Management of Substance Abuse in the Military Veteran Population

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Disclosure Statement

- I, Roberta Halley, do not have a vested interest in or affiliation with any corporate organization offering financial support or grant money for this continuing education program, or any affiliation with an organization whose philosophy could potentially bias my presentation.

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Objectives for Pharmacists

- **After completion of this presentation, the Pharmacist should be able to:**
  - Identify pharmacotherapy used in treating substance use disorders
  - Compare and contrast management of substance intoxication and withdrawal
  - Recognize factors contributing to substance use disorders in military veterans

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Objectives for Technicians

- **After completion of this presentation, the Pharmacy Technician should be able to:**
  - Identify pharmacotherapy used in treating substance use disorders
  - Identify pharmacotherapy used to treat substance intoxication and withdrawal
  - Recognize factors contributing to substance use disorders in military veterans

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Objectives for Nurses

- **After completion of this presentation, the Nurse should be able to:**
  - Identify signs and symptoms of substance intoxication and withdrawal
  - Identify pharmacotherapy commonly used to treat substance intoxication and withdrawal
  - Recognize monitoring parameters in patients experiencing substance intoxication and withdrawal

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Outline

- Epidemiology of Substance Use
- Diagnosis of Substance Use Disorder (SUD)
- Marijuana Use
- Opiate Use
  - Management of Opiate Overdose
  - Management of Opiate Withdrawal
  - Opiate Dependence Treatment
- Alcohol Use
  - Management of Acute Alcohol Intoxication
  - Management of Alcohol Withdrawal
  - Alcohol Dependence Treatment
- Resources for Veterans

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Epidemiology of Substance Abuse

- Of U.S. veterans returning from deployment, 39% screened positive for probable alcohol abuse
- An estimated 3% screened positive for probable drug use
- Odds of diagnosis of substance use disorder and major depression were increased when veterans were deployed vs. non-deployed
- Opioid prescriptions written by military physicians increased 4-fold from 2001 to 2009 to almost 3.8 million
- A Department of Defense study found that prescription drug misuse was 4.4% in civilians and 11.7% in veterans

Eisin SV, Schultz MR, Vogt D, et al. Mental and physical health status and alcohol and drug use following return from deployment to Iraq or Afghanistan. *Am J Public Health.* 2012 Mar; 102 Suppl 1:S6-73.

Shen YC, Arkes J, Williams TV. Effects of Iraq/Afghanistan deployments on major depression and substance use disorder: analysis of active duty personnel in the US military. *Am J Public Health.* 2012 Mar; 102 Suppl 1:S80-7.

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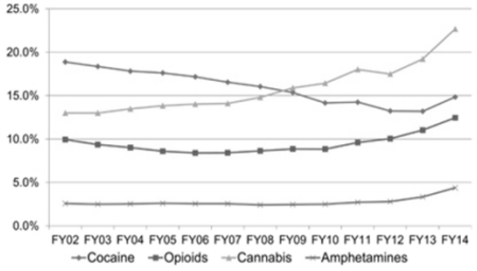
Trends in Rates of Past-Year SUD Diagnoses by Drug among Veterans with PTSD & SUD Diagnoses Treated in VA Health Care



Veterans Health Administration, 2015

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The Cost of Substance Abuse

- Substance abuse associated with ≥ 1 in 4 military deaths
- Alcohol use associated with financial and productivity losses in the U.S. military of about $1.2 billion per year
- Medical expenditures: annual cost $425 million
- 320,000 work days lost
- 10,400 active-duty military unable to deploy due to alcohol use

Schumm JA and Chard KM. Alcohol and Stress in the Military. *Alcohol Research: Current Reviews*. 34(4). Available at: https://pubs.niaaa.nih.gov/publications/arcr344/401-407.htm. Accessed February 8, 2017.

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Risk Factors for Substance Use Disorders

- Post-traumatic stress disorder (PTSD)
  - > 20% of veterans with PTSD have a comorbid substance use disorder
  - Veterans with dual diagnosis tend to be binge drinkers
  - Nearly 1 in 3 veterans seeking SUD treatment also have PTSD
  - Only 40% of veterans who screen positive for mental health or SUD seek professional help
- Deployment
- Depression
- Exposure to combat
- Serious injuries
  - Especially traumatic brain injuries
- Lack of support system

Bowe A and Rosenheck R. PTSD and substance use disorder among veterans: characteristics, service utilization and pharmacotherapy. *J Dual Diagn.* 2015;11(1):22-32.

US Department of Veteran Affairs. PTSD and Substance Abuse in Veterans. Available at: http://www.ptsd.va.gov/public/problems/ptsd_substance_abuse_veterans.asp. Accessed February 8, 2017.

