

The Alcohol Use Disorder and Comorbid PTSD/TBI Landscape

Understanding the Problem of Alcohol Use (AUD) Disorders in the Military

- ❖ AUDs tend to be chronic, relapsing conditions, with craving as a core feature associated with relapse.
- ❖ 37% of those with a drinking problem also have a mental health condition (National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2009).
- ❖ Nearly one-third of adults in the United States had an AUD at some time in their lives, but only about 20% seek AUD treatment; rates of AUD were greater among men than women. Among adults between ages 18 and 29, more than 7% had an AUD within the past year, suggesting a need for more-effective prevention and intervention efforts among young people. (Grant et al., 2016)
- ❖ With what is termed the “Warrior ethos” of the military, admitting to either mental health or substance use problems could make military personnel less likely to seek help when it is needed (Institute of Medicine, 2012).
- ❖ The hazardous use of alcohol is highly related to other behaviors, such as risky driving, problem gambling, and losing control of anger and related physical aggression, sexual assault, and mortality (including both injury-related and non-injury-related) (Army Center for Substance Abuse Program, 2011; Institute of Medicine, 2012; Fudalej et al., 2010).
- ❖ The recent Institute of Medicine report titled, *Substance Use Disorders in the U.S. Armed Forces*, viewed alcohol as the key substance use problem in need of intervention and/or treatment among military personnel (Army Center for Substance Abuse Program, 2011).
- ❖ The use of alcohol is common in all branches of the military. Heavy drinking, in particular, has historically been part of the culture of the military (Ames and Cunradi, 2004; Ames et al., 2009; Bryant, 1979; Ingraham et al., 1984).
- ❖ The periodic assessment of health behaviors conducted among active duty personnel indicates a growth in heavy use of alcohol since 1998, holding at 20% in 2008 (Bray et al., 2010). In addition, binge drinking increased from 35% in 1998 to 47% in 2008, a 12% increase in a decade, with 20% reporting heavy drinking. These alarmingly high rates of binge drinking are especially problematic among reserve component members.
- ❖ Rates of lifetime AUDs among Veterans: 32% (Lan et al. 2016).
- ❖ Data from the National Survey on Drug Use and Health indicate that approximately 7.1% of Veterans (estimated 1.8M) meet criteria for a current (i.e., past 12 months) substance use disorder (SUD) (Substance Abuse Mental Health Services Administration [SAMHSA], 2007). This rate is almost twice as high as shown in the National Comorbidity Survey Replication study, which estimated rates of past 12 months SUDs to be 3.8% in the general population (Kessler et al., 2005).

Post-Traumatic Stress Disorder (PTSD) in the Military

- ❖ PTSD is a chronic, debilitating anxiety disorder that may develop after direct or indirect exposure to traumatic events. Among the general population, current (i.e., past 12 months) rates of PTSD are estimated to be between 3.5–7.8% (Kessler et al., 1995, 2005). In comparison, Milliken et al.’s large-scale investigation of over 88,000 Veterans serving in the

Iraq War found that 11.8% had symptoms of PTSD soon after deployment, and 16.7% had symptoms of PTSD at 6 months post-deployment (2007). These are almost twice the community rates of PTSD.

- ❖ Among 1,965 Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) Service members across branches of Service, rank, and military occupational specialty from 24 geographic areas, up to 15% were estimated to have PTSD (Tanielian et al., 2008). One study of 2,525 Army infantry soldiers evidenced PTSD rates of up to 44%, depending on the extent of injury suffered during the traumatic event (Hoge et al., 2008). This is a tenfold increase over the community rates of PTSD.

Mild TBI (mTBI) in the Military

- ❖ Over 2 Million Veterans have served in the Iraq (OEF/OIF) and Afghanistan conflicts, and 23–30% may have sustained mTBI (Miller et al., 2013).
- ❖ Neurocognitive impairments associated with mTBI and AUD include impulsivity, irritability/mood instability, depression, suicide risk, attention deficits, concentration, visual-spatial memory, and executive functioning, including decision-making, risk-benefit analysis, and behavioral inhibition. (Bates et al., 2005).

