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VA Medical Center (116D)
215 North Main Street
White River Junction
Vermont 05009-0001 USA

(802) 296-5132
FAX (802) 296-5135
Email: ncptsd@va.gov

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Opioid Use Among Individuals with Posttraumatic Stress Disorder

Nancy Bernardy, PhD
National Center for PTSD, Executive Division

Macgregor Montaño, PharmD, BCPP
National Center for PTSD, Executive Division

We live in a time of increasing concerns among individuals, families and communities across our country regarding the consequences of opioid use. What began as a seemingly compassionate and efficient means to address pain – a prevalent, disabling, and costly condition that impacts 1 in 5 Americans – gradually became a nightmare that has devastated communities and claimed the lives of almost 400,000 people in an 18-year span (Hodge et al., 2018; Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018). Liberal prescribing of opioid pain medication based on misinformation from pharmaceutical companies was a major factor in escalating rates of opioid use, misuse and opioid use disorder (OUD; Peltz & Südhof, 2018). A higher frequency of opioid prescribing coincided with the return of military members from the Iraq and Afghanistan conflicts, a group with high rates of pain and various mental health disorders. Providers attempting to relieve distress caused by these multiple morbidities often prescribed opioid pain medication and sedatives such as benzodiazepines, thus dangerously increasing overdose risk among returning Veterans (Bernardy, Lund, Alexander, & Friedman, 2014).

Prescribing opioids to treat chronic pain is not a simple issue and clinicians and institutions are working to update pain management practices and use opioid analgesics in a safer, more judicious manner. Overprescribing of opioids reflects in part the limited alternatives for treating chronic pain. There is a clear need for safer, more effective treatments. Any movement, however, to eliminate opioids as a treatment option is an overreaction because opioids have a legitimate role in the medical management of pain. There is a growing recognition in the management of chronic pain that in addition to opioid dose, co-morbid mental health illness plays a critical role in adverse effects from opioid use (Park et al., 2016). This guide to the literature focuses on current knowledge of opioid use among people with PTSD and concludes by citing references suggesting that integration of care for both PTSD and painful medical conditions and OUD should be offered where possible.

PTSD and Opioid Pathway Intersections

PTSD is characterized by avoidance of thoughts associated with the trauma as well as increased arousal. Chronic arousal results in elevated physiologic responses such as hypervigilance and exaggerated startle. In response, many individuals with PTSD will use substances such as alcohol, cannabis, or opioids to reduce the discomfort of symptoms such as hyperarousal (Shorter, Hsieh, & Kosten, 2015). Additionally, abnormalities in the endogenous opioid system have been associated with PTSD (Rasmusson & Shalev, 2014) that may have a bearing on both individuals with PTSD prescribed opioids for pain and on individuals with comorbid PTSD and OUD. Among patients with PTSD, there are increased rates of various substance use disorders (SUDs). The co-occurrence of PTSD with an alcohol use disorder is approximately 42%, nicotine dependence is close to 38%, and other drug use disorders involving cocaine, opiates, sedatives, stimulants and other substances constitute another 22% of patients (Pietrzak, Goldstein, Southwick, & Grant, 2011). One of the difficulties of determining the rate of OUD among PTSD patients is that specific OUD has often been grouped in the "other drug use disorder" category, limiting our knowledge of the extent of the opioid problem among this population. The prevalence of OUD has now been found to be higher among those with PTSD than among those without. Not only are individuals with PTSD and chronic pain more likely to develop OUD, specific types of pain conditions such as musculoskeletal pain impact the nature of the comorbidity (Bilevicius, Sommer, Asmundson, & El-Gabalawy, 2018).

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Nancy Bernardy, PhD and **Macgregor Montaño, PharmD, BCPP** are affiliated with the National Center for PTSD Executive Division, VA Medical Center (116D) 215 North Main St. White River Junction, VT 05009. Email Addresses: Nancy.Bernardy@va.gov and Macgregor.Montano2@va.gov.

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This may be particularly problematic as musculoskeletal pain is one of the most common types of pain reported among returning Iraq and Afghanistan Veterans, and appears to have an additive relationship with PTSD on the development of OUD.

Characteristics of People with PTSD and OUD

Due to the focus on chronic pain and opioid prescribing, there is growing data available on rates of PTSD and OUD. Veterans are diagnosed with OUD at higher rates than non-Veterans. Overall, the number of Veterans diagnosed with OUD treated in the U.S. Department of Veterans Affairs (VA) nearly tripled from 2003 to 2017, from 25,000 to over 69,000 (Wyse et al., 2018). Among patients treated in the VA with a new diagnosis of PTSD, the rate of diagnosis of OUD grew from 2.5% in 2004 to 3.4% in 2013 (24,872), a 37% relative increase (Shiner, Westgate, Bernardy, Schnurr, & Watts, 2018). These rates are comparable to civilian prescription OUD rates in those with PTSD (3%), which are far higher than the estimates in the general population (0.7%) (Hassan, Le Foll, Imtiaz, & Rehm, 2017). However, a sharp increase in OUD-related diagnoses (abuse and dependence) was seen across U.S. military branches between 2002 and 2008, with prescription opioid dependence and abuse among Servicemembers rising from 1% to 10% (Dabbs, Watkins, Fink, Eick-Cost, & Millikan, 2014).

