MAT TRAINING

PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

"Opioid Use Disorder in the Military and Veterans' Treatment Options"

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Ayman Fareed, MD, Disclosures

- Dr. Fareed served on a clinical advisory board for Orexo, AB pharmaceutical company
- Dr. Fareed is currently a consultant to Reckitt Benckiser pharmaceutical company
- Dr. Fareed is currently funded by the department of Veterans Health Administration (VHA)for serving as a site principle investigator on a VHA cooperative study

- This activity's planning committee has reviewed the content of Dr. Fareed's module and determined that this disclosure information poses no bias or conflict to this presentation.

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.

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Frances Levin, MD is a consultant for GW Pharmaceuticals and receives study medication from US Worldmed. This activity's planning committee has determined that Dr. Levin's disclosure information poses no bias or conflict to this presentation.

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Educational Objectives

- At the conclusion of this activity participants should be able to understand:
  - Prevalence of comorbid PTSD, pain and opioid use disorder in Veterans
  - Pathophysiology of comorbid PTSD, pain and opioid use disorder
  - Management of comorbid PTSD and opioid use disorder
  - Psychotherapeutic interventions for comorbid PTSD and opioid use disorder
  - Management of pain in veterans who are at risk or have opioid use disorder
  - Opioid agonists treatment with buprenorphine or methadone for veterans

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Accreditation Statement

- American Academy of Addiction Psychiatry (AAAP) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

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  - Date of Release
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Participation in this CME Activity

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- After successfully passing, you will receive an email detailing correct answers, explanations and references for each question of the Post Test.

Case Vignette

- **Case Vignette:** Veteran is a 30-year-old, 2 x divorced, Caucasian male. He sought substance use disorder treatment because "I want to come off those medicines, still a difficult process for me." Veteran described a history consistent with PTSD, chronic (combat); Opiate Use Disorder, severe; and Tobacco Use Disorder. Veteran denied a family history of psychiatric illness and substance use disorder (SUD).

- Veteran stated he began to use narcotic pain medication including Oxycodone 6 years ago when he was prescribed (RX) these medications for chronic pain stemming from injuries incurred during an explosion. Veteran was prescribed morphine 3 years ago. Veteran stated he is currently being prescribed morphine 30mg 3 to 4 x per day. He stated he is also prescribed Lortab, dose unspecified, last took "1 week ago" 4 pills. Veteran stated he last took opiates, Morphine, today 1 pill 30mg. He swallows the pills, no crushing, or chewing.

Case Vignette

- Veteran endorsed the following Opioid Use Disorder criteria for the past year:
  - Opioids are often taken in larger amounts or over a longer period than was intended – YES, taking more than RX, running out of his RX early
  - There is a persistent desire or unsuccessful efforts to cut down or control opioid use- YES; longest period of abstinence is 3 or 4 days.
  - A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects- YES, reported buying off the street
  - Craving, or a strong desire or urge to use opioids- YES
  - Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home- YES
  - Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids- YES
  - Important social, occupational, or recreational activities are given up or reduced because of opioid use- YES
  - Recurrent opioid use in situations in which it is physically hazardous- YES
  - Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance- YES
  - Tolerance, - YES
  - Withdrawal, - YES, feels shaky/sweaty & nauseous

Clinical Questions for Case Vignette:

- 1. What treatment option is better for this patient, opioid detoxification or opioid maintenance treatment?
- 2. Can opioid maintenance treatment reduce his comorbid pain?
- 3. Which psychosocial treatment approach would be most beneficial for this patient's comorbid PTSD/ Opiate Use Disorder, severe?

Complete the Post-Test for answers.

Prevalence of comorbid PTSD, pain and opioid use disorder in Veterans

- It was reported that individuals with opioid use disorder had the highest prevalence of PTSD (33%) compared to all other substances (Mill et al. 2007).
- The veteran population is more susceptible to get addicted to opioids due to their high risk for combat inflicted traumatic injuries and PTSD.
- Opioids may ameliorate symptoms of PTSD and could be abused to self-medicate for the symptoms especially during periods of high stress.
- The U.S. faced a heroin epidemic in the 1960s which coincided with the Vietnam War.

Prevalence of comorbid PTSD, pain and opioid use disorder in Veterans

- The availability of heroin and exposure to life threatening experiences could explain the increased prevalence among US troops serving in Vietnam.
- It was reported at that time that 10-15% of US troops were suffering from heroin addiction, with rates as high as 25% in some units (Jaffe 2010).
- Despite the increased prevalence of heroin while they were in Vietnam, many of those veterans quit using it when they returned home.
- It was reported that only 5% of veterans who were addicted to heroin in Vietnam had become re-addicted within one year of returning home.