Studies of AUD and Comorbid mTBI

- ❖ Evidence indicates that the prevalence of alcohol and other SUDs in OEF/OIF Veterans with TBI is approximately twice that of Veterans without TBI (Taylor et al., 2012).
- ❖ Post mTBI, more Service members have diagnoses of alcohol/substance abuse than any other selected condition, except headache (Russel, 2013).
- ❖ Cognitive functioning has been shown to improve even after brief periods of abstinence from alcohol (Durazzo et al., 2007).
- ❖ The Food and Drug Administration (FDA) has not approved a medication to treat AUDs with comorbid TBI.

AUD and PTSD Comorbidity in the Military

- ❖ Like PTSD, Alcohol and Substance Use Disorders (ASUDs) are chronic and relapsing conditions.
- ❖ Compared to individuals with PTSD or AUD alone, those with PTSD and co-existing AUD exhibit greater severity of PTSD and AUD symptoms (Jacobsen et al., 2001; Norman et al., 2012).
- ❖ PTSD treatment research has predominantly excluded patients with comorbid AUD. Nonetheless, recent studies underscore the feasibility and importance of treating PTSD and AUD concurrently to facilitate improvements in PTSD symptoms and reductions in comorbid alcohol use (Foa et al., 2013; Kaysen et al., 2014; Langdon et al., 2016; Petrakis et al., 2016; Zandberg et al., 2016).
- ❖ In comparison to the general population, military personnel and Veterans are at increased risk of developing both SUDs and PTSD (Hoge et al., 2004; Hoge et al., 2006; Seal et al., 2011).
- ❖ Despite estimates that comorbidity between PTSD and AUD are higher in Veterans than civilians (Roberts et al., 2015), there have been few randomized controlled trials (RCTs) of medications in Veterans (Petrakis et al., 2012; Batki et al., 2014), and clinical studies devoted to investigating the treatment of PTSD and SUDs have yielded little progress in developing new therapeutics.

- ❖ The current services offered to Veterans do not adequately address co-occurring SUDs and PTSD, and there is an immediate need for the development of novel, evidence-based treatments.
- ❖ The hazards for AUD were significantly elevated in those with mTBI compared to controls (Miller et al., 2013).
- ❖ Veterans with both PTSD and AUD exhibit more persistent, severe, and treatment-resistant symptoms and are at much higher risk for suicide than Veterans who have either disorder alone (McCarthy and Petrakis, 2010).
- ❖ Addiction is characterized by cycles of binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation, with high rates of relapse. Repeated cycles of withdrawal and relapse promote adverse neuroadaptation.
- ❖ Stress and prior trauma are important risk factors for substance abuse, which is influenced by a complex combination of biological (e.g., genetics), psychological, and social factors, as well as age or stage of development
- ❖ There is a need to find novel, safe, well-tolerated, and low-cost medications for the treatment of AUD especially related to PTSD and TBI.

Pharmacotherapies for PTSD in Combat Veterans

- ❖ The FDA has approved two selective serotonin re-uptake inhibitor (SSRI) oral medications, Zoloft (sertraline) and Paxil (paroxetine), for treating PTSD.
- ❖ The VA/Department of Defense (DoD) (2010) Clinical Practice Guideline for Management of PTSD recommends selective SSRIs (fluoxetine, paroxetine, or sertraline) or the serotonin norepinephrine re-uptake inhibitor (SNRI), venlafaxine.
- ❖ Studies in combat Veterans with PTSD, however, have reported variable responses to SSRI therapy. These findings suggest that SSRIs might not be as useful in Veterans with combat-related PTSD as they are in civilian patients with PTSD (Alexander, 2012).
- ❖ SSRIs are more effective in women than in men and more effective in acute PTSD than in chronic disease (Hertzberg et al., 2000).
- ❖ Early study with sertraline demonstrated clinical efficacy in patients with PTSD and comorbid alcohol dependence (Brady et al., 1995).
- ❖ The impediment to development of PTSD treatments has been the high placebo-response rates across PTSD clinical trials (> 25%), using subjective PTSD symptom ratings (Baker et al., 2009).
- ❖ Topiramate (an anticonvulsant that reduces excitatory neurotransmission) is not recommended by the VA/DoD (2010) Clinical Practice Guideline for Management of PTSD because a Randomized Controlled Trial (RCT) conducted in Veterans in 2010 reported that topiramate was not effective for reducing PTSD symptoms (Lindley et al., 2007).
- ❖ However, a second RCT in Veterans with both PTSD and AUD reported that topiramate decreased PTSD symptom severity, as well as alcohol use (Batki et al., 2014).
- ❖ Two RCTs in civilians have also shown that topiramate reduces PTSD symptoms (Tucker et al., 2007; Yeh et al., 2011).