Chronic opioid use among Veterans who served in Iraq and Afghanistan is more likely in younger males, those who are white, married, and living in a rural setting (Hudson et al., 2017). Odds of using opioids chronically is higher in Veterans with PTSD, major depressive disorder, and tobacco use disorder (Hudson et al., 2017). Patients with PTSD treated in the VA with an OUD diagnosis are younger males, more likely to be part of the Iraq and Afghanistan cohort, less likely to be married, less likely to live in rural settings, and less likely to have been exposed to combat. In addition, they are much more likely to be homeless and to have experienced sexual trauma while in the military (Shiner et al., 2018). They use more overall VA services compared to the rest of the PTSD population and are more physically ill despite their younger age. Finally, they are more complex patients, with considerably higher rates of every neuropsychiatric and other SUD diagnosis examined (Shiner et al., 2018). Among active duty military personnel, male Servicemembers and those with lower levels of education had significantly higher odds of OUD than female Servicemembers or than males with higher education levels (Dabbs et al., 2014). Higher rates of OUD were observed in Servicemembers who were not married, those who served in the Army, and those who had lower military ranks. Interestingly, Servicemembers who had no history of deployment or at least one deployment had higher odds of OUD when compared to Soldiers with more than four deployments (Dabbs et al., 2014). Having a prior PTSD diagnosis significantly increased the odds of having an OUD diagnosis. Across populations, baseline PTSD increases the risk of developing OUD after exposure to opioid analgesics (Hassan et al., 2017). Among civilians, there are concerning gender-specific trends. Women with chronic pain conditions are more likely to be treated with opioids and to use prescription opioids for longer periods and at higher doses. In addition, women also become physically dependent on opioid pain medication more quickly than men, progressing to an OUD faster than men from first use (U.S. Department of Health and Human Services, Office on Women's Health, 2017). One implication of these findings for clinicians is the importance of engagement and outreach efforts to patients who have chronic pain at an earlier point in care with attention to gender-related risk factors and screening for PTSD.

Treatment Considerations

OUD can have an excellent prognosis if treated with the one of the U.S. Food and Drug Administration-approved well-established medical treatments that are available: naltrexone, methadone or buprenorphine (Volkow & Wargo, 2018). The VA has developed various successful initiatives to re-address chronic pain management and identify and treat OUD. A relatively high percentage of those Veterans getting their care in the VA who have OUD diagnoses receive medication assisted treatment (MAT), primarily buprenorphine (Shiner et al., 2018) and access to naloxone (Oliva et al., 2017), the overdose reversal medication. In a recent VA clinical trial, treatment with opioids was not superior to treatment with nonopioid medications for improving chronic pain-related function over a year (Krebs et al., 2018). Multimodal care with non-pharmacologic and non-opioid treatments has now become the preferred treatment for chronic pain conditions.

Treating OUD with effective MAT alone may not get at the underlying mental health condition that was originally driving use (Ecker & Hundt, 2018). There are some theoretical reasons why individuals with PTSD might be at increased risk to develop an OUD. One prevailing thought is that a mutual-maintenance model may exist in that PTSD and chronic pain influence each other, resulting in an exacerbation of symptoms. This cycle of pain symptoms increasing PTSD symptoms and vice versa, results in the individual turning to opioids for rapid relief (Shorter et al., 2015). Another thought is the self-medication theory which suggests that individuals with chronic pain who are using opioids do so to self-medicate to avoid the experience of PTSD symptoms (Shorter et al., 2015). There is evidence that the use of opioids during acute trauma care may reduce the risk of subsequent development of PTSD (Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010). The authors suggest that reduction in perceived pain levels through the use of opioids may contribute to lower rates of subsequent PTSD. However, clinicians who opt to prescribe opioid analgesics may consider screening for existing baseline PTSD during assessment and provide education on effective treatment options if screening is positive for PTSD (Ecker & Hundt, 2018).

There is limited evidence that buprenorphine can impact PTSD symptoms in Veterans with chronic pain and OUD. In an observational study, Seal and colleagues (2016) found that twice as many Veterans in a buprenorphine group (24%) compared to those in an opioid therapy group (12%) showed modest improvement in PTSD symptoms using a brief PTSD primary care screen that was maintained and continued to show improvement up to 24 months. Incidentally, those receiving opioid therapy in this study endorsed worsening PTSD symptoms over time. This preliminary work suggests that buprenorphine or MAT alone may

be efficacious in reducing chronic PTSD symptoms among those with OUD but more conclusive evidence from additional controlled trials with improved measurement of PTSD are needed.

At this point, we do not know if treating co-occurring PTSD and OUD with a combination of evidence-based psychotherapy or medication for PTSD along with MAT for OUD will improve PTSD and/or OUD outcomes. Several clinical practice guidelines for PTSD now recommend trauma-focused psychotherapy treatment as the first-line treatment for PTSD. If medication is preferred to treat PTSD, the VA/U.S. Department of Defense (DoD) guideline recommends specific antidepressants: sertraline, paroxetine, fluoxetine and venlafaxine (U.S. Department of Veterans Affairs & U.S. Department of Defense, 2017). Among VA patients receiving care for PTSD and OUD, approximately 50% receive effective antidepressants for PTSD (Shiner et al., 2018). There are no single medications at this point that are recommended to treat both PTSD and OUD.

Recent research has focused on evidence-based psychotherapy treatment for co-occurring PTSD/OUD. Two small studies utilizing trauma-focused psychotherapy noted significant reductions in PTSD and relatively low dropout rates in those on MAT. The first, an uncontrolled pilot study of twelve Israeli women on methadone using Prolonged Exposure (PE) therapy, noted significant reductions in PTSD and depression with low dropout (Schiff, Nacasch, Levit, Katz, & Foa, 2015). The other study found that monetary incentives improved attendance in PE therapy in patients in methadone maintenance resulting in PTSD improvements, retention in methadone treatment and no increased substance use (Schacht, Brooner, King, Kidorf, & Peirce, 2017). In a VA study that involved chart reviews, concurrent trauma treatment for those patients with PTSD who were receiving buprenorphine, saw improved outcomes in retention in OUD treatment (Meshberg-Cohen, Black, DeViva, Petrakis, & Rosen, 2019). Although preliminary, results from these studies suggest that providing concurrent trauma-focused treatment in patients receiving MAT may improve outcomes in PTSD and OUD treatment.