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DSM-5 Diagnosis of Substance Use Disorders

- 10 classes of drugs identified for substance-related disorders
- Substance-related disorders are divided into substance use disorders and substance-induced disorders
- Substance-induced disorders include intoxication and withdrawal

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.

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DSM-5 Diagnosis of Substance Use Disorders

- A problematic pattern of use leading to clinically significant impairment or distress, as manifested by at least two of the following symptoms, occurring within a 12-month period:
  - Substance is often taken in larger amounts or over a longer period than was intended
  - Persistent desire or unsuccessful efforts to cut down or control substance use
  - Great deal of time spent in activities necessary to obtain the substance, use the substance, or recover from its effects
  - Craving or strong desire to use the substance
  - Recurrent substance use resulting in failure to fulfill major role obligations at work, school, or home
  - Continued substance use despite persistent or recurrent social or interpersonal problems caused or exacerbated by effects of the substance
  - Important social, occupational, or recreational activities are given up or reduced because of substance use

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.

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DSM-5 Diagnosis of Substance Use Disorders

- Recurrent substance use in situations in which it is physically hazardous
- Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem likely to have been caused or exacerbated by the substance
- Tolerance, as defined by either of the following:
  - Need for markedly increased amounts of the substance to achieve intoxication or desired effect
  - Markedly diminished effect with continued use of the same amount of the substance
- Withdrawal, as manifested by either of the following:
  - Characteristic withdrawal symptoms for that substance
  - Substance is taken to relieve or avoid withdrawal symptoms

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.

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Marijuana Use in Military Veterans

- Medical marijuana approved in several states as treatment for PTSD
- Currently no controlled studies regarding efficacy
- Cannabis use increased from 13.0% in 2002 to 22.7% in 2014
- Cannabis use disorder has been the most diagnosed SUD in VA health care since 2009
- More than 40,000 veterans with PTSD have cannabis use disorder

Bonn-Miller MO, Rousseau GS. US Department of Veteran Affairs. Marijuana Use and PTSD Among Veterans. Available at: http://www.ptsd.va.gov/professional/co-occurring/marijuana_use_ptsd_veterans.asp. Accessed February 8, 2017.

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Assessment Question #1

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Opiate Use in Military Veterans

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Opiate Use in Military Veterans

- Rates of chronic pain and opioid use are higher in infantry than civilian populations (44.0% and 15.1% vs. 26.0% and 4.0%, respectively)
- Between 2004 and 2008, ~32% of patients treated through the VA received at least one prescription for opioids
- Oxycodone and hydrocodone are among the prescription drugs commonly abused by military personnel
- Veterans may have increased risk of overdose due to increase in prescribing of opiates

Toblin RL, Quartana PJ, Riviere LA, et al. Chronic pain and opioid use in US soldiers after combat deployment. *JAMA Intern Med.* 2014 Aug;174(8):1400-1.

Bohnert A, Valenstein M, Bair MJ, et al. Associate between opioid prescribing patterns and opioid overdose-related deaths. *JAMA. 2011;305:1315-1321.*

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Opiate Overdose: Clinical Presentation

- Physical Examination: Signs/Symptoms
  - Respiratory depression
  - Depressed mental status
  - Decreased tidal volume
  - Decreased bowel sounds
  - Pupil constriction
  - Seizure

Stolbach A and Hoffman R. Acute opioid intoxication in adults. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

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Management of Opiate Overdose

- Administer naloxone (Evzio®, Narcan®)
  - Preferably IV
    - 0.04 to 0.05 mg initially
    - Titrate until respiratory rate is ≥12 breaths per minute
  - Intranasal, SC, or IM if IV access not feasible
- Short duration of action
  - May need repeat doses
- Activated charcoal and gastric emptying typically not used due to risk of aspiration

Stolbach A and Hoffman R. Acute opioid intoxication in adults. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

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Management of Opiate Overdose

- Naloxone monitoring parameters
  - Therapeutic effects
    - Resolution of respiratory depression and CNS depression
  - Side effects
    - Hypotension
    - Ventricular tachycardia
    - Pulmonary edema
    - Opiate withdrawal symptoms

Stolbach A and Hoffman R. Acute opioid intoxication in adults. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

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Assessment Question #2

Opiate Withdrawal: Clinical Presentation

- Physical examination: Signs/Symptoms
  - Nausea/vomiting
  - Abdominal cramping
  - Diarrhea
  - Dysphoria
  - Rhinorrhea
  - Lacrimation
  - Myalgia/arthralgia
  - Pupillary dilation
- Onset
  - 6 to 12 hours after last dose of short-acting opioid
  - 24 to 48 hours after cessation of methadone
- Severity depends on tolerance

Stolbach A and Hoffman R. Opioid withdrawal in the emergency setting. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Management of Opiate Withdrawal

