

**Pharmacologic
Guidelines for
Treating Individuals
with Post-Traumatic Stress
Disorder and Co-Occurring
Opioid Use Disorders**



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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration

Pharmacologic Guidelines for Treating Individuals with Post-Traumatic Stress Disorder and Co-Occurring Opioid Use Disorders

Acknowledgments

This document was produced for the Substance Abuse and Mental Health Services Administration (SAMHSA) by Westat under the Co-Occurring Mental Health and Substance Abuse Disorder (COD) Knowledge Synthesis, Product Development, and Technical Assistance (CODI) contract (reference number 283-07-0610). Charlene E. Le Fauve, Ph.D.; Tison Thomas, M.S.W.; Onaje Salim, M.A., L.P.C.; Jayme S. Marshall, M.S.; and Deborah Stone, Ph.D. served as the Government Project Officers.

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Recommended Citation

Substance Abuse and Mental Health Services Administration, *Pharmacologic Guidelines for Treating Individuals with Post-Traumatic Stress Disorder and Co-Occurring Opioid Use Disorders*. HHS Publication No. SMA-12-4688, Rockville, MD: Substance Abuse and Mental Health Services Administration, 2012.

Originating Office

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HHS Publication No. SMA-12-4688.
Printed 2012

Individuals with co-occurring mental and substance use disorders (COD) are common in behavioral health and primary health settings. These individuals frequently benefit from pharmacologic interventions, whether for mental disorders, substance use disorders, or both. While principles for providing COD services establish a framework for prescribing pharmacologic agents to individuals diagnosed with COD, specific combinations of disorders have unique features that must be considered in developing pharmacologic strategies.

Currently, there are no documents that address Post-Traumatic Stress Disorder (PTSD) and co-occurring opioid use disorders in a brief, easy-to-use format that provides guidance to both frontline practitioners, as well as to system or program policymakers. As a companion to the Substance Abuse and Mental Health Services Administration's (SAMHSA's) *General Principles for the Use of Pharmacological Agents to Treat Individuals with Co-Occurring Mental and Substance Use Disorders*, this document provides guidelines for pharmacologic interventions for individuals with PTSD and co-occurring opioid use disorders.

Development of the Guidelines

The *Pharmacologic Guidelines for Treating Individuals with Post-Traumatic Stress Disorder and Co-Occurring Opioid Use Disorders* were assembled by a task order work group, which included federal SAMHSA staff and contractors.

These guidelines were developed from a search of relevant, peer-reviewed literature available on PubMed, and from practice guidelines currently in clinical use. Treatment recommendations were made if supported by more than one clinical study or randomized, double-blind clinical trial showing the efficacy of a treatment or medication, or if a pharmacotherapy were specifically approved by the U.S. Food and Drug Administration for treatment of PTSD or opioid dependence. Each of the guidelines is supported by an evidence base—a reference list accompanies this document.

The guidelines were reviewed and rated by an expert Consensus Panel (i.e., on a 5-point scale, “How much

do you agree or disagree that each statement should be included in the final Guidelines Document?”). The panel was convened on January 27 and March 1, 2011 to discuss the guidelines. The role of the Consensus Panel was to provide guidance based on up-to-date research, their experiences, and expertise. The panel was made up of 33 individuals who are identified as experts in psychiatry, pharmacotherapy, COD, mental health, addictions, health center administration, and health reform. All panelists were nominated by national professional organizations or the SAMHSA federal staff. The Consensus Panel process and Consensus Panel membership are discussed in more detail in a separate summary report.

Target Audience

The primary target audience for these guidelines is providers who prescribe medication for adults with COD. This includes psychiatrists, primary care physicians, nurse practitioners and other nurse prescribers, physician assistants, and other licensed prescribers. In the document, the term “prescribers” is used to describe this audience.

The secondary target audience is individuals who work in administrative and leadership roles at the program, agency, or system level. This may include medical directors, clinical directors, executives, quality managers, and regulators. These guidelines can assist in the design of policies and protocols to support best practice pharmacologic interventions for individuals with COD in all settings. They are intended to support the attainment of valued recovery outcomes and the more efficient and effective use of resources for individuals with complex challenges.

Structure of the Document

The guidelines are organized in the sequence that a practitioner will likely meet, engage, and intervene with an individual with co-occurring PTSD and opioid disorders. These guidelines are not intended to set a standard of care for individuals with these CODs, but rather suggest parameters that clinicians should consider in their prescribing practices.