Prevalence of comorbid PTSD, pain and opioid use disorder in Veterans

- The new epidemic of prescribed opioid abuse is coinciding with the Persian Gulf and Afghanistan wars.
- A recent study concluded that among US veterans of Iraq and Afghanistan, mental health diagnoses, especially PTSD, were associated with an increased risk of receiving opioids for pain, high-risk opioid use, and adverse clinical outcomes (Seal et al. 2012).
- In this study, compared with 6.5% of veterans without mental health disorders, 17.8% of veterans with PTSD and 11.7% with other mental health diagnoses but without PTSD were significantly more likely to receive opioids for pain diagnoses.
- Receiving prescription opioids (vs not) was associated with an increased risk of adverse clinical outcomes for all veterans, which was most pronounced in veterans with PTSD.

Pathophysiology of comorbid PTSD, pain and opioid use disorder

- It was reported that there may be a relationship between PTSD and use of pain medications warranting further examination of the endogenous opiate system in the pathophysiology of PTSD (Schwartz et al. 2006) .
- Another study reported that PTSD significantly predicted pain rating and related functional impairment. Patients with PTSD had a significantly higher rate of prescribed opioid use compared with those without PTSD (Phifer et al. 2011).

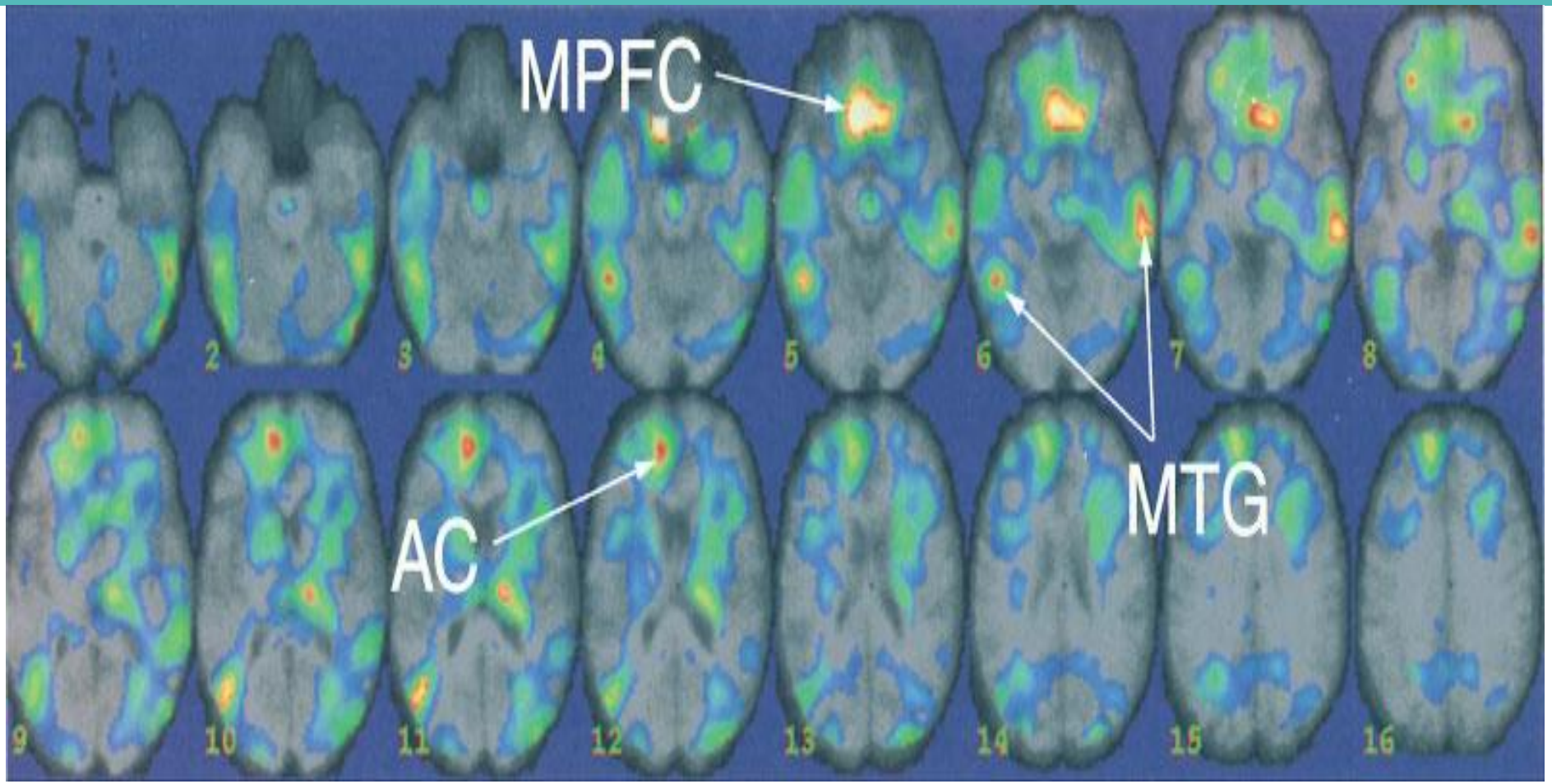
Pathophysiology of comorbid PTSD, pain and opioid use disorder