- Withdrawal due to interruption of opioid use
  - Fluid resuscitation if needed
  - Methadone 10 mg IM or 20 mg PO
- Withdrawal due to opioid antagonist
  - Fluid resuscitation if needed
  - Non-opioid adjunctive medications
    - Clonidine 0.1 to 0.3 mg every hour until symptoms resolve
    - Diazepam 10 to 20 mg IV every 5 to 10 minutes
    - Promethazine 25 mg IM or IV
    - Loperamide 4 mg PO or octreotide 50 mcg SC

Stolbach A and Hoffman R. Opioid withdrawal in the emergency setting. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Opiate Dependence Treatment

- Pharmacotherapy
  - Opioid agonists
    - Methadone (Dolophine®)
    - Buprenorphine (Belbuca®, Butrans®, Probuphine®)
  - Opioid antagonists
    - Naltrexone (Revia®)
  - Opioid agonist/antagonist
    - Buprenorphine/naloxone (Suboxone®)
- Nonpharmacological therapy
  - Individual or group addiction counseling

Opioid Agonists

- Mechanism of Action
  - Mu-opioid receptor agonist (methadone)
  - Mu-opioid receptor partial agonist (buprenorphine)
- Side effects
  - Constipation
  - Mild drowsiness
  - Sweating
  - Peripheral edema
  - Erectile dysfunction
  - QT prolongation
  - Hyperalgesia
- Associated with lower mortality rates

Gibson A, Degenhardt L, Mattick RP, et al. Exposure to opioid maintenance treatment reduces long-term mortality. *Addiction.* 2008; 103(3):462.

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Methadone (Dolophine®)

- Dosing
  - Initial: Up to 40 mg on Day 1
  - Titrate to maintenance dose
    - Prevents withdrawal symptoms for 24 hours
    - Typically 80 to 120 mg per day
- Drug interactions
  - P450 3A4 substrate
- Regulations*
  - Patient must have documented opioid use disorder for at least one year of continuous use
  - Patient must be 18 years of age

* Exceptions to these criteria exist

Strain E. Pharmacotherapy for opioid use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 26

Buprenorphine (Belbuca®, Butrans®, Probuphine®)

- Formulations
  - Buccal film (Belbuca®)
  - Transdermal patch (Butrans®)
  - Subdermal implant (Probuphine®)
- Dosing
  - Buccal film and transdermal patch
    - Initial dose determined based on type of opioid dependence, time since last use, and level of dependence
    - Titrate as rapidly as possible to effective dose
    - Typical range 4 to 24 mg per day
    - Taper gradually by 2 mg every one to two weeks
  - Subdermal implant
    - 4 single-rod implants (74.2 mg each) inserted into upper arm and removed after 6 months
- Drug interactions
  - P450 3A4 substrate

Strain E. Pharmacotherapy for opioid use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 27

Methadone vs. Buprenorphine

- Buprenorphine does not require observed ingestion in a clinic
- Patients equally likely to continue therapy when fixed medium or high doses are used
- Methadone has higher potential for lethal overdose
- Buprenorphine causes less respiratory depression
- Patients taking buprenorphine are less likely to use illicit opioids than those taking methadone

Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rv.* 2014 Feb 6;(2):CD002207.

Bell JR, Butler B, Lawrance A, et al. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend.* 2009 Sep 1;104(1-2)73-7.

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Naltrexone (Revia®, Vivitrol®)

- Mechanism of Action
  - Pure opioid antagonist
- Formulations
  - Oral tablet (Revia®)
  - Intramuscular depot injection (Vivitrol®)
- Dosing
  - Start 3 to 6 days after last use of short-acting opioids, or
  - Start 7 to 10 days after last use of methadone or buprenorphine
  - Tablet: 50 mg per day
  - Depot injection: 380 mg IM every 4 weeks
- Naloxone challenge test required first
- Side effects
  - Nausea
  - Dizziness
  - Headache
  - Fatigue

Strain E. Pharmacotherapy for opioid use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 29

Buprenorphine/naloxone (Suboxone®)

- Mechanism of action
  - Mu-opioid receptor partial agonist/mu-opioid receptor antagonist
- Dosing
  - Day 1
    - Buprenorphine 2 mg/naloxone 0.5 mg, or buprenorphine 4 mg/naloxone 1 mg
    - Titrate up by 2 to 4 mg buprenorphine every 2 hours to target dose of buprenorphine 8 mg/naloxone 2 mg
  - Day 2
    - Up to buprenorphine 16 mg/naloxone 4 mg
  - Maintenance
    - Buprenorphine 8 mg/naloxone 2 mg to buprenorphine 24 mg/naloxone 6 mg per day

Strain E. Pharmacotherapy for opioid use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 30