Conclusions - A New Approach to Treating Patients with PTSD, Pain, and OUD

It is clear that there is an increased prevalence of co-occurring PTSD and OUD. Despite this co-occurrence, treatment of PTSD is rarely integrated into OUD treatment. Likewise, consistent screening practices and coordinated treatment have not been routine in the treatment of comorbid chronic pain and PTSD. Best approaches have not yet been adequately investigated. Some models might include integrating PTSD, OUD and pain treatments within a specialty clinic setting through interdisciplinary care models or through collaborations between primary and specialty care (Volkow & Collins, 2017). A focus on both provider outcomes (e.g., changes in knowledge and attitudes) as well as patient clinical outcomes (e.g., proportion treated, retained in care, changes in PTSD, pain and OUD symptoms and functional status) would be important (Ecker & Hundt, 2018). Problems associated with opioid use have thus highlighted the serious unmet need for better recognition and treatment of common mental health problems such as PTSD in patients with chronic pain and OUD.

FEATURED ARTICLES

Bilevicius, E., Sommer, J. L., Asmundson, G. J. G., & El-Gabalawy, R. (2018). **Posttraumatic stress disorder and chronic pain are associated with opioid use disorder: Results from a 2012-2013 American nationally representative survey.** *Drug and Alcohol Dependence*, *188*, 119-125. doi:10.1016/j.drugalcdep.2018.04.005 *Background:* Chronic pain conditions and posttraumatic stress disorder (PTSD) commonly co-occur and are associated with opioid use disorder (OUD). The aims of this paper were to identify prevalence estimates of OUD among individuals with and without PTSD and assess independent and combined contributions of PTSD and chronic pain conditions on OUD in a nationally representative sample. *Methods:* Data were extracted from 36,309 individuals from the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions. Past-year PTSD and OUD were assessed using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-5 edition. Respondents reported physician-confirmed, past-year chronic pain conditions, categorized into musculoskeletal pain (e.g., arthritis), digestive pain (e.g., pancreatitis), and nerve pain (e.g., reflex sympathetic dystrophy). We examined the weighted prevalence of OUD among those with and without PTSD. Multiple logistic regressions examined the association between PTSD and chronic pain conditions on OUD. *Results:* The prevalence of OUD was higher among those with PTSD than those without. Comorbid PTSD/musculoskeletal pain and PTSD/nerve pain conditions were associated with increased odds of OUD, compared to those with neither PTSD nor chronic pain conditions. Digestive pain conditions were not associated with OUD. Comorbid PTSD/musculoskeletal pain conditions demonstrated an additive relationship on OUD compared to musculoskeletal pain conditions and PTSD alone. *Conclusions:* Results reveal that musculoskeletal pain and nerve pain conditions are associated with increased odds of OUD, but only musculoskeletal pain conditions display an additive relationship on OUD when combined with PTSD. These findings have implications for opioid management and screening among those with comorbid conditions.

Ecker, A., & Hundt, N. (2018). **Posttraumatic stress disorder in opioid agonist therapy: A review.** *Psychological Trauma: Theory, Research, Practice, and Policy, 10*, 636-642. doi:10.1037/tra0000312 *Objective:* Posttraumatic stress disorder (PTSD) and opioid use disorder (OUD) co-occur at high rates, and this co-occurrence is associated with a range of problems related to mental and physical health. OUD is commonly treated with opioid agonist therapies (OAT), which have been shown to be effective for reducing opiate use and related negative health consequences. Given the high comorbidity of PTSD and OUD, many individuals in OAT have PTSD and continue to experience symptoms of both disorders despite OAT treatment. In this review, the extant literature on PTSD among individuals in OAT is presented. *Method:* Relevant studies (N = 26) were identified systematically through a search of PubMed and PsychInfo databases. *Results:* Literature regarding prevalence and clinical characteristics of patients with PTSD in OAT and treatment outcomes related to both OUD and PTSD is reviewed. *Conclusion:* Clinical implications of the body of work and recommendations for future research are provided.

Hassan, A. N., Le Foll, B., Imtiaz, S., & Rehm, J. (2017). **The effect of post-traumatic stress disorder on the risk of developing prescription opioid use disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III.** *Drug and Alcohol Dependence, 179*, 260-266. doi:10.1016/j.drugalcdep.2017.07.012 *Objective:* To evaluate the effect of baseline post-traumatic stress disorder (PTSD) and each symptoms cluster on the risk of developing opioid use disorder (OUD) in those exposed to opioid painkillers and to assess the effect of comorbid PTSD and OUD on functioning, OUD severity, and treatment seeking compared with individuals with OUD only. *Methods:* We obtained data from 4025 individuals exposed to opioid painkillers from the National Epidemiologic Survey on Alcohol and Related Conditions III. We matched individuals with baseline PTSD with individuals without PTSD on demographics, developmental background, family history, personalities, and exposure to stressful life events with propensity score methodology. We controlled for clinical diagnoses and other risk factors that may have occurred after PTSD onset. Quality of life was assessed with the SF-12; the number of diagnostic criteria met indicated OUD severity. *Results:* Baseline PTSD predicted OUD after controlling for matching variables and other risk factors, including baseline mood/anxiety disorders and other substance use disorders (odds ratio[OR]: 1.58; 95% confidence interval[CI]: 1.14–2.17; p = 0.02). Among individuals with PTSD, arousal/reactivity cluster predicted OUD. Individuals with comorbid PTSD and OUD had lower mean scores on the SF-12 scale and greater severity of OUD than individuals with OUD. There were no differences in help-seeking. *Conclusion:* Baseline PTSD increases the risk of developing OUD after exposure to opioid painkillers. Clinicians should screen for PTSD diagnosis and arousal/reactivity symptoms prior to prescribing painkillers. Integrated treatments are strongly recommended for patients with this dual diagnosis.