- A study reported that no evidence indicated a relationship between PTSD symptom clusters and crack/cocaine or alcohol use disorders (Tull et al. 2010).
- However, this study suggested an inverse relationship between hyperarousal and avoidance symptoms and heroin use disorder—that is, the more severe the PTSD symptoms, the greater the risk of opioid use disorder.
- There may be a difference in the drug of choice (i.e., illicit heroin versus prescribed opioids), but these studies suggest a link between PTSD, pain and opiate use disorder.
- An underlying common mechanism may explain this link.

Pathophysiology of comorbid PTSD, pain and opioid use disorder

- Brain regions that are believed to play an important role in PTSD, pain and opiate use disorder include the hippocampus, anterior cingulate cortex, and medial prefrontal cortex (mPFC).
- The hippocampus, anterior cingulate cortex, and mPFC could show decreased activity in response to traumatic cues in individuals with PTSD (Bremner et al. 1999).
- However, the same regions show increased activity in response to opiate-related cues in individuals with opioid use disorder (Langleben et al. 2008).
- These contrasting changes in brain activity in response to traumatic or opiate cues may explain why individuals with comorbid PTSD, pain and opioid use disorder may use opioids to alleviate PTSD symptoms.

Pathophysiology of comorbid PTSD, pain and opioid use disorder



Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS. 1999c. Neural correlates of memories of childhood sexual abuse in women with and without posttraumatic stress disorder. Am J Psychiatry 156:1787–1795

Pathophysiology of comorbid PTSD, pain and opioid use disorder

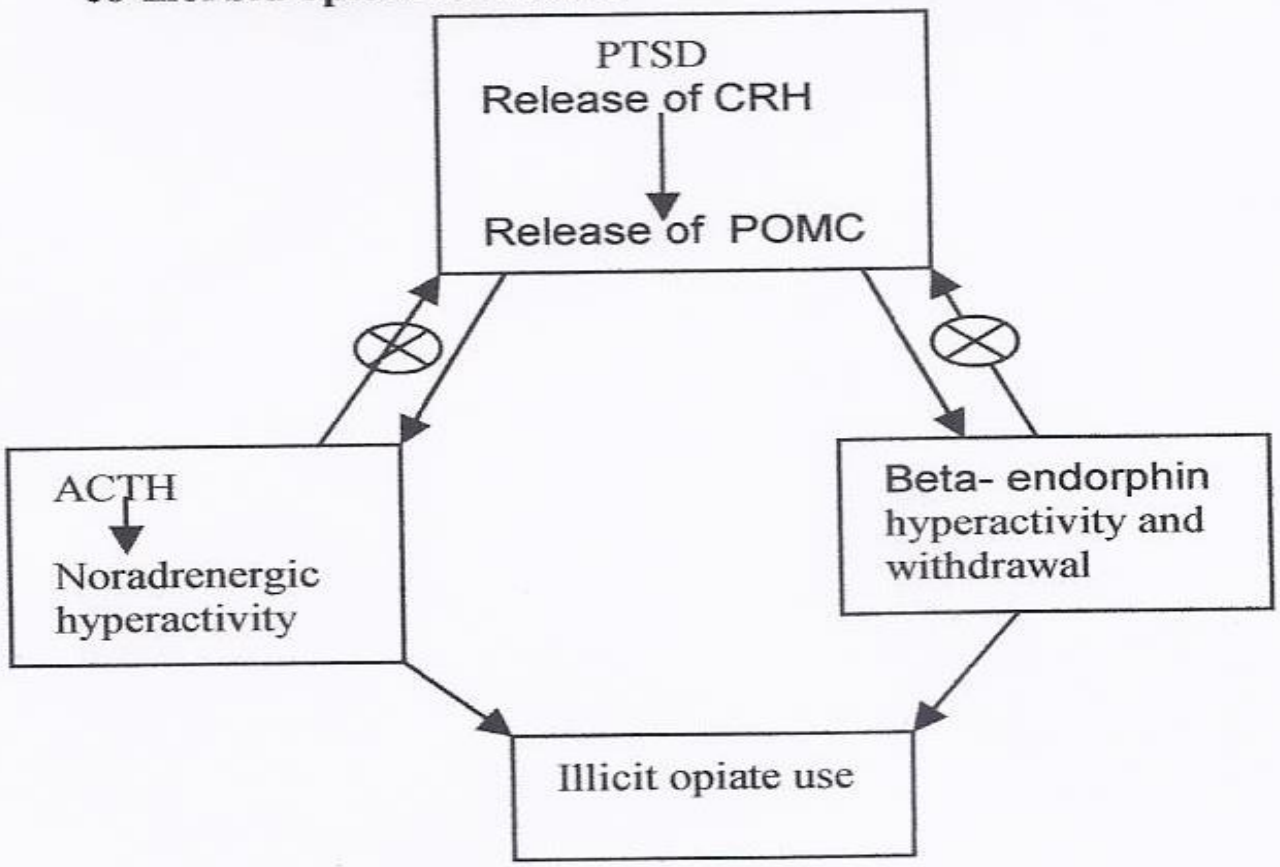
- The emotional numbness due to increased level of noradrenalin and decreased level of dopamine in these brain regions may trigger those individuals to use opiates to modulate the brain activity in the hippocampus, anterior cingulate cortex and mPFC to improve their dysphoric mood and emotional numbness.
- Recently reported data have suggested that acute morphine administration for pain may serve as a protective factor against the development of PTSD , and is associated with decreased number of PTSD symptoms and decreased PTSD symptom severity (Phifer et al. 2011).
- These new data may suggest a common neurobiologic circuit for the co-morbidity between PTSD, pain and opiate use disorder.