Opioid Agonists vs. Antagonists

- Opioid agonists are recommended as first-line therapy
- Opioid antagonists are a first-line alternative in some patient populations
  - Motivated patients with mild opioid use disorder
  - Patients unable to use opioid agonists in their occupation
- Switch to opioid antagonist if patient continues to use opioids

Strain E. Pharmacotherapy for opioid use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 31

Non-pharmacological Treatment of Opiate Dependence

- Individual or group counseling
  - Cognitive behavioral therapy
  - Narcotics Anonymous
  - Group medication management
    - Retrospective chart review: veterans receiving buprenorphine/naloxone prescriptions in a group setting had better program retention rates than those receiving prescriptions individually (69% vs. 27%, $p<0.03$)

Berger R, Pulido C, Lacro J, et al. Group medication management for buprenorphine/naloxone in opioid-dependent veterans. *J Addict Med.* 2014 Nov-Dec;8(6):415-20.

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Assessment Question #3

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Assessment Question #4

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Alcohol Use in Military Veterans

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Alcohol Use in Military Veterans

- 47% of active duty service members admitted to binge drinking in 2008
- Service members who deploy and are exposed to combat have increased risk for new-onset heavy weekly drinking, binge drinking, and alcohol-related problems

Jacobson IG, Ryan MA, Hooper TI. Alcohol use and alcohol-related problems before and after military combat deployment. *JAMA.* 2008 Aug 13;300(6):663-75.

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Dual Diagnosis – Treatment Disparities

- Patients with alcohol use disorder (AUD) and comorbid psychiatric illnesses often receive medication for their psychiatric illness but not for their AUD
  - PTSD (121,630 patients):
    - 68.6% received medication for PTSD, while only 8.1% received medication for AUD
  - MDD (172,180 patients):
    - 76.1% received medication for MDD, while only 8.2% received medication for AUD

Rubinsky AD, Chen C, Batki SL, et al. Comparative utilization of pharmacotherapy for alcohol use disorder and other psychiatric disorders among U.S. Veterans Health Administrative patients with dual diagnosis. *J Psychiatr Res*. 2015 Oct;69:150-7. 37

Alcohol Intoxication: Clinical Presentation

Blood Alcohol Concentration	Clinical Signs
0.01% - 0.10%	Euphoria Mild deficits in coordination, attention, and cognition
0.10% - 0.20%	↑coordination/psychomotor deficits, ataxia ↓attention, impaired judgment, slurred speech, mood lability
0.20% - 0.30%	Lack of coordination, confusion, nausea, vomiting
>0.30%	Loss of consciousness, coma, respiratory depression, death

- Consumption of alcohol with other substances may either antagonize (e.g., stimulants) or augment (e.g., benzodiazepines) effects of alcohol

Cowan E and Su M. Ethanol intoxication in adults. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 38

Management of Acute Alcohol Intoxication

- Mild Intoxication
  - Observation
- Moderate Intoxication
  - May require IV fluids
- Severe Intoxication
  - Aggressive supportive care
  - IV hydration with isotonic crystalloid
  - Thiamine
  - Activated charcoal and gastric lavage are **not** recommended

Cowan E and Su M. Ethanol intoxication in adults. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 39

Alcohol Withdrawal: Clinical Presentation

- Minor withdrawal symptoms
  - Usually within 6 hours of alcohol cessation
    - Insomnia
    - Anxiety
    - Tremor
    - Headache
    - Diaphoresis
    - Palpitations
- Withdrawal seizures
  - Usually within 12 to 48 hours of alcohol cessation
    - Tonic-clonic convulsions
- Alcoholic hallucinosis
  - Usually within 12 to 24 hours of alcohol cessation
    - Visual, auditory, and/or tactile hallucinations
    - Vital signs will usually be normal
- Delirium tremens
  - Usually within 48 to 96 hours of alcohol cessation
    - Delirium
    - Agitation
    - Tachycardia
    - Fever
    - Diaphoresis

Hoffman R and Weinhouse G. Management of moderate and severe alcohol withdrawal syndromes. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 40

Management of Alcohol Withdrawal

- Benzodiazepines
  - Lorazepam (Ativan®) 2 to 4 mg IV every 15 to 20 minutes*
  - Diazepam (Valium®) 5 to 10 mg IV every 5 to 10 minutes*
  - Chlordiazepoxide (Librium®) 25 to 100 mg PO every hour*

  * Until sedation is achieved
- Supportive care with IV fluids
- Nutritional support – "banana bag"
  - Thiamine
  - Glucose
  - Multivitamin with folate
- Monitoring Parameters
  - Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) used to determine dose
  - Richmond Agitation-Sedation Scale (RASS) used in intensive care

Hoffman R and Weinhouse G. Management of moderate and severe alcohol withdrawal syndromes. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 41