Pharmacologic Treatment for AUD

- ❖ Pharmacologic treatment of drug withdrawal often involves substituting a long-acting agent for the abused drug, then gradual tapering its dosage (Kosten and Connor, 2003).
- ❖ Desirable qualities for outpatient medications include administration by mouth, low potential for abuse and overdose, and low incidence of side effects.

- ❖ Outpatient management is appropriate for patients with mild-to-moderate withdrawal symptoms who have no important coexisting conditions and have supportive personnel willing to monitor their progress.
- ❖ Patients often attain abstinence without pharmacologic interventions.

FDA-Approved Medications for AUD

- ❖ **Naltrexone**
 - Mechanism of action: oral opioid antagonist
 - Oral formulation (approved 1994)
 - Inexpensive, modest efficacy
 - Long-acting, IM naltrexone (approved 2006)
 - Improved compliance, well-tolerated, effective
- ❖ **Antabuse** (in use for over 50 years)
 - Mechanism of action: inhibits aldehyde dehydrogenase
 - Efficacy linked to compliance
- ❖ **Campral** (approved 2004)
 - Synthetic derivative of homotaurine (analogue of GABA); may effect GABA or glutamate system
 - Most studies conducted in Europe; more recently tested in USA; dose-response effect
 - Not widely used due to limited effectiveness (Brady et al., 2000).

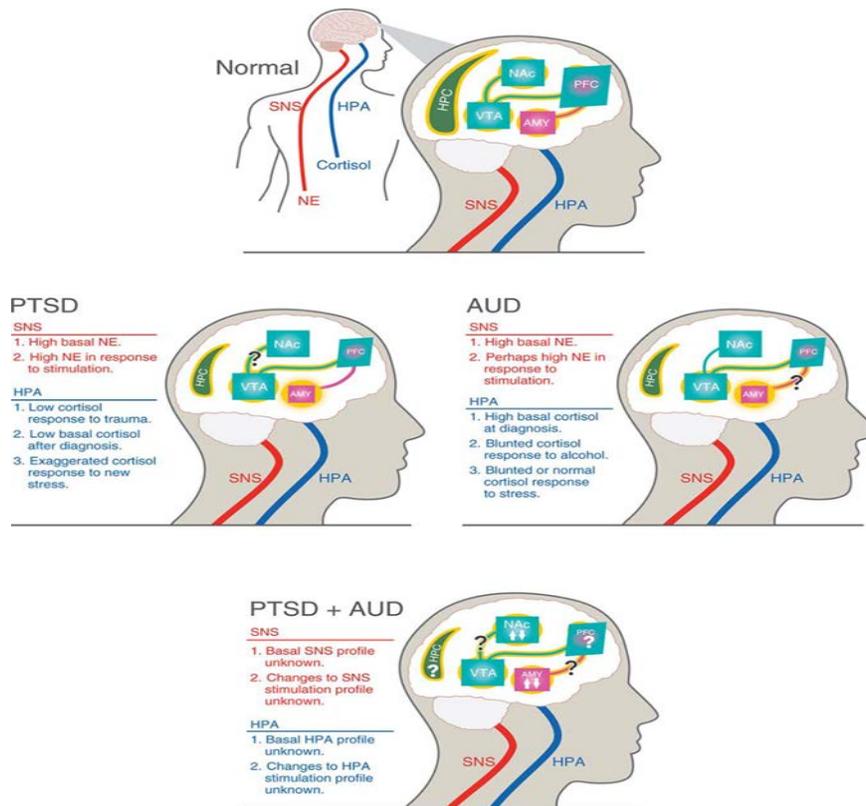
Pharmacotherapies for AUD

- ❖ Although not FDA-approved, topiramate is recommended for treating AUD by the NIAAA and the VA/DoD (2015) Clinical Practice Guideline for Management of Substance Use Disorders.
- ❖ A number of studies in AUD (Alderman et al., 2009; Baltieri et al., 2009; Johnson, 2004; Johnson et al., 2005; Johnson, 2008) found that topiramate:
 - reduces the percentage of heavy drinking days, promotes abstinence,
 - reduces alcohol craving, body mass, cholesterol levels, blood pressure, and smoking
 - four studies in PTSD (Akuchekian and Amanat, 2004; Alderman et al., 2009; Tucker et al., 2004; Andrus and Gilbert, 2010)
 - successfully used as an add-on agent to treat Veterans with refractory symptoms of PTSD
 - monotherapy to treat combat and non-combat symptoms of PTSD
 - Main problem with topiramate: significant side effects and up to 8 weeks to get to a therapeutic dose level