Pathophysiology of comorbid PTSD, pain and opioid use disorder

- Continuous exposure to stressful situations leads to compensatory mechanisms to reduce the chronic activation of the adrenocorticotropic hormone (ACTH) and beta endorphin brain systems.
- ACTH tends to inhibit the additional release of corticotropin releasing hormone (CRH).
- Habituation of the endogenous endorphin system occurs as a result of chronic stimulation of the system. The end of the trauma results in a deficit in the endorphin functioning and consequently, endorphin withdrawal
- Therefore, individuals with PTSD are at increased risk for opioid addiction as a result of acute and chronic exposure to stress

Pathophysiology of comorbid PTSD, pain and opioid use disorder

Figure 1: PTSD increases the predisposition to co-morbid opioid addiction



Fareed A, Eilender P, Haber M, Bremner DJ, Whitfield N, Drexler K, Co-morbid Post Traumatic Stress Disorder and Opiate addiction, a Literature Review, Journal of Addictive Diseases 2013;32(2):168-79

Management of comorbid PTSD and opioid use disorder

- Few studies addressed the co-morbidity of opioid use disorder and PTSD.
- A study found that among childhood victimized women, PTSD was associated with more frequent use of heroin at a 1-year follow-up, even after controlling for duration of the stay at the clinic, background, other traumatic experiences, and heroin use 1 year prior the assessment of their PTSD (Schiff et al. 2010)
- This study reports a poor treatment outcome for the opioid use disorder in this population despite receiving opioid substitution treatment with methadone.

Management of comorbid PTSD and opioid use disorder

- A study found that despite the significant improvements in heroin use, PTSD was associated with continued physical ($P < .01$) and mental disability ($P < .01$) and reduced occupational functioning throughout the 2-year follow-up. This study suggested that an intervention targeting both heroin use disorder and PTSD may help improve the outcomes of those with comorbid PTSD (Mills et al. 2007) .
- Another study concluded that opioid substitution therapy is as effective at reducing substance use in PTSD patients as it is in patients without PTSD, but additional services are needed for treatment of psychological problems that are largely unchanged by treatment for substance use (Trafton et al. 2006)
- These two studies report good outcome for opiate use disorders with opioid substitution but less favorable outcome for the co-morbid PTSD that warrant additional psychotherapeutic interventions targeting both disorders.