Assessment Question #5

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Alcohol Dependence Treatment

- Pharmacotherapy
  - FDA approved
    - First-line
      - Naltrexone (Revia®, Vivitrol®)
      - Acamprosate (Campral®)
    - Second-line
      - Disulfiram (Antabuse®)
  - Non-FDA approved
    - Topiramate (Topamax®)
    - Gabapentin (Neurontin®)
    - Baclofen (Lioresal®)
    - Selective serotonin reuptake inhibitors (SSRIs)
    - Ondansetron (Zofran®)
- Nonpharmacological therapy
  - Individual or group addiction counseling

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Pharmacotherapy for Alcohol Dependence

- Goals of treatment
  - Abstinence from alcohol
  - Alternatively, decrease in heavy drinking
- Initiation of therapy
  - Naltrexone (Revia®, Vivitrol®)
    - May be started while patient is still drinking
  - Acamprosate (Campral®)
    - Use once abstinence is achieved
  - Disulfiram (Antabuse®)
    - Use in abstinent patients to maintain abstinence
- Duration
  - At least 6 months of medication with 6 months of follow-up is recommended
  - The medications mentioned above do not require tapering

Johnson BA. Pharmacotherapy for alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 44

Naltrexone (Revia®, Vivitrol®)

- Please refer to slide # 28 for drug information
- Efficacy
  - Shown to reduce the risk of heavy drinking by 17% and decrease drinking days by 4%
  - Patients receiving Vivitrol® 380 mg monthly demonstrated a 25% greater reduction in heavy drinking after 24 weeks compared to placebo

Rosner S, Hackl-Herrwerth A, Leucht S, et al. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev.* 2010 Dec 8;(12):CD001867.

Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA.* 2005 Apr 6;293(13):1617-25.

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Acamprosate (Campral®)

- Mechanism of Action
  - Modulates transmission of glutamate and GABA by stimulating GABA-ergic neurotransmission and antagonizes effects of glutamate
- Formulations
  - Delayed release oral tablet
- Dosing
  - 666 mg by mouth 3 times daily
  - Dose reduced by 50% in renal impairment
  - Dose reduced to 1,333 mg daily for weight <60 kg
- Side effects
  - Diarrhea
  - Nervousness
  - Fatigue

Johnson BA. Pharmacotherapy for alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

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Naltrexone vs. Acamprosate

- 2003 study comparing these medications, with and without combined behavioral interventions (CBI)
  - Naltrexone resulted in higher percentage of days abstinent and reduced risk of heavy drinking
  - Acamprosate showed no significant effect on drinking vs. placebo, with or without CBI
- 2010 meta-analysis
  - Both naltrexone and acamprosate were associated with reduction in return to drinking
  - No significant difference between the two

Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA.* 2006 May 3;295(17):2003-17.

Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA.* 2014 May 14;311(18):1889-900.

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Disulfiram (Antabuse®)

- Mechanism of Action
  - Irreversibly inhibits aldehyde dehydrogenase, which causes accumulation of acetaldehyde
  - Result is an undesirable physiological reaction with use of alcohol
- Dosing
  - Initial: 500 mg per day for 1 to 2 weeks
  - Maintenance: 250 mg per day
  - Dosing range: 125 to 500 mg per day
- Side effects
  - Headache
  - Fatigue
  - Monitor for hepatotoxicity
- Efficacy
  - 2014 meta-analysis found no significant difference between disulfiram and placebo in maintenance of abstinence
  - A large, 52-week study found disulfiram to be no more effective than placebo in maintaining abstinence

Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA.* 2014 May 14;311(18):1889-900.

Laaksonen E, Koski-Jannes A, Salaspuro M, et al. A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone, and acamprosate in the treatment of alcohol dependence. *Alcohol Alcohol.* 2008 Jan-Feb;43(1):53-61.

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Assessment Question #6

Topiramate (Topamax®)

- Mechanism of action
  - Augments activity of GABA at GABA-A receptors
  - Antagonizes glutamate receptor subtypes
- Dosing
  - Initial: 50 mg per day
  - Titrate to maximum dose of 150 mg twice daily
- Side effects
  - Cognitive impairment
  - Weight loss
  - Fatigue
  - Dizziness
  - Depression

Johnson BA. Pharmacotherapy for alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Topiramate (Topamax®)

- Efficacy
  - 2014 meta-analysis of 3 trials
    - Reduced percentage of heavy drinking days
    - Reduced number of drinks on drinking days
  - Comparison of topiramate to naltrexone
    - Topiramate was superior to placebo with respect to:
      - Time to relapse
      - Duration of cumulative abstinence
      - Weeks of heavy drinking
      - Percentage of subjects abstinent at 4 and 8 weeks
    - Topiramate not superior to placebo with respect to:
      - Percentage of subjects abstinent at 12 weeks
    - No significant difference between topiramate and naltrexone

Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA*. 2014 May 14;311(18):1889-900.
Baltieri DA, Daro FR, Ribiero PL, et al. Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction*. 2008 Dec;103(12):2035-44.