Introduction

The co-occurrence of PTSD and co-occurring opioid use disorders was selected for guideline development because of the high rates of trauma in substance users and high rates of PTSD amongst those with substance use disorders. The lifetime prevalence of PTSD in adults in the United States is approximately 7 percent (Hildago & Davidson, 2000; Kessler, Berglund, et al., 2005), and past year prevalence is about 4 percent (Kessler, Chiu, et al., 2005). The lifetime prevalence of PTSD among women (9.7%) is 2.5 times that of men (3.6%), and the 12-month prevalence for women (5.2%) is nearly three times that of men (1.8%) (National Comorbidity Survey, 2005). Veterans have a greater prevalence of PTSD than the general population. Lifetime prevalence for Vietnam veterans is 30.9 percent for men and 26.9 percent for women, with current prevalence of 15.2 percent for men and 8.1 percent for women (Kulka et al., 1990). Veterans from the Afghanistan and Iraq wars have a current PTSD prevalence of approximately 14 percent (Tanielian & Jacox, 2008). Among those with PTSD, substance use disorders occur in 21-43 percent of the population (Jacobson et al., 2001). In those with substance use disorders, lifetime prevalence of PTSD ranges from 26-52 percent (Mills et al., 2005; Reynolds et al., 2005), and current PTSD ranges from 15-41 percent (Clark et al., 2004; Dom et al., 2007; Schafer & Najavits, 2007).

Some of the most problematic substances of abuse in PTSD are opioids. For example, for returning veterans from Iraq and Afghanistan, both the widespread availability of opioids and their use in managing the pain of injured soldiers will likely increase the prevalence of this co-occurring condition in clinical settings in this country.

Untreated PTSD in opioid dependent individuals receiving opioid dependence therapies (methadone or buprenorphine maintenance, detoxification treatment, and drug-free residential treatment) has been associated with ongoing mental, physical, and occupational disability, despite improvements in substance abuse (Mills et al., 2007). Symptoms of PTSD do not improve with opioid therapy in those with co-occurring PTSD and opioid dependence (Trafton et al., 2006). Therefore, it is important to screen those presenting for treatment with opioid dependence for co-occurring PTSD. Likewise, it is important to screen those with trauma symptoms for concurrent opioid abuse. It is essential to develop a treatment plan that will appropriately address both disorders.

Effective treatments for PTSD in individuals with opioid disorders include both psychosocial interventions (e.g., relapse prevention, contingency management, prolonged exposure, and teaching coping skills) and pharmacotherapies. The types and sequencing of these modalities will vary between individuals and be influenced by individual choice. Prescribers should discuss risks and benefits of medications so every individual can make an informed choice regarding different treatment options. Psychosocial interventions are key to effective treatment of both conditions. They serve to educate individuals about both disorders, improve awareness on how these problems interact to contribute to poor outcomes, and assist in the development of coping skills to manage PTSD and opioid use disorder symptoms (both in the early and later phases of treatment). A review of effective psychosocial interventions is beyond the scope of these guidelines (publications and practice guidelines are located at <http://apa.org/pubs> and <http://www.psych.org>).

Guidelines

1 Screening

Because of the significant rates of COD, those with opioid use disorders should be proactively screened and assessed for PTSD, and those with PTSD should be proactively screened and assessed for opioid use disorders (American Psychiatric Association, 2006a,b).

2 Concomitant Treatment

If an individual is diagnosed with COD, specific treatment should be initiated for both disorders and should occur concurrently using coordinated, evidence-based treatments including effective psychosocial interventions and pharmacotherapies (American Psychiatric Association, 2006a,b).

3 Pharmacotherapy – PTSD

Pharmacotherapies for individuals with COD should be based on the following:

- An understanding of effective medications for each disorder;
- An assessment that includes consideration of current target symptoms;
- The severity of the opioid use disorder and the PTSD;
- The response to previous treatments for PTSD and/or opioid dependence;
- The presence of other substance use disorders, mental disorders, and/or medical disorders;
- Other concomitant medications;
- Psychiatric stability including risk of harm to self or others;
- The need for structure and support in treatment;
- The need for and ability to access other psychotherapeutic options for PTSD in conjunction with opioid dependence pharmacotherapy treatment;
- An analysis of the risks and benefits of any medication therapy; and
- Individual preferences.