Psychotherapeutic interventions for comorbid PTSD and opioid use disorder

- The presentation of comorbid Substance Use Disorders (SUD) and PTSD is common. Patient's presenting with both disorders endorse higher impairment in their daily functioning than individuals presenting with either disorder alone. The comorbidity of SUD and PTSD has been observed in numerous studies. In the 2010 National Epidemiologic Survey on Alcohol and Related Conditions, nearly half of patients diagnosed with PTSD also met diagnostic criteria for SUD (McCauley et al. 2012).
- It has been a long held belief among providers of SUD and PTSD treatment that individuals who suffer from comorbid SUD and PTSD must first undergo SUD treatment and remain abstinent for an arbitrary period of time, prior to engaging in treatment for PTSD. This sequential model of treatment has remained the standard of care for years.

Psychotherapeutic interventions for comorbid PTSD and opioid use disorder

- Over the past 10 to 15 years, several innovative programs have been developed to simultaneously address comorbid SUD and PTSD. These integrated approaches have fallen into two main camps; non-exposure based psychosocial treatment and exposure-based psychosocial treatment. These integrated models have received growing evidence-based support (van Dam, et al. (2012). While none of the programs focuses on Opioid Use Disorder specifically, all but one, encompass all substances of use without exclusion criteria based on abstinence.
- An integrated approach that incorporates exposure therapy is showing the most promise to address PTSD/SUD concurrently (Berenz & Coffey 2012). More research is needed to further validate specific treatment models. There is a growing awareness that patients receive concurrent treatment for SUD/PTSD. Providers will require training for specific integrated treatment programs.

Non-Exposure Based Psychosocial Treatment Approaches

- **Integrated Cognitive Behavioral Therapy (CBT)** is a manual-guided individual therapy format adapted from a CBT program originally developed for individuals with PTSD and severe mental illness. CBT models focus on reducing anxiety and avoidance of trauma triggers/memories. The model stresses awareness of dysfunctional belief systems to lessen intrusive symptoms i.e. re-experiencing, affective flattening, hyper-vigilance, and increased arousal (Ford & Russo 2006).Integrated CBT is conducted over 12 to 14 weeks of individual therapy. There is modest preliminary support for Integrated CBT as a treatment for PTSD-SUD (Berenz & Coffey 2012).
- **Transcend** is a 12-session module - group format treatment for comorbid PTSD and SUD for Veterans. The first 6 weeks address coping skill development and the later 6 weeks focus on processing trauma. Transcend includes concepts from CBT, twelve-step, and psychodynamic theory; in addition substance use education, relapse prevention, development of a support network (peer support), and twelve-step attendance is encouraged. Data is promising but at present preliminary (McCauley et al. 2012).
- **Trauma Adaptive Recovery Group Education and Therapy (TARGET**) is a manual based, trauma-focused, present-centered, emotional self-regulation approach to integrated treatment for PTSD and SUD. It is conducted in a group and individual format. TARGET focuses on the patients' core values and resilience with the development of skills in sequence using the acronym, FREEDOM; which stands for Focus, Recognize, Emotions, Evaluate, Define, Option, and Make a Contribution. The development of coping skills mirrors the neurobiology of adaptive development and the three phases of PTSD treatment. Phase I addresses stabilization and self-regulation; phase 2 focuses on trauma processing; and phase 3 prioritizes the development of the patient's overall lifestyle, values, goals, and plans (Ford & Russo 2006). A brief 9-session TARGET version versus treatment as usual was found to be significantly better in regard to abstinence self-efficacy (Ford & Russo 2006).

Non-Exposure Based Psychosocial Treatment Approaches

- **Seeking Safety** (SS) is a non-exposure based treatment program for individuals suffering from PTSD and comorbid SUD. Seeking Safety is a highly structured module format with 25 possible sessions, which can be adapted to be fewer or longer. The modules can be conducted in any order with each topic independent of one another. Therapy can be implemented in a group or individual format. Seeking Safety is designed to be implemented with other treatment modalities such as pharmacotherapy and twelve-step groups. (Najavits, L.M et al. 2009). Seeking Safety focuses on developing and maintaining safety, the primary goal, by decreasing risky behaviors, establishing boundaries, and learning coping skills to combat substance triggers. Exploration of past traumas is excluded. Among studies with rigorous methodologies ,SS evidenced limited benefit over treatment as usual and should be utilized in conjunction with other treatment modalities (Berenz & Coffey 2012). Of note, a small study using SS with exposure based PTSD therapy found positive treatment outcome for both PTSD and SUD. Patients selected the number of sessions for each treatment modality. In addition, patients rated the exposure-based sessions as the most effective component of the program (Berenz & Coffey 2012).