Hodge, J. G., Gulinson, C., Barraza, L., Johnson, W., Hensley, D., & Augur, H. (2018). **Exploring legal and policy responses to opioids: America's worst public health emergency.** Retrieved from SSRN database. doi:10.2139/ssrn.3293347 On October 26, 2017, the Department of Health and Human Services (HHS) formally declared a national state of public health emergency (PHE) in response to the opioid epidemic. Since renewed multiple times, HHS' PHE assimilates emergency declarations among a handful of state, tribal, and local governments. Countless public and private sector entities have engaged in additional opioid emergency response efforts across the United States. These emergency declarations and measures collectively respond to the worst PHE confronting the country since the origination of this specific emergency classification in 2001. Americans across all socioeconomic groups are at risk of, or already addicted to, opioids in one form or another. Several hundred thousand Americans have lost their lives to prescription or illicit opioid misuse over the course of the epidemic. Nearly 130 more Americans die each day from opioid misuse. Millions are directly impacted by excess morbidity arising from opioid use disorders (OUDs). Most people know someone who is at risk of, or has succumbed to, opioid abuse. This epidemic is truly the juggernaut of PHEs. While emergency responses to date are purposeful and often well-intended, for manifold reasons they have also proven inadequate in authorizing and funding sufficient, efficacious responses. More significant approaches and greater investments are needed to prevent excess mortality and morbidity. Commencing with an assessment of the impacts of the opioid crisis, existing legal and policy responses, and failures to control the epidemic, a series of interventions are proposed to (1) stymie opioid-related overdoses and deaths in real time and (2) obviate deleterious impacts for future generations.

Hudson, T. J., Painter, J. T., Martin, B. C., Austen, M. A., Williams, J. S., Fortney, J. C., . . . Edlund, M. J. (2017). **Pharmacoepidemiologic analyses of opioid use among OEF/OIF/OND veterans.** *Pain, 158*, 1039-1045, doi:10.1097/j.pain.0000000000000874 There is a great deal of concern about opioid use in veterans, particularly those who served in Afghanistan (OEF) and Iraq (OIF and OND). The current study provides a detailed pharmacoepidemiologic analysis of opioid use among OEF/OIF/OND veterans from FY09 to FY12. Data from 3 data repositories from the Veterans Health Administration (VHA) were used to describe demographic, clinical, and medication characteristics associated with opioid use among OEF/OIF/OND veterans and among those with TBI. Logistic regression models were used to identify risks associated with chronic opioid use in FY12. Approximately 23% of all OEF/OIF/OND veterans and 35% of those with TBI received any opioid medications. Most received moderate doses ranging from 26 to 30 mg morphine equivalent dose daily. Median days of opioid use for all OEF/OIF/OND veterans were 30 to 40 days. Factors associated with chronic use in both groups included young age, male sex, white race, being married, and living in rural areas. A diagnosis of PTSD (odds ratio [OR] = 1.22, $P < 0.0001$), major depressive disorder (OR = 1.14, $P < 0.0001$), and tobacco use disorder (OR = 1.18, $P < 0.0001$) were strongly associated with chronic opioid use. Back pain was also strongly associated with chronic use (OR = 2.50, $P < 0.0001$). As pain severity increased the odds of chronic opioid use also increased: mild pain (OR = 3.76, $P < 0.0001$), moderate pain (OR = 6.80, $P < 0.0001$), and severe pain (OR = 8.49, $P < 0.0001$). Opioid use among OEF/OIF/OND veterans is characterized by moderate doses that are used over relatively long periods of time by a minority of veterans.

Krebs, E. E., Gravely, A., Nugent, S., Jensen, A. C., DeRonne, B., Goldsmith, E. S., . . . Noorbaloochi, S. (2018). **Effect of opioid vs. nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: The SPACE randomized clinical trial.** *JAMA, 319*, 872-882. doi:10.1001/jama.2018.0899 *Importance:* Limited evidence is available regarding long-term outcomes of opioids compared with nonopioid medications for chronic pain. *Objective:* To compare opioid vs nonopioid medications over 12 months on pain-related function, pain intensity, and adverse effects. *Design, Setting, and Participants:* Pragmatic 12-month, randomized trial with masked outcome assessment. Patients were recruited from Veterans Affairs primary care clinics from June 2013 through December 2015; follow-up was completed December 2016. Eligible patients had moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use. Of 265 patients enrolled, 25 withdrew prior to randomization and 240 were randomized. *Interventions:* Both interventions (opioid and nonopioid medication therapy) followed a treat-to-target strategy aiming for improved pain and function. Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the nonopioid group, the first step was acetaminophen (paracetamol)