Additional information regarding Guideline 3

Pharmacotherapies shown to be effective for PTSD include:

- Selective Serotonin Reuptake Inhibitors (SSRI) are first-line treatments (sertraline and paroxetine are FDA-approved) (Brady et al., 2000; Brady & Verduin, 2005; Davidson et al., 2001; Marshall et al., 2001; Tucker et al., 2001). Of note, paroxetine has the potential to inhibit methadone metabolism, which could result in increased blood levels of methadone because paroxetine is an inhibitor of cytochrome P450 2D6, which is a metabolic pathway for methadone metabolism (Ferrari et al., 2004).

Other medications for PTSD have been studied and found to have varying degrees of evidence for effectiveness. These medications are listed below. It is important to note that none of these clinical trials have been undertaken in individuals with opioid use disorders, and use of these medications is off-label, but consideration of these medications for symptomatic relief, particularly in combination with FDA-approved medications for treatment of PTSD, might be considered on a case-by-case basis.

- SNRI medications: Venlafaxine has been associated with improvement in some for symptoms of numbing and/or re-experiencing the trauma (Davidson, et al., 2006).
- Tricyclic antidepressants (TCAs): Imipramine (Kosten et al., 1991) and amitriptyline (Davidson et al., 1990) have been shown to significantly reduce PTSD symptoms. In those with opioid dependence and possibly other co-occurring drug use disorders, caution should be exercised in considering TCAs because of the risk of cardiac toxicity, seizures, and potential lethality in overdose or suicide attempt in this population.

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- Monoamine Oxidase Inhibitors: Phenelzine has been shown to significantly reduce PTSD symptoms in controlled clinical trials (Kosten et al., 1991). However, the need to avoid tyramine containing foods, alcohol, certain medications (SSRIs, stimulants, meperidine, decongestants), and illicit drugs, indicates that caution with detailed attention to the individual's history, including impulsivity, be considered before recommending monoamine oxidase inhibitors.
 - Other Antidepressants:
 - Mirtazepine and Nefazodone have been studied in small clinical trials with some positive response on improvement in depressive symptoms, sleep, and anxiety. These are considered second line medications according to VA/DoD Practice Guidelines (<http://www.Healthquality.Va.Gov/PTSD-FULL-2010c.pdf>) (The Management of Post-Traumatic Stress Working Group, 2010).
 - Prazosin is reported to reduce PTSD-associated psychological distress during the daytime, and it has been reported to decrease trauma-associated nightmares and non-nightmare distressed awakenings (Taylor et al., 2006; Thompson et al., 2008).
 - Atypical Antipsychotics: Risperidone has been associated with improvement in PTSD symptoms of hyperarousal and intrusive thoughts in several studies (Padala et al., 2006; Reich et al., 2004) and may be helpful as an augmentation strategy for those who do not respond to Sertraline in selected individuals (Rothbaum et al., 2008).
 - Benzodiazepines may be used in other anxiety disorders in unique circumstances with clear guidelines, but they should not be used to treat PTSD.
 - In PTSD, early use of benzodiazepines (within 1 week of trauma [range 2- to 18-days]) has been associated with higher incidence of PTSD at one and six month follow-up (Gelpin et al., 1996).
 - Benzodiazepines have been associated with toxic drug interaction with opioids, including methadone and buprenorphine. Diazepam and alprazolam, used in this context, can be associated with performance impairment (Lintzeris et al., 2006, 2007; Rogers et al., 1997).
 - Benzodiazepines are also one of the most frequently mentioned classes of drugs found to be present in deaths associated with methadone or buprenorphine use (Maxwell & McCance-Katz, 2010).

4 Pharmacotherapy – Opioid Dependence

Current FDA-approved pharmacotherapies for opioid dependence include buprenorphine, methadone, and naltrexone (oral and extended-release injectable formulations) (Center for Substance Abuse Treatment, 2005). There is no endorsement of one of these medications over another in those with COD.

When prescribing medications for PTSD in opioid-dependent individuals receiving either methadone or buprenorphine, consideration must be given to the potential for drug interactions between the opioid and the psychotropic medication. Information on drug interactions between opioids and other medications can be found at:

<http://www.atforum.com/rx-methadone/index.php#drugint>.