- **Trauma Exposure & Empowerment Model (TREM)** was developed for women with PTSD and severe mental disorders including SUD. TREM is provided in a group format and addresses the unique way in which women process and cope with trauma and substance use. TREM develops awareness of personal and relational skills and psycho-education focusing on psychosexual development delays due to trauma (Ford & Russo 2006). Preliminary data in a uncontrolled study is promising (McCauley et al. 2012).

Exposure-Based Psychosocial Treatment Approaches

- **Concurrent treatment of PTSD and Substance Use Disorders with Prolonged Exposure (COPE)** formerly known as Concurrent Treatment for PTSD and Co-occurring Cocaine Dependence, is a manual based treatment format for individuals suffering from PTSD and SUD. It was modified to address all substances and consequently re-named. The program combines imaginal and in vivo exposure techniques to address PTSD symptoms and cognitive behavioral techniques to focus on substance use disorders.
- COPE is conducted in 12 weeks of individual, weekly, 90-minute psychotherapy sessions combining evidence based CBT for SUD and prolonged exposure for PTSD (Killeen et al. 2011). Coping skills training is conducted throughout all sessions of COPE (Berenz & Coffey 2012). COPE addresses PTSD symptoms by providing psycho-education about the relationship between PTSD and substance use and normalizes one's reactions to trauma. The exposure techniques are utilized to facilitate the processing of trauma experiences.
- The SUD component of COPE addresses recognizing/ managing cravings and development of a relapse prevention plan by identifying high-risk environments/ triggers (McCauley et al. 2012). COPE does not utilize confrontational techniques common in traditional SUD treatment programs, as this can trigger PTSD symptoms. COPE utilizes motivational enhancement therapy.
- Preliminary research has found COPE to be associated with significant improvement in both PTSD and SUD symptoms (Killeen et al. 2011).

Exposure-Based Psychosocial Treatment Approaches

- **Substance Dependence PTSD Therapy (SDPT)** addresses a patient's PTSD symptoms through an adaptation of coping skills and cognitive techniques with focus on triggers/cues in one's environment. SDPT incrementally incorporates in vivo exposure. SDPT was developed as a 2-phase model of treatment. Treatment is conducted individually, twice weekly for 20 weeks. The transition from phase I to phase II is based on clinical criteria. Transition to phase II is based on a patient's progress in phase I by achieving a decrease in substance use, not abstinence. In addition, a patient will appear able to manage the negative affect that can emerge during phase II without a significant relapse (Triffleman, E. et al. 1999). Additional research is needed to validate SDPT as an evidence based PTSD/SUD concurrent treatment model.
- In regard to SDPT and Opioid Use Disorder specially, Triffleman et al. (1999) stated SDPT is appropriate for patients on agonist therapy; however, also noted that Opioid Use Disorder patients not utilizing agonist treatment must be free of opiates for 2 months prior to starting SDPT.

Management of pain in veterans who are at risk or have opioid use disorder

At-risk Behaviors may include
(Ling et al 2011):

- Running out of the prescription before the due date
- Lost or stolen prescriptions
- Seeking multiple providers to get an opioid prescription
- The degree of physical pain does not match the need for a high opioid dose
- Obtaining opioids from illegal sources or from other family members
- Positive urine drug screens for other illicit drugs

Management of pain in veterans who are at risk or have opioid use disorder

- A few studies used buprenorphine for pain management for patients who were at risk of developing opiate use disorder.
- Opioid maintenance treatment compared to opioid taper seems to be more effective in reducing illicit opioid use and reducing pain for patients with comorbid non cancer pain and opioid use disorder.
- A multicenter study reported that buprenorphine taper was associated with a higher relapse rate compared to buprenorphine maintenance treatment regardless of adjunctive counseling (Weiss et al. 2011).
- Some studies transitioned patients from short-acting opioids to buprenorphine, which is one of two opioid medications approved for treatment of opioid use disorder in the US.
- A study reported that sublingual (SL) buprenorphine/naloxone was well tolerated and safe for patients with long-term chronic non cancer pain who failed long-term opioid analgesic therapy (Malinoff et al. 2005) .

Management of pain in veterans who are at risk or have opioid use disorder

- A review study reported that buprenorphine could be a good option for treatment of comorbid pain and opiate use disorder, opiate use disorder only and pain only (Heit et al. 2008) .
- An observational study reported that buprenorphine is an effective analgesic in patients who have failed or become tolerant to traditional opiate therapy for chronic pain (Daitch et al. 2012).
- They added that patients taking buprenorphine do not appear to exhibit hyperalgesia and tolerance to the medication.