Gabapentin (Neurontin®)

- Mechanism of action
  - Structurally similar to GABA
- Dosing
  - 900 to 1800 mg per day
- Side effects
  - Sedation and dizziness at higher doses
  - May be abused by patients with SUD
- Efficacy
  - Study conducted in 2014
    - Gabapentin significantly improved rates of abstinence
    - Effectively treated symptoms related to relapse
  - When combined with naltrexone
    - Longer abstinence period than seen with naltrexone alone

Mason BJ, Quello S, Goodell V, et al. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med.* 2014 Jan;174(1):70.7
Anton RF, Myrick H, Wright TM. Gabapentin combined with naltrexone for the treatment of alcohol dependence. *Am J Psychiatry*. 2011 Jul;168(7):709-17.

Baclofen (Lioresal®)

- Mechanism of action
  - Agonizes pre-synaptic GABA-B receptors
- Dosing
  - 30 mg per day
- Side effects
  - Nausea
  - Vertigo
  - Transient drowsiness
  - Abdominal pain
- Drug interactions
  - Concomitant use with opioids may cause increase in risk of CNS depression

Johnson BA. Pharmacotherapy for alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 53

Baclofen (Lioresal®)

- Efficacy: mixed results
  - 2007 study of 84 patients with liver cirrhosis conducted in Italy
    - Higher rate of achieving abstinence and increased duration of abstinence than placebo
  - 2002 study with 39 patients
    - Decrease in cravings and alcohol intake vs. placebo
    - Decrease in anxiety but no difference in depressive symptoms
  - 2010 study of 80 subjects over 12 weeks with use of psychosocial intervention
    - No evidence of superiority over placebo with regard to abstinence, time to first drink, and relapse to heavy drinking

Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet.* 2007 Dec 8;370(9603):1915-22.
Addolorato G, Caputo F, Capristo E, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol Alcohol.* 2002 Sep-Oct;37(5):504-8.
Garbutt JC, Kampov-Polevoy AB, Gallop R, et al. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcohol Clin Exp Res.* 2010 Nov;34(11):1849-57. 54

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Not found to be useful in treating alcohol dependence in patients who do no have a psychiatric disorder
- May reduce alcohol intake when patient has alcohol dependence and comorbid depression

Torrens M, Fonseca F, Mateu G, et al. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug Alcohol Depend.* 2005 Apr 4;78(1):1-22.
Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA.* 2004 Apr 21;291(15):1887-96. 55

Ondansetron (Zofran®)

- Mechanism of action
  - Selective 5-HT3 receptor antagonist
  - Early-onset alcohol use disorder (<25 years of age) is more associated with serotonergic abnormalities
- Dosing
  - 0.25 mg twice daily or 2 mg twice daily
  - 1 mcg/kg, 4 mcg/kg, or 16 mcg/kg
  - 4 mcg/kg twice daily
- Side effects
  - Diarrhea
  - Headache
  - Fever
  - QT prolongation
- Drug interactions
  - Contraindicated with various drugs that prolong QT interval
  - CYP3A4 substrate

Johnson BA. Pharmacotherapy for alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017. 56

Ondansetron (Zofran®)

- Efficacy
  - 1994 study investigated use in male patients with non-severe alcohol dependence over 6 weeks
    - Trended toward reduction in drinking but not statistically significant
  - 2000 study investigated use in 271 patients combined with cognitive behavioral therapy
    - 4 mcg/kg dose increased percentage of days abstinent
  - 2011 study investigated use in patients with genetic variations in the serotonin transporter gene
    - Patients with genetic variant of interest showed a higher percentage of days abstinent and fewer drinks per drinking day compared to placebo

Sellers EM, Toneatto T, Romach MK, et al. Clinical efficacy of the 5-HT3 antagonist ondansetron in alcohol abuse and dependence. *Alcohol Clin Exp Res.* 1994 Aug;18(4):879-85.
Johnson BA, Roache JD, Javors MA, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. *JAMA.* 2000 Aug 23-30;284(8):963-71.
Johnson BA, Ait-Daoud N, Seneviratne C, et al. Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. *Am J Psychiatry.* 2011 Mar;168(3):265-75.