or a nonsteroidal anti-inflammatory drug. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response. *Main Outcomes and Measures:* The primary outcome was pain-related function (Brief Pain inventory [BPI] Interference scale) over 12 months and the main secondary outcome was pain intensity (BPI severity scale). For both BPI scales (range, 0-10; higher scores = worse function or pain intensity), a 1-point improvement was clinically important. The primary adverse outcome was medication-related symptoms (patient-reported checklist range. 0-19). *Results:* Among 240 randomized patients (mean age. 58.3 years; women. 32 (13.0%)). 234 (97.5%) completed the trial. Groups did not significantly differ on pain-related function over 12 months (overall P = .58); mean 12-month BPI interference was 3.4 for the opioid group and 3.3 for the nonopioid group (difference. 0.1 [95% CI. -0.5 to 0.7]). Pain intensity was significantly better in the nonopioid group over 12 months (overall P = .03): mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference. 0.5 [95% CI. 0.0 to 1.01). Adverse medication -related symptoms were significantly more common in the opioid group over 12 months (overall P - .03); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the nonopioid group (difference, 0.9 [95% CI. 0.3 to 1.51). *Conclusions and Relevance:* Treatment with opioids was not superior to treatment with nonopioid medications for improving pain-related function over 12 months. Results do not support initiation of opioid therapy for moderate to severe chronic back pain or hip or knee osteoarthritis pain.

Meshberg-Cohen, S., Black, A. C., DeViva, J. C., Petrakis, I. L., & Rosen, M. I. (2019). **Trauma treatment for veterans in buprenorphine maintenance treatment for opioid use disorder.** *Addictive Behaviors, 89*, 29-34. doi:10.1016/j.addbeh.2018.09.010 *Introduction:* Opioid use disorder (OUD) rates are high among veterans. PTSD is also prevalent among veterans; those with comorbidity have worse outcomes than those without comorbidity. This study assessed buprenorphine retention rates in veterans initiating OUD treatment, comparing veterans without PTSD to veterans with PTSD who were receiving versus not receiving concurrent trauma treatment. *Methods:* This retrospective chart review examined consecutive referrals to buprenorphine maintenance (*N* = 140). PTSD diagnosis was identified by chart review and retention was defined as continuous buprenorphine maintenance 6-months post-admission. Logistic regression analyses compared buprenorphine retention for veterans without PTSD and PTSD-diagnosed veterans who received concurrent trauma treatment to a reference group of PTSD-diagnosed veterans who did not receive trauma treatment. Models adjusted for opioid type, age, and service-connected status. *Results:* Sixty-seven (47.9%) buprenorphine-seeking veterans carried a PTSD diagnosis; only 31.3% (*n* = 21) received trauma treatment while in buprenorphine maintenance, with 11.9% (*n* = 8) receiving evidence-based psychotherapy for PTSD. Among PTSD-diagnosed veterans who received trauma treatment, 90.5% (*n* = 19/21) were in buprenorphine maintenance at 6-months, compared to 23.9% (*n* = 11/46) of PTSD-diagnosed veterans without trauma treatment, and 46.6% (*n* = 34/73) of veterans without PTSD. In the full model, veterans with trauma treatment had 43.36 times greater odds of remaining in buprenorphine treatment than the reference group. *Conclusions:* Most PTSD-diagnosed veterans in buprenorphine treatment were not receiving trauma treatment. Those receiving concurrent trauma treatment had better retention, suggesting OUD and trauma can be simultaneously addressed. Future clinical trials should investigate trauma-focused treatment for veterans with comorbid PTSD who are seeking buprenorphine for OUD.

Park, T. W., Lin, L. A., Hosanagar, A., Kogowski, A., Paige, K., & Bohnert, A. S. B. (2016). **Understanding risk factors for opioid overdose in clinical populations to inform treatment and policy.** *Journal of Addiction Medicine, 10*, 369-381. doi:10.1097/ADM.0000000000000245 Overdoses involving opioid analgesics represent a significant public health problem in the United States. We reviewed the literature on risk factors for overdose, with a focus on studies that examine clinical populations of patients receiving opioids for pain and potential risk factors for overdose in these populations. A structured review resulted in 15 articles published between 2007 and 2015 that examined risk factors for fatal and nonfatal overdose in patients receiving opioid analgesics. Opioid dosage was the factor most consistently analyzed and also associated with increased risk of overdose. Other risk factors include concurrent use of sedative-hypnotics, use of extended-release/long-acting opioids, and the presence of substance use and other mental health disorder comorbidities. Future research is needed to better characterize populations taking opioids for pain to help clarify discrepancies between existing studies and identify previously unexplored risk factors for overdose. Given that policy and clinical practice have shifted as a result of prior studies reviewed here, further efforts in understanding patient groups and opioid-related prescribing practices associated with overdose risk have great potential to impact policy and practice in the treatment of pain while improving the safety around opioid prescribing.

Peltz, G., & Südhof, T. (2018). **The neurobiology of opioid addiction and the potential for prevention strategies.** *JAMA, 319*, 2071-2072. doi:10.1001/jama.2018.3394 The health consequences of the opioid epidemic have led the United States to an inflection point at which its biomedical research–driven plan should be changed to effectively address this epidemic. To do so, 2 important changes in the focus for National Institutes of Health (NIH)–funded research are needed, which hopefully will develop actionable information and critically needed new treatments for opioid addiction. First, NIH-funded research currently focuses on the later stages of drug addiction1 that are associated with drug craving and relapse. However, because the opioid epidemic has a large iatrogenic component, prevention strategies that target the early stage of drug addiction should be developed. Second, a far deeper understanding of opioid neurobiology is required to change the focus. Instead of examining opiate-induced changes only at the neural circuit level or with brain imaging to identify involved brain regions, opiate-induced changes in synaptic signaling should be characterized.