Management of pain in veterans who are at risk or have opioid use disorder

- A small pilot study suggested that buprenorphine/naloxone should be used for patients at risk of addiction only when the baseline doses are within suggested range (>/60 mg and <200 mg equivalent of morphine) to reduce adverse effects at transitioning (Rosenblum et al. 2012) .
- These studies support the utilization of buprenorphine for patients with chronic non-cancer patients who are at risk for opioid use disorder. However, they have several limitations including being observational, non-randomized, and a small sample size. More studies are needed.

Management of pain in veterans who are at risk or have opiate addiction

- Methadone is the other medication approved for treatment of opioid use disorder in the US.
- Methadone is a long-acting opioid agonist which is also approved for treatment of chronic pain.
- 2 Review studies reported that methadone can help with comorbid non chronic pain for patients with opioid use disorder (Miotto et al. 2005, Ling et al. 2012)
- Transitioning from short-acting or long-acting opioids to methadone is much easier than transitioning to buprenorphine.
- Buprenorphine is a partial mu receptor agonist and switching from a full mu receptor opioid agonist to an opioid partial agonist may precipitate opioid withdrawal.

Management of pain in veterans who are at risk or have opioid use disorder

- Methadone is also much cheaper than buprenorphine which is another advantage for some patients.
- Buprenorphine offers a much better safety profile in regard to medication overdose since it has a ceiling effect due to its partial agonist effect on the mu receptor.
- It is also less cardiotoxic than methadone which has been reported to be associated with prolongation of corrected QT (QTc) interval on the electrocardiogram (EKG).
- Both medications could be used for targeting patients with comorbid pain and opioid use disorder which is a common comorbidity for veterans with PTSD.

Opioid agonist treatment with buprenorphine

- Buprenophine is a partial agonist of the mu receptor and thus has less abuse potential.
- It has a strong affinity and slow dissociation from the receptor i.e. very mild withdrawal compared to other opioids.
- It is long-acting and avoids breakthrough withdrawal.
- It has a ceiling effect and thus is safe in overdose of buprenorphine alone
- Schedule III i.e. can be prescribed by qualified physicians in office based treatment.
- Available in 2 sublingual forms:
  . buprenorphine only.
  . combined buprenorphine and naloxone (opioid antagonist).
- More expensive than methadone.

Opioid agonist treatment with buprenorphine

- Induction on buprenorphine can be done in the office where the patient would be monitored during the induction or at home without monitoring but with recommended instructions and availability of a clinician by phone.
- Veterans should be opioid free for 10-12 hours (if it is a short-acting opioid) and 36-48 hours (if it is a long-acting opioid) before starting the first dose of Buprenorphine.
- Check the veteran for signs and symptoms of opioid withdrawal - use Clinical Opioid Withdrawal Scale, (COWS).
- Give 2-4 mg of Buprenorphine and observe the veteran over the next 1-2 hours.
- If after 2-4 hours the veteran is still in withdrawal, give another 2-4 mg of Buprenorphine. DO NOT EXCEED 8 MG ON DAY ONE.

Opioid agonist treatment with buprenorphine

- On day 2-4, the veteran will need to be reassessed and the dose can be adjusted as needed. DO NOT EXCEED 24 MG PER DAY.
- By the end of the first week the veteran usually feels normal, i.e. no opioid withdrawal and the stabilizing buprenorphine dose would have been determined.
- Most veterans respond to a stabilizing dose between 12-16 mg sl daily.
- The maximum daily dose is 32 mg sl daily.
- Veterans with comorbid pain may benefit from divided doses rather than a single daily dose since analgesic effects of buprenorphine last only 6-9 hours.

Opioid agonist treatment with buprenorphine

- During the stabilization phase, veterans receive weekly prescription refills.
- By the end of the first month, most veterans would be stable on their long-term maintenance dose.
- Veterans who comply with treatment recommendations including providing negative random urin drug test (UDS), attending group therapy sessions as needed and their scheduled appointments with the physician are considered responding to treatment.
- It is very important to educate the veteran about the risk of mixing buprenorphine with other central nervous system depressants like illicit opioids, alcohol and benzodiazepines.

Opioid agonist treatment with buprenorphine

- The veteran will need to be reassessed on a biweekly or monthly basis for the following months while he/she is in the maintenance phase.
- Gradual dose titration of up to 32 mg SL daily can be considered during the biweekly/monthly visits based on UDS results and/or patient's subjective complaints of severe craving or comorbid pain.
- UDS are an objective way to measure a veteran's response to treatment.
- Checking for the presence of buprenorphine and norbuprenorphine in the patient's urine is a confirmation of compliance with treatment and reduces risk of diversion.