Pharmacotherapy Utilization for Alcohol Dependence in Military Veterans

- Study published in 2012 examined use of medications from 2006 (n=267,982) to 2009 (n=331,635)
  - Acamprosate: 0.6% → 0.7%
  - Oral naltrexone: 1.7% → 2.8%
  - Naltrexone IM depot: 0 → 0.1%
  - Disulfiram: 1.4% → 1.5%
  - Any: 3.6% → 4.7%
- Use of medications in veterans for alcohol dependence is underutilized but is slowly increasing
- Use of medications varied by facility

Harris AH, Oliva E, Bowe T, et al. Pharmacotherapy of Alcohol Use Disorders by the Veterans Health Administration: Patterns of Receipt and Persistence. *Psychiatr Serv.* 2012 Jul;63(7):679-85.

Non-pharmacological Treatment of Alcohol Dependence

- Individual or group counseling
  - Motivational interviewing
  - Cognitive behavioral therapy
  - Alcoholics Anonymous
- Goals of psychosocial treatment
  - Promote abstinence or reduction in alcohol use
  - Support adherence to pharmacotherapy
  - Involve family and community in recovery
  - Utilize employment resources
  - Improve physical health

Aronson M. Psychosocial treatment of alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Assessment Question #7

Assessment Question #8

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In the Pipelines…

- Open/active studies
  - Cognitive Behavioral Therapy (CBT) for PTSD in Veterans With Co-Occurring SUDs
  - Exercise: Addressing Stress in Relapse Prevention for Substance Use Disorders
  - Integrative Collaborative Care for Substance Use Disorders
- Studies in recruitment phase
  - Designing a Mobile App for Veterans with Substance Use Problems
  - Mobile Psychosocial Interventions for MMT Clients
  - Peer Supported Web-based CBT for OEF/OIF Veterans with PTSD and Substance Misuse
  - Mindfulness-Based Recovery in Veterans
  - NAC for Treating Comorbid PTSD and AUD
  - Oxytocin Suppresses Substance Use Disorders Associated with Chronic Stress

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Resources for Veterans

- Department of Veteran's Affairs Alcohol and Drug Dependence Rehabilitation Program
  - Detoxification
  - Rehabilitation
  - Psychiatric care
- Requirements
  - Enrollment in the VA health care system
  - Character of discharge other than dishonorable conditions

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Resources for Veterans

- Substance Use Disorder Program Locator
  - https://www.va.gov/directory/guide/SUD.asp
  - Locally: Tallahassee Health Care Center
    2181 East Orange Avenue, Tallahassee, FL 32311
    Phone: 800-541-8387 or 850-878-0191
- PTSD Program Locator
  - https://www.va.gov/directory/guide/PTSD.asp
- Hotline: 1-800-273-TALK/8255

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Resources for Veterans

- Alcoholics Anonymous (AA)
  - To find an AA meeting: http://alcoholicsanonymous.com/find-a-meeting/
  - To find an alcohol detox center: 1-800-839-1686
- Narcotics Anonymous (NA)
  - To find an NA meeting: http://www.naws.org/meetingsearch/

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Summary

- Substance use disorders are disproportionally prevalent in military veterans and are associated with significant costs
- Opiate overdose is treated with naloxone
- Opiate withdrawal is treated either with methadone or with non-opioid adjunctive medications
- First-line pharmacological agents for opiate dependence are methadone and buprenorphine
- Acute alcohol intoxication is treated with IV fluids, thiamine, and supportive care
- Alcohol withdrawal is managed with benzodiazepines, IV fluids, and nutritional support
- FDA approved pharmacotherapy for alcohol dependence includes naltrexone, acamprosate, and disulfiram
- Non-FDA approved agents include topiramate, gabapentin, baclofen, SSRIs, and ondansetron
- The latest research is exploring the utilization of technology in treating substance use disorders and tends to be focused on nonpharmacological treatment

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References

Addolorato G, Caputo F, Capristo E, et al. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol Alcohol.* 2002 Sep-Oct;37(5):504-8.

Addolorato G, Leggio L, Ferrulli A, et al. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet.* 2007 Dec 8;370(9603):1915-22.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington 2013.

Anton RF, Myrick H, Wright TM. Gabapentin combined with naltrexone for the treatment of alcohol dependence. *Am J Psychiatry.* 2011 Jul;168(7):709-17.

Anton RF, O'Malley SS, Ciraulo DA, et al. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA.* 2006 May 3;295(17):2003-17.

Aronson M. Psychosocial treatment of alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Baltieri DA, Daro FR, Ribiero PL, et al. Comparing topiramate with naltrexone in the treatment of alcohol dependence. *Addiction.* 2008 Dec;103(12):2035-44.

Bell JR, Butler B, Lawrance A, et al. Comparing overdose mortality associated with methadone and buprenorphine treatment. *Drug Alcohol Depend.* 2009 Sep 1;104(1-2)73-7.