Novel Pharmacological Approaches to Drug Abuse Treatment

- ❖ Each drug of abuse, while sharing a common final neural pathway of increasing dopaminergic tone, has unique and individual characteristics that are important in developing improved and varied treatments (Edens et al., 2008).
- ❖ Addiction treatment is focused on four areas:
 - reducing withdrawal discomfort
 - diminishing cravings
 - blocking rewarding effects of the drug
 - treating comorbidities, such as depression or PTSD

Neurobiology of Comorbid PTSD and AUD*



*Neurobiology of comorbid post-traumatic stress disorder and alcohol use disorder (Gilpin and Weiner (2016)

Sharing Of Common Neural Substrates

- Hypoactive ventromedial prefrontal cortex (PFC) = structural and functional changes associated with executive dysfunction
- Hyperactive/hyper-reactive amygdala = trauma processing abnormalities
- Decreased PFC-amygdala connectivity = increased anxiety
- Hypofunctional reward pathway
- Hypothalamic–pituitary–adrenal (HPA) axis function = low cortisol immediately post trauma is predictive of PTSD
- Hyperactive central and peripheral norepinephrine (NE) signaling
- Hippocampal defects = deficits in memory function and stress hormone signaling

Relevant Studies of AUD and Comorbid PTSD in Military and Veteran Populations

- ❖ Study of Prazosin for PTSD and Comorbid AUD: n = 96 Veterans (Petrakis et al., 2016)
 - Target underlying neurobiology of both disorders: Noradrenergic activity in PTSD and AUD and its implication in stress-induced relapse.
 - FINDINGS: Prazosin had no significant effect on either PTSD symptoms or alcohol consumption.

- ❖ A Pilot Trial of Prazosin, an Alpha-1 Adrenergic Antagonist, for Comorbid Alcohol Dependence and Post-Traumatic Stress Disorder: n = 90 Veterans (Simpson et al., 2015)
 - FINDINGS: Prazosin had no effect on PTSD symptoms, but significantly decreased the percentage of drinking days/week and the percentage of heavy drinking days/week.
- ❖ Concurrent Naltrexone and Prolonged Exposure Therapy for Patients with Comorbid Alcohol Dependence and PTSD: n = 165 Veterans and non-veterans (Foa et al., 2013)
 - This study compared the efficacy of naltrexone and prolonged exposure therapy, which is an evidence-based treatment for PTSD separately and in combination with supportive counseling.
 - FINDINGS: PTSD symptoms were reduced in all treatment groups, although the main effect of prolonged exposure therapy was not statistically significant. All treatment groups also showed a large reduction in percentage of days drinking, with the greatest effect observed in the naltrexone and supportive counseling group. Prolonged exposure therapy was not associated with an exacerbation of alcohol use disorder.
- ❖ Noradrenergic vs. Serotonergic Antidepressant with or without Naltrexone for Veterans with PTSD and Comorbid Alcohol Dependence: n = 88 Veterans (Petrakis et al., 2012)
 - This study compared the serotonin uptake inhibitor, paroxetine, to the norepinephrine uptake inhibitor, desipramine. It also evaluated the adjunctive efficacy of naltrexone, relative to placebo.
 - FINDINGS: Paroxetine and desipramine equally reduced PTSD symptoms. Desipramine improved retention and alcohol use outcomes. Naltrexone had no effect on any drinking measures.
- ❖ Sertraline in the Treatment of Co-occurring Alcohol Dependence and Post-Traumatic Stress Disorder: n = 94 Veterans (Brady et al., 2005)
 - FINDINGS: Sertraline modestly improved PTSD symptoms and improved AUD symptoms only in patients with early-onset PTSD and less severe AUD.
- ❖ Topiramate Treatment of Alcohol Use Disorder in Veterans with Post-Traumatic Stress Disorder: A Randomized Controlled Pilot Trial; n = 30 Veterans (Batki et al., 2014)
 - FINDINGS: Topiramate improved PTSD symptoms and decreased alcohol use and craving. Treatment was associated with mild cognitive impairment that recovered by the end of the 12-week treatment period.
- ❖ Naltrexone and Disulfiram in Patients with Alcohol Dependence and Comorbid PTSD: n = 254 Veterans (Petrakis et al., 2006)
 - FINDINGS: Naltrexone and disulfiram, alone or in combination, decreased alcohol-use measures; however, there was no benefit of combining these medications. Only complete abstainers showed an improvement of PTSD symptoms and, within this group, disulfiram was the most effective medication.