Additional information regarding Guideline 4

When prescribing medications to an individual diagnosed with COD, several drug interactions should be considered:

- Methadone:
 - If medications that might increase methadone concentrations are to be used to treat PTSD symptoms, then obtaining a cardiogram that gives a corrected QT interval (a measure of electrical function of the heart) should be considered. Those at higher risk for prolongation of the QT interval include those with family history of long QT syndrome or a history of risk factors including structural heart disease, syncope, and arrhythmia (Krantz et al., 2009).
 - Individuals should be followed for evidence of opioid toxicity, including altered mental status and decreased respiration. Some drugs that are frequently co-administered with methadone and reportedly increase plasma methadone concentrations include several antibiotics (ciprofloxacin, fluconazole), psychotropics (quetiapine, amitriptyline), and HIV medications (delavirdine) (McCance-Katz et al., 2010).
 - If drugs are administered that could lower methadone plasma concentrations resulting in an increase in daily methadone dose, care should be taken to adjust methadone dose downward to avoid methadone toxicity if the medication(s) contributing to the lower methadone concentrations is/are discontinued.
- Buprenorphine:
 - Drug interaction studies in humans between buprenorphine and psychotropic drugs are limited.

Clinicians should, however, be aware that drugs used in the treatment of PTSD (and other medical/mental disorders) could possibly alter buprenorphine metabolism.

Pharmacotherapies for the treatment of opioid use disorders are described in SAMHSA's Treatment Improvement Protocols (TIP);

- TIP 40: Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (http://buprenorphine.samhsa.gov/bup_guidelines.pdf) (McNicholas, 2004); and
- TIP 43: Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs (<http://store.samhsa.gov/product/sma08-4214>) (Center for Substance Abuse Treatment, 2005).

5 Longitudinal Care

After the resolution of symptoms associated with either PTSD or opioid use disorders, clinicians should continue to assess for symptoms of each disorder and provide any needed treatment. For example, it is possible that as opioid use diminishes through treatment, PTSD symptoms may either emerge or worsen. This is because substances sometimes obscure PTSD symptoms (American Psychiatric Association, 2006b).

6 Polysubstance Abuse

Polysubstance abuse occurs frequently in those with opioid dependence and/or PTSD. The potential adverse impact of polysubstance abuse (McFarlane et al., 2009; Price et al., 2004; Salgado et al., 2007) underscores the importance of prescribers to screen, assess, and treat for these conditions.

Additional information regarding Guideline 6

Common co-occurring substances used include:

- Alcohol use disorders frequently occur in those with opioid use disorders and PTSD frequently co-occurs in those with opioid and alcohol use disorder (American Psychiatric Association, 2006a,b; Bonin et al., 2000; McNicholas, 2004; National Comorbidity Survey, 2005). While opioid therapy does not effectively treat alcohol problems in this population (Srivastava et al., 2008), several medications are available for the treatment of alcohol use disorders including:
 - Naltrexone (oral and extended-release injectable formulations), Acamprosate (Willenbring et al., 2009), and Disulfiram (Barth & Malcolm, 2010), which are FDA-approved for the treatment of alcohol dependence. Note, Naltrexone cannot be used in individuals who require agonist therapy for opioid dependence; and
 - Topiramate, with evidence supporting its use in treatment of alcohol use disorders, is not currently FDA-approved for that indication (Willenbring et al., 2009).
- Nicotine dependence, cannabis, cocaine, and amphetamine use disorders (Norman et al., 2010) frequently co-occur in those with PTSD, and treatment of nicotine dependence has been associated with improved outcomes in smoking cessation in veterans with PTSD (McFall et al., 2010).
 - FDA-approved pharmacotherapies for nicotine dependence include nicotine replacement therapies, bupropion, and varenicline (Fant et al., 2009).
 - While there are no accepted effective pharmacotherapies for cannabis, cocaine, or amphetamine use disorders, ongoing use of these substances may reduce the effectiveness of treatments initiated for opioid dependence and PTSD, and consequently should be addressed in substance abuse treatment settings (Center for Substance Abuse Treatment, 2005).

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Acknowledgments

We wish to acknowledge the many people who contributed to all aspects of this project. In particular, we wish to acknowledge the following contributors and consultants.

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A special thank you to Dr. Elinore McCance-Katz and Dr. Lawrence D. Rickards for providing the first drafts of the *Pharmacologic Guidelines for Treating Individuals with Post-Traumatic Stress Disorder and Co-Occurring Opioid Use Disorders* and *General Principles for the Use of Pharmacological Agents to Treat Individuals with Co-Occurring Mental and Substance Use Disorders*, respectively.



SMA-12-4688. First printed 2012.
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