Berger R, Pulido C, Lacro J, et al. Group medication management for buprenorphine/naloxone in opioid-dependent veterans. *J Addict Med.* 2014 Nov-Dec;8(6):415-20.

67

References

Bohnert A, Valenstein M, Bair MJ, et al. Associate between opioid prescribing patterns and opioid overdose-related deaths. *JAMA. 2011;305:1315-1321.*

Bonn-Miller MO, Rousseau GS. US Department of Veteran Affairs. Marijuana Use and PTSD Among Veterans. Available at: http://www.ptsd.va.gov/professional/co-occurring/marijuana_use_ptsd_veterans.asp. Accessed February 8, 2017.

Cowan E and Su M. Ethanol intoxication in adults. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Eisin SV, Schultz MR, Vogt D, et al. Mental and physical health status and alcohol and drug use following return from deployment to Iraq or Afghanistan. *Am J Public Health.* 2012 Mar; 102 Suppl 1:S6-73.

Garbutt JC, Kampov-Polevoy AB, Gallop R, et al. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcohol Clin Exp Res.* 2010 Nov;34(11):1849-57.

Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA.* 2005 Apr 6;293(13):1617-25.

Gibson A, Degenhardt L, Mattick RP, et al. Exposure to opioid maintenance treatment reduces long-term mortality. *Addiction.* 2008; 103(3):462.

Harris AH, Oliva E, Bowe T, et al. Pharmacotherapy of Alcohol Use Disorders by the Veterans Health Administration: Patterns of Receipt and Persistence. *Psychiatr Serv.* 2012 Jul;63(7):679-85.

68

References

Hoffman R and Weinhouse G. Management of moderate and severe alcohol withdrawal syndromes. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Jacobson IG, Ryan MA, Hooper TI. Alcohol use and alcohol-related problems before and after military combat deployment. *JAMA.* 2008 Aug 13;300(6):663-75.

Johnson BA. Pharmacotherapy for alcohol use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Johnson BA, Ait-Daoud N, Seneviratne C, et al. Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. *Am J Psychiatry.* 2011 Mar;168(3):265-75.

Johnson BA, Roache JD, Javors MA, et al. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. *JAMA.* 2000 Aug 23-30;284(8):963-71.

Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA.* 2014 May 14;311(18):1889-900.

Laaksonen E, Koski-Jannes A, Salaspuro M, et al. A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone, and acamprosate in the treatment of alcohol dependence. *Alcohol Alcohol.* 2008 Jan-Feb;43(1):53-61.

Mason BJ, Quello S, Goodell V, et al. Gabapentin treatment for alcohol dependence: a randomized clinical trial. *JAMA Intern Med.* 2014 Jan;174(1):70.7

Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rv.* 2014 Feb 6;(2):CD002207.

69

References

Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA.* 2004 Apr 21;291(15):1887-96.

Rosner S, Hackl-Herrwerth A, Leucht S, et al. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev.* 2010 Dec 8;(12):CD001867.

Rubinsky AD, Chen C, Batki SL, et al. Comparative utilization of pharmacotherapy for alcohol use disorder and other psychiatric disorders among U.S. Veterans Health Administrative patients with dual diagnosis. *J Psychiatr Res.* 2015 Oct;69:150-7

Schumm JA and Chard KM. Alcohol and Stress in the Military. *Alcohol Research: Current Reviews.* 34(4). Available at: https://pubs.niaaa.nih.gov/publications/arcr344/401-407.htm. Accessed February 8, 2017.

Sellers EM, Toneatto T, Romach MK, et al. Clinical efficacy of the 5-HT3 antagonist ondansetron in alcohol abuse and dependence. *Alcohol Clin Exp Res.* 1994 Aug;18(4):879-85.

Shen YC, Arkes J, Williams TV. Effects of Iraq/Afghanistan deployments on major depression and substance use disorder: analysis of active duty personnel in the US military. *Am J Public Health.* 2012 Mar; 102 Suppl 1:S80-7.

Stolbach A and Hoffman R. Acute opioid intoxication in adults. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Stolbach A and Hoffman R. Opioid withdrawal in the emergency setting. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

Strain E. Pharmacotherapy for opioid use disorder. In: UpToDate, Post TW (Ed), Waltham, M. Accessed February 8, 2017.

70

References

Toblin RL, Quartana PJ, Riviere LA, et al. Chronic pain and opioid use in US soldiers after combat deployment. *JAMA Intern Med.* 2014 Aug;174(8):1400-1.

Torrens M, Fonseca F, Mateu G, et al. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug Alcohol Depend.* 2005 Apr 4;78(1):1-22.

US Department of Veteran Affairs. PTSD and Substance Abuse in Veterans. Available at: http://www.ptsd.va.gov/public/problems/ptsd_substance_abuse_veterans.asp. Accessed February 8, 2017.

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