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.

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

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
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

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

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

References:
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


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


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

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


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


Assessment Question #1