Limitations of Current Pharmacotherapies for AUD and PTSD

Medication	Pros	Cons
Naltrexone	FDA approved (oral & IM)	Limited efficacy, cost, opioid antagonist precludes use in patients requiring opioid analgesics
Disulfiram	FDA approved	Limited efficacy, requires abstinence from alcohol
Acamprosate	FDA approved	Limited efficacy
Topiramate	Moderate efficacy, used off label	Cognitive impairments preclude use in patients with mTBI and PTSD

Novel Anticonvulsants for AUD being studied by the ASADRP

- ❖ Zonisamide and carisbamate have pharmacological profiles similar to topiramate, but potentially fewer side effects.
 - Neuromodulator of neuronal GABA system: Mechanism of action thought to be interfering with the neuronal GABA systems, specifically the dopamine mesolimbic reward pathway, which has been implicated in excessive drinking (Enoch, 2008; Johnson et al., 2005; Koob, 2004; Maccioni et al., 2008; Vengeliene et al., 2008).
- ❖ Zonisamide
 - Three small clinical trials (Arias et al., 2010; Knapp et al., 2010; Rubio et al., 2010); reduces heavy drinking, drinks per week, and craving; did not show prominent cognitive or mental side effects, suggesting that it may be better tolerated than topiramate in this population.
- ❖ Carisbamate
 - Pre-clinical placebo-controlled studies in alcohol-preferring rats have shown that: (1) acute treatment with carisbamate selectively and dose-dependently reduces alcohol intake (Rezvani et al., 2009); and (2) chronic treatment with carisbamate suppresses alcohol intake with less development of tolerance than naltrexone (Rezvani et al., 2012).
 - Significantly more tolerable with fewer side effects in humans; does not require titration.
- ❖ Gabapentin
 - Effective in the treatment of mood and anxiety disorders. In recent single site trial, gabapentin increased abstinence and number of no heavy drinking days. National Clinical Investigations Group at NIAAA completed a multisite clinical trial recruiting 348 AUD patients.

Novel Pharmacological Treatments of AUD being studied by the ASADRP

- ❖ **Glucocorticoid receptor (GR) antagonists**
 - An emerging awareness of the overlap in PTSD/AUD phenomenology, neural circuitry and neurobiology provides a rationale to exploit these overlaps for pharmaceutical development for comorbid PTSD/AUD treatment.
 - GR antagonists have been proposed as short-term (7- or 14-day) treatments to “reset” the HPA axis in these conditions. It remains unclear whether the reset occurs peripherally via feedback mechanisms or centrally via direct GR antagonism within key circuits, but efficacy has been observed pre-clinically and clinically in AUD (Vendruscolo et al., 2015).
 - Studies indicate that attenuation of GR function by **mifepristone** reduces compulsive-like alcohol intake in alcohol-dependent rats and reduces both excessive drinking and alcohol craving in recently abstinent alcoholics — in addition to improving liver-function markers in subjects with a history of heavy drinking — without any major adverse effects. (Vendruscolo et al., 2015)
 - Adequately powered clinical trial of mifepristone to replicate and extend these findings to treatment seekers with alcohol dependence is indicated.
- ❖ **Oxytocin (OT)**
 - OT is a neuropeptide that modulates activation of fear extinction-based neural circuits and fear responses and is a promising candidate to ameliorate the effects of both stress and drug seeking. There is accumulating evidence of an interaction between the neural substrates of affiliative behavior and those of drug reward, with a role for brain oxytocin systems in modulating acute and long-term drug effects (McGregor 2006).