Schacht, R. L., Brooner, R. K., King, V. L., Kidorf, M. S., & Peirce, J. M. (2017). **Incentivizing attendance to prolonged exposure for PTSD with opioid use disorder patients: A randomized controlled trial.** *Journal of Consulting and Clinical Psychology, 85*, 689-701. doi:10.1037/ccp0000208 *Objective:* To determine whether contingent monetary incentives increase opioid use disorder patients' attendance to Prolonged Exposure (PE) therapy and whether attendance is associated with improvement in posttraumatic stress disorder (PTSD) and substance use disorder (SUD) outcomes.

Method: Patients (*N* = 58) with PTSD were offered PE or PE with incentives (PE + I; max $480) to attend PE sessions. Participants were assessed at baseline and weeks 6, 12, and 24 postrandomization. *Results:* Participants were mostly women (79%) and Caucasian (71%); mean age 37.43 years (*SD* = 11.33). PE + I participants attended a median of 9 (of 12) sessions compared to 1 session for PE participants (p < .001), which included more exposure sessions (PE + I mdn = 6; PE mdn = 0; *p* < .001). A Time × treatment condition interaction indicated that PE + I participants exhibited a greater decrease in PTSD severity over time than PE participants (*OR* = 3.1; 95% CI = 0.4–5.7; *p* = .024). PE + I participants remained in substance use treatment longer than PE participants (mdn days = 262 vs. 192; p = .039). There were no group differences in drug use. *Conclusions:* Monetary incentives increased SUD patients' attendance to an otherwise poorly attended treatment for PTSD. Better attendance in the incentivized group was associated with greater PTSD improvement, better SUD treatment retention, and no increased drug use. Incentives are well supported for improving adherence to substance use treatment goals and promising as a means to improve therapy attendance, which may improve the effectiveness of existing psychotherapies in difficult-to-treat populations.

Schiff, M., Nacasch, N., Levit, S., Katz, N., & Foa, E. B. (2015). **Prolonged exposure for treating PTSD among female methadone patients who were survivors of sexual abuse in Israel.** *Social Work in Health Care, 54*, 687-707. doi:10.1080/00981389.2015.1058311 The aims of this pilot study were: (a) to test the feasibility of prolonged exposure (PE) therapy conducted by a social worker staff on female patients in methadone program clinics who were survivors of child sexual abuse or rape and (b) to examine preliminary outcomes of PE on posttraumatic stress disorder (PTSD), depression, and illicit drug use at pre- and posttreatment, and up to 12-month follow-ups. Twelve female methadone patients who were survivors of child sexual abuse or rape diagnosed with PTSD were enrolled in 13-19 weekly individual PE sessions. Assessments were conducted at pre-, mid-, and posttreatment, as well as at 3, 6, and 12-month follow-ups. The treatment outcomes measures included PTSD symptoms, depressive symptoms, and illicit drug use. Ten of the 12 study patients completed treatment. PTSD and depressive symptoms showed significant reduction. No relapse to illicit drug use was detected. These preliminary results suggest that PE may be delivered by methadone social workers with successful outcomes. Further research should test the efficacy of PE among methadone patients in a randomized control trial with standard care as the control condition.

Seal, K. H., Maguen, S., Bertenthal, D., Batki, S. L., Striebel, J., Stein, M. B., . . . Neylan, T. C. (2016). **Observational evidence for buprenorphine's impact on posttraumatic stress symptoms in veterans with chronic pain and opioid use disorder.** *Journal of Clinical Psychiatry, 77*, 1182-1188. doi:10.4088/JCP.15m09893 *Objective:* Posttraumatic stress disorder (PTSD), chronic pain, and substance use disorders are prevalent co-occurring conditions that are challenging to treat individually, and there is no evidence-based treatment for all 3. Buprenorphine, used to treat opioid use disorder and chronic pain, is a partial nociceptin opioid receptor agonist. In preclinical studies, a nociceptin opioid receptor agonist was shown to mitigate PTSD symptoms in acute trauma. We compared buprenorphine to other opioid medications in its impact on PTSD symptoms in patients with chronic pain and opioid and/or other substance use disorders. *Method:* We assembled a retrospective cohort of 382 Iraq and Afghanistan veterans in US Department of Veterans Affairs health care from October 1, 2007, to July 29, 2013, with *ICD*-9-CM diagnoses of PTSD, chronic pain, and substance use disorders. We used time-varying general estimating equation models to assess the primary outcome, which was change in PTSD symptoms (measured using the PTSD Checklist and the Primary Care PTSD Screen) among veterans initiated on sublingual buprenorphine versus those maintained on moderately high-dose opioid therapy. *Results:* Twice as many veterans in the buprenorphine group (23.7%) compared to those in the opioid therapy group (11.7%) experienced improvement in PTSD symptoms (*P* = .001). Compared to veterans in the opioid therapy group, veterans receiving buprenorphine showed significant improvement in PTSD symptoms after 8 months, with increasing improvement up to 24 months (incidence rate ratio = 1.79; 95% CI, 1.16-2.77; *P* = .009). There were no differences in the longitudinal course of pain ratings between groups. *Conclusions:* This observational study is the first to report an incidental effect of buprenorphine compared to opioid therapy in improving PTSD symptoms in veterans.