Opioid agonist treatment with buprenorphine

- Optimizing the dose of buprenorphine is warranted to block the euphoric effect of the abused opioid, minimize the pain, craving and prevent relapse on opioids.
- Some veterans may respond to a moderate dose range of buprenorphine between 12 – 16 mg SL daily to achieve that goal (recommended maintenance dose).
- Other veterans may need a higher dose range 16-32 mg SL daily to achieve the same goal.

Opioid agonist treatment with buprenorphine

- The severity of the pain and duration of opioid use disorder may reflect the need for higher or lower buprenorphine doses to achieve adequate mu receptor blockade and prevent relapse on opioids.
- Therefore, using flexible dosing to target opioid craving, pain control and negative UDS may offer a good strategy for improving response to treatment without the need for some veterans to be on the high-dose range to achieve that goal.

Opioid agonist treatment with methadone

- Methadone is a full agonist of the mu receptor i.e. good analgesia.
- It is long-acting i.e. no breakthrough withdrawal.
- Methadone overdose is lethal due to the linear relationship between the dose and respiratory depressant effect.
- It is a schedule II and is restricted to specialized clinics for the treatment of opioid use disorder i.e. not available for office-based treatment except for treatment of pain.
- It is not expensive but requires daily visits which may add to the overall cost.
- It is available in oral form, which can decrease the spread of HIV and Hepatitis in IV drug users.

Opioid agonist treatment with methadone

- Initiating treatment with methadone for opioid substitution is always monitored in an outpatient clinic setting.
- Sometime the induction may take place in an inpatient setting for certain high-risk patients (eg. pregnant women with opioid use disorder)
- Unlike buprenorphine, methadone induction does not require that the veteran should be exhibiting opioid withdrawal because it is a mu receptor agonist and it does not displace other opioids from the receptor.

Opioid agonist treatment with methadone

- Starting dose of methadone should not exceed 40 mg on the first day of methadone induction per federal regulations. Most patients respond to 20-30 mg on the first day of the induction.
- It is very important to educate the veteran about the risk of mixing methadone with other central nervous system depressants like illicit opioids, alcohol and benzodiazepines.
- A dose titration by 5-10 mg every 3 to 5 days is recommended for veterans with opioid withdrawal or expressing craving for illicit opioids or comorbid pain.

Opioid agonist treatment with methadone

- It usually takes three to four weeks to reach a therapeutic dose of methadone.
- The target for a therapeutic dose is 60 mg or above daily as recommended by the federal regulations.
- Doses above 100 mg daily have been used by clinicians for veterans who still use illicit opioids on the lower dose range but there is very limited randomized studies to support the efficacy and safety of this practice.
- Random UDS should be collected more frequently during the induction/stabilization phases to measure the response to treatment.

Opioid agonist treatment with methadone

- Positive UDS for opioids and craving for opioids is an indication for a dose titration.
- Checking for methadone peak and trough levels before dose escalation is indicated to ensure compliance with treatment and reduce of the risk of diversion.
- Quick dose titration should be avoided to prevent the risk of methadone overdose due to the cumulative effect of the rapid dose escalation on the respiratory drive.
- Methadone peak and trough levels are another helpful tool to provide more objective information for dose adjustment.

Opioid agonist treatment with methadone

- Methadone is usually dispensed once daily for the sake of opioid n=maintenance treatment, but if the ratio of the peak-to-trough level is more than 2:1, a split dosing could be considered for some veterans who may complain of opioid withdrawal near the end of the dosing interval.
- Split dosing can also be considered for veterans with comorbid chronic pain.
- Pregnant female veterans may need a dose increase to prevent opioid withdrawal during the third trimester due to increased methadone metabolism and clearance at that time.

Opioid agonist treatment with methadone

- A panel of experts recommended EKG screening for patients on MMT due the risk of QTc interval prolongation associated with MMT (Martin et al 2011).
- The panel recommends to screen for QTc prolongation before induction on methadone, one month after induction and annually.
- While this is a good and safe practice the panel revised their statement to reflect that the EKG screening should not be a barrier for patients who are seeking MMT since the benefit of MMT outweighs the risk of the rare cardiac arrhythmia (Torsade de Pointe) associated with QTc prolongation.

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Funding for this initiative was made possible (in part) by Providers' Clinical Support System for Medication Assisted Treatment (1U79TI024697) from SAMHSA. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

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