- Intra-nasal OT is clinically available for treatment of social anxiety disorders (Guastella et al., 2008; Di Simplicio et al., 2009) and reduces symptoms of PTSD in Veterans during personal combat imagery (Pitman et al., 1993).
- OT levels are decreased in critical brain areas after various stress and drug-seeking experiences, and systemic OT infusions can rescue both stress and addictive phenotypes in preclinical studies (Kovacs et al., 1998; McGregor et al., 2008; Baskerville and Douglas, 2010; Carson et al., 2010a; Cox et al., 2013).
- OT attenuates amygdalar activation in response to stressful and fearful stimuli (Labuschagne et al., 2010) and has recently shown efficacy in reducing craving for marijuana (McRae-Clark et al., 2013). Moreover, OT strengthens resting connectivity between the amygdala, a critical mediator of responses to stressful and fearful stimuli, and the medial PFC, a brain region critical to social cognition and emotional regulation (Sripada et al., 2013.)
- The unfavorable physiochemical and pharmacokinetic properties of oxytocin itself may limit its clinical use, and the future of oxytocin-based therapeutics for addiction may well rest with novel oxytocin receptor agonists.

❖ **N-Acetylcysteine (NAC)**

- FDA-approved; used as a mucolytic and in the treatment of acetaminophen overdose.
- NAC's potential as a treatment for SUDs is related to its roles in oxidative homeostasis and glutamate activity (Dean et al, 2011).
- NAC may regulate elevated extracellular glutamate resulting from acute and chronic alcohol exposure (Holmes et al., 2013), thus repairing faulty communication between nucleus accumbens and the PFC (Berglind et al, 2009)
- Pre-clinical and clinical studies suggest that NAC has a utility in controlling reward-driven behavior in addictive disorders, potentially moderated through the glutamate system.
- NAC is available “over the counter,” is well tolerated, and has minor side effects.

❖ **Tolcapone**

- Catechol-O-Methyltransferase (COMT) inhibitor; FDA-approved for Parkinson's disease.
- Tolcapone can preferentially increase dopamine tone in the frontal cortex, which is thought to improve decision-making.
- Tolcapone significantly increases choice of delayed monetary rewards in the delay discounting task in healthy control subjects (Kayser et al., 2012).
- Liver enzymes need to be monitored due to reports of reversible liver injury.

❖ **Ondansetron**

- A serotonin-3 (5-HT₃) receptor antagonist that may modulate some of the behavioral effects of alcohol and may decrease alcohol consumption.

❖ **Kappa opioid antagonists**

- Pre-clinical studies continue of kappa-opioid receptors (KORs) and their endogenous ligands dynorphins (DYNs) and the role they play in the regulation of escalated alcohol consumption, negative affect and cognitive dysfunction associated with alcohol dependence.

Definitions

- ❖ Alcohol use disorder — Alcohol use disorder is the medical term for alcohol addiction or what most people think of as alcoholism. Alcohol use disorder can be mild to severe.

- ❖ A standard "drink" in the United States contains about 0.6 fluid ounces or 14 grams of "pure" alcohol and is the equivalent of: 12 ounces of regular beer, 8-9 ounces of malt liquor, 5 ounces of wine, or 1.5 ounces of 80 proof spirits.
- ❖ Moderate drinking is defined as: Women: No more than one drink per day; Men: No more than two drinks per day; People 65 and older: No more than one drink per day (Department of Health and Human Services and Department of Agriculture).
- ❖ Heavy alcohol use is defined as binge drinking 5 or more days in the last month (Substance Abuse and Mental Health Services Administration (SAMHSA)).
- ❖ Binge drinking is a pattern of drinking that brings blood alcohol concentration levels to 0.08 g/dL. This typically occurs after four drinks for women and five drinks for men in about 2 hours (NIAAA).

Joint DoD/VA/NIH Treatment Capability Gaps in ASUD

- ❖ Effective medications for substance abuse and comorbidities
 - Effective medications for different substances of abuse with and without comorbidities (PTSD and TBI)
- ❖ Effective psychotherapies for substance abuse and comorbidities
 - Examining integrated and sequential approaches for addressing substance use disorders and PTSD in military/veteran populations
- ❖ Effective complementary and integrated approaches for substance abuse and co-occurring conditions
 - Testing a variety of non-pharmacological approaches to treating pain and comorbidities in military/veteran populations (e.g., mindfulness, hypnosis/meditation, etc.)

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