Shiner, B., Westgate, C. L., Bernardy, N. C., Schnurr, P. P., & Watts, B. V. (2018). **Trends in opioid use disorder diagnoses and medication treatment among veterans with posttraumatic stress disorder.** *Journal of Dual Diagnosis, 13*, 201-212. doi:10.1080/15504263.2017.1325033 *Objective:* Despite long-standing interest in posttraumatic stress disorder (PTSD) and opioid use disorder comorbidity, there is a paucity of data on the prevalence of opioid use disorder in patients with PTSD. Therefore, there is limited understanding of the use of medications for opioid use disorder in this population. We determined the prevalence of diagnosed opioid use disorder and use of medications for opioid use disorder in a large cohort of patients with PTSD. *Methods:* We obtained administrative and pharmacy data for veterans who initiated PTSD treatment in the Department of Veterans Affairs (VA) between 2004 and 2013 (*N* = 731,520). We identified those with a comorbid opioid use disorder diagnosis (2.7%; n = 19,998) and determined whether they received a medication for opioid use disorder in the year following their initial clinical PTSD diagnosis (29.6%; *n* = 5,913). Using logistic regression, we determined the predictors of receipt of opioid use disorder medications. *Results:* Comorbid opioid use disorder diagnoses increased from 2.5% in 2004 to 3.4% in 2013. Patients with comorbid opioid use disorder used more health services and had more comorbidities than other patients with PTSD. Among patients with PTSD and comorbid opioid use disorder, use of medications for opioid use disorder increased from 22.6% to 35.1% during the same time period. Growth in the use of buprenorphine (2.0% to 22.7%) was accompanied by relative decline in use of methadone (19.3% to 12.7%). Patients who received buprenorphine were younger and more likely to be rural, White, and married. Patients who received methadone were older, urban, unmarried, from racial and ethnic minorities, and more likely to see substance abuse specialists. While use of naltrexone increased (2.8% to 8.6%), most (87%) patients who received naltrexone also had an alcohol use disorder. Controlling for patient factors, there was a substantial increase in

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the use of buprenorphine, a substantial decrease in the use of methadone, and no change in use of naltrexone across years. *Conclusions:* Opioid use disorder is an uncommon but increasing comorbidity among patients with PTSD. Patients entering VA treatment for PTSD have their opioid use disorder treated with opioid agonist treatments in large and increasing numbers. There is a need for research both on the epidemiology of opioid use disorder among patients with PTSD and on screening for opioid use disorder.

Shorter, D., Hsieh, J., & Kosten, T. R. (2015). **Pharmacologic management of comorbid post-traumatic stress disorder and addictions.** *The American Journal on Addictions, 24*, 705-712. doi:10.1111/ajad.12306 *Background and Objectives:* Post-traumatic Stress Disorder (PTSD) and substance use disorders (SUD) frequently co-occur, and their combination can increase poor health outcomes as well as mortality. *Methods:* Using PUBMED and the list of references from key publications, this review article covered the epidemiology, neurobiology and pharmacotherapy of PTSD with comorbid alcohol, opiate, and cannabis use disorders. These SUD represent two with and one without FDA approved pharmacotherapies. *Results:* SUD is two to three times more likely among individuals with lifetime PTSD, and suicide, which is made more likely by both of these disorders, appears to be additively increased by having this comorbidity of SUD and PTSD. The shared neurobiological features of these two illnesses include amygdalar hyperactivity with hippocampal, medial prefrontal and anterior cingulate cortex dysfunction. Medications for comorbid PTSD and SUD include the PTSD treatment sertraline, often used in combination with anticonvulsants, antipsychotics, and adrenergic blockers. When PTSD is comorbid with alcohol use disorder (AUD), naltrexone, acamprosate or disulfiram may be combined with PTSD treatments. Disulfiram alone may treat both PTSD and AUD. For PTSD combined with opiate use disorder methadone or buprenorphine are most commonly used with sertraline. Marijuana use has been considered by some to be a treatment for PTSD, but no FDA treatment for this addiction is approved. Pregabalin and D-cycloserine are two innovations in pharmacotherapy for PTSD and SUD. *Conclusions and Scientific Significance:* Comorbid PTSD and SUD amplifies their lethality and treatment complexity. Although they share important neurobiology, these patients uncommonly respond to a single pharmacotherapy such as sertraline or disulfiram and more typically require medication combinations and consideration of the specific type of SUD.

ADDITIONAL CITATIONS

Bernardy, N. C., Lund, B. C., Alexander, B., & Friedman, M. J. (2014). **Increased polysedative use in veterans with posttraumatic stress disorder.** *Pain Medicine, 15*, 1083-1090. doi:10.1111/pme.12321 This study examined polysedative prescribing among Veterans with PTSD over an 8-year period using national VA data among regular medication users. In 2004, 9.8% of Veterans with PTSD concurrently received medications from three or more sedative classes. By 2011, the prevalence of concurrent use involving three or more classes increased to 12.1%. The most common combination was an opioid plus a benzodiazepine, taken concurrently by 15.9% of Veterans with PTSD.

ADDITIONAL CITATIONS *continued*

Dabbs, C., Watkins, E. Y., Fink, D. S., Eick-Cost, A., & Millikan, A. M. (2014). **Opiate-related dependence/abuse and PTSD exposure among the active-component U.S. military, 2001 to 2008.** *Military Medicine, 179*, 885-890. doi:10.7205/MILMED-D-14-00012 This study determined whether individuals diagnosed with opiate dependence and abuse are at increased odds of having a prior diagnosis for PTSD compared to matched controls within a large military population. After adjusting for sociodemographic and military characteristics, the odds of having a prior diagnosis of PTSD was 28 times greater for Servicemembers with opiate abuse/dependency compared to controls. These findings suggest active duty military personnel diagnosed with PTSD should be closely monitored to reduce the likelihood of future morbidity because of opiate dependence or abuse.

Holbrook, T. L., Galarneau, M. R., Dye, J. L., Quinn, K., & Dougherty, A. L. (2010). **Morphine use after combat injury in Iraq and post-traumatic stress disorder.** *New England Journal of Medicine, 362*, 110-117. doi:10.1056/NEJMoa0903326 This article examined the acute administration of opioids within hours of their combat injuries among 696 OIF U.S military personnel (243 who had PTSD and 453 who did not) during early resuscitation and trauma care. Among the patients in whom PTSD developed, 61% received morphine; among those in whom PTSD did not develop, 76% received morphine (odds ratio, 0.47; $P < 0.001$). The findings suggest that the use of morphine during trauma care may reduce the risk of subsequent development of PTSD after serious injury.

Oliva, E. M., Christopher, M. L. D., Wells, D., Bounthavong, M., Harvey, M., Himstreet, J., . . . Veterans Health Administration Opioid Overdose Education and Naloxone Distribution National Support and Development Workgroup. (2017). **Opioid overdose education and naloxone distribution: Development of the Veterans Health Administration's national program.** *Journal of the American Pharmacists Association, 57*, S168-S179. doi:10.1016/j.japh.2017.01.022 This article highlights the efforts undertaken by the VA to disseminate opioid overdose education broadly to VA staff and Veterans and naloxone distribution, detailing the national opioid safety program in VA.

Pietrzak, R. H., Goldstein, R. B., Southwick, S. M., & Grant, B. F. (2011). **Prevalence and Axis I comorbidity of full and partial posttraumatic stress disorder in the United States: Results from wave 2 of the National Epidemiologic Survey on Alcohol and Related Conditions.** *Journal of Anxiety Disorders, 25*, 456-465. doi:10.1016/j.janxdis.2010.11.010 This study used data from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions (n = 34,653) to examine lifetime Axis I psychiatric comorbidity of posttraumatic stress disorder (PTSD) in a nationally representative sample of U.S. adults. Lifetime prevalences±standard errors of PTSD and partial PTSD were 6.4%±0.18 and 6.6%±0.18, respectively. PTSD and partial PTSD were associated with elevated lifetime rates of mood, anxiety, and SUDs, and suicide attempts.

Rasmusson, A. M., & Shalev, A. Y. (2014). **Integrating the neuroendocrinology, neurochemistry, and neuroimmunology of PTSD to date and the challenges ahead.** In M. J. Friedman, T. M. Keane, & P. A. Resick (Eds.), *Handbook of PTSD: Science and practice* (2nd ed., pp. 275-299). New York, NY: Guilford Press. This chapter provides a comprehensive review of neurotransmitter,

ADDITIONAL CITATIONS *continued*

neuropeptide, neurohormonal and neuroinflammatory alterations associated with PTSD. It includes a special section on abnormalities in the endogenous opioid system.

Scholl, L., Seth, P., Kariisa, M., Wilson, N., & Baldwin, G. (2019). **Drug and opioid-involved overdose deaths – United States, 2013-2017**. *Morbidity and Mortality Weekly Report, 67*, 1419-1427. doi:10.15585/mmwr.mm675152e1 This Centers for Disease Control and Prevention report provides numbers of U.S. drug and opioid overdose deaths across age groups, racial/ethnic groups, county urbanization levels, and in different states. It highlights implications for public health practice.

U.S. Department of Health and Human Services, Office on Women's Health. (2017). ***Final report: Opioid use, misuse, and overdose in women.*** Retrieved from https://www.womenshealth.gov/files/documents/final-report-opioid-508.pdf This final report was developed as part of an initiative of the U.S. Department of Health and Human Services Office on Women's Health to examine prevention, treatment, and recovery issues for women who misuse opioids, have OUD, and/or overdose on opioids.

U.S. Department of Veterans Affairs, & U.S. Department of Defense. (2017). ***VA/DoD clinical practice guideline for the management of posttraumatic stress disorder and acute stress disorder*** (Version 3.0). Retrieved from https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal012418.pdf This update to the 2010 VA/DoD Clinical Practice Guideline for PTSD offers treatment recommendations for PTSD and acute stress disorder.

Volkow, N. D., & Collins, F. S. (2017). **The role of science in addressing the opioid crisis.** *New England Journal of Medicine, 377*, 391-394. doi:10.1056/NEJMsr1706626 This article reviews where the state of science is now in treating pain and addressing opioid use and discusses what is needed to move the field forward.

Volkow, N. D., & Wargo, E. M. (2018). **Overdose prevention through medical treatment of opioid use disorders.** *Annals of Internal Medicine, 169*, 190-192. doi:10.7326/M18-1397 This article outlines the success of medically treating OUD and recommends future directions of research.

Wyse, J. J., Gordon, A. J., Dobscha, S. K., Morasco, B. J., Tiffany, E., Drexler, K., . . . Lovejoy, T. I. (2018). **Medications for opioid use disorder in the Department of Veterans Affairs (VA) health care system: Historical perspective, lessons learned, and next steps.** *Substance Abuse, 39*, 139-144. doi:10.1080/08897077.2018.1452327 This study used VA data to examine the history of medication assisted therapy (e.g., methadone, buprenorphine, injectable naltrexone) used in the treatment of OUD within VA to document early and ongoing efforts to increase access and build capacity, primarily through the use of buprenorphine, and summarizes research examining barriers and facilitators to prescribing and medication receipt. The authors find that there has been a slow but steady increase in the use of medications for OUD and, despite system-wide mandates and directives, uneven uptake across VA facilities and within patient sub-populations, including some of those most vulnerable.