprenorphine Clinic) in order to screen for potential participants. When we identify a patient who may meet the study criteria we will reach out to their provider and we will ask the provider to give the patient our contact information, if they may be interested in the study. Patients who are interested in the study will be able to walk in to our research office or call us on the phone for more information and to complete the screening procedures (outlined earlier in the protocol as well as below).

Research staff will discuss the study treatment and eligibility requirements with the interested person. If the person believes they may qualify for the study, an appointment will be made for consent and screening. During this appointment, potential participants will have the study explained to them in a safe and private location. The potential participant will be given a copy of the informed consent document to read. After the subject, has read the informed consent they will be given the opportunity to take the consent home to discuss the research with family and friends. The research team will be available to answer any questions about the research. Once the potential participant has reached a decision, the advising staff member will go over the risks and benefits of the study and ensure the subject understands the research. The advising staff member will have the individual sign the consent form. A copy of the signed informed consent will be given to the subject. The advising staff member will document the informed consent process in the medical record of the participant.

Following the baseline assessment, participants who meet the inclusion criteria for the study will be randomized into the study. For individuals not meeting study inclusion criteria, the study staff will provide options for follow-up outside of the study.

- **Protection Against Risk:**
  - *General procedures to protect against risks:* Before initiating any research activity, each subject must give informed consent that will detail the risks of study participation. Eligibility will be determined by the medical and psychiatric history, drug use history, and the laboratory studies done prior to beginning this research protocol. Subjects will be provided a number to call to reach an on-call psychiatrist (24 hours/day) should unpleasant effects occur after subjects have left the testing facility.
  - *Protection against adverse events from buprenorphine maintenance:* Subjects will be monitored carefully for the development of adverse side effects (including symptoms of withdrawal) during the study. Subjects will be withdrawn if they show severe psychological or symptomatic deterioration or if clinically necessary for ethical or safety purposes. Any psychiatric hospitalization will be reported to the Principal Investigator for review regarding the appropriateness for continuation in the study. Similarly, medical complications will be reviewed in the manner described above. Subjects who may no longer participate for these reasons, or who choose to terminate from the study, will be offered treatment at the VA according to the individual's needs. If a subject shows clinical deterioration the PI will determine: 1) whether the subject can remain in the study, or; 2) whether a higher level of care (e.g. referral back to treating psychiatrist or referral to emergency or inpatient care) is needed.
  - *[Protection against adverse events from Cognitive Processing Therapy (CPT) Individual Drug Counseling (IDC) and Medication Management (MM):]* The therapists and research team will closely monitor for any increase in distress during all treatment sessions. Any indication that the participant is considering suicide will be handled using standard clinical procedures, and referral for additional assessment or treatment for distress will be done in accordance with the local site policies and procedures. If a participant becomes upset in-between sessions, he or she will be encouraged to contact their regular clinician. If a participant needs or desires immediate attention and their therapist is not available, arrangements will be made for an appointment with an experienced mental health provider. The informed consent document provides direction to contact the study staff during duty hours and/or the Emergency Room at any time for worsening of symptoms.

- *Loss of confidentiality:* Data collected will be coded using an assigned number. All data will be secured in locked cabinets in locked offices. Every member of the Research Team will be trained and monitored about how to handle and protect both medical and research records.
    - Database Server. All data will be stored on VA servers behind VA firewalls. All de-identified data will be scanned and saved on VA servers. SPSS software will be used for data maintained and analysis.
    - Security. Access to the research data will be restricted to research personnel affiliated with the study.
    - Audio recording security: Audio recordings will be stored as computer files on a secure server and only include subject IDs to label the interview. To assure the confidentiality and protection of study participants, we will (a) give participants the right to refuse digital recording, to stop the recording at any time, or to request that we erase all recordings involving them, (b) have all recordings take place in privacy, (c) only permit access to the recordings by research staff for supervision purposes and by raters who will be specially trained to rate the recordings using the YACS, and (d) erase the recordings one year upon study completion.

Data Safety and Monitoring Plan (DSMP). The risk associated with participating in this study is moderate, because the treatments administered may be associated with mild to moderate side effects. Serious side effects associated with this treatment are not expected. This project will be monitored by a Data and Safety Monitoring Board (DSMB), because the study involves randomized treatment of Veterans and civilians with PTSD and OUD. This board is composed of persons not otherwise affiliated with the clinical study who are experienced in various aspects of the conduct of clinical trials for the treatment of addictive disorders. We propose three investigators located here in Connecticut who are not directly involved in this study – Declan Berry, Ph.D., Sherry McKee, Ph.D., and David Fiellin, M.D. as the members of the DSMB.

We will report recruitment, follow-up, and adverse events to this panel on a quarterly fashion. Prior to study initiation, critical parameters for collection of side effects and for study discontinuation will be recommended to the DSMB who may use these or other measures to monitor safety of the ongoing trial. The DSMB will be available to convene outside of scheduled meetings, if necessary, due to concerns regarding a particular subject or due to any troublesome developments in subjects' experiences during the study. The DSMB will make appropriate recommendations for changes in the study protocol, if needed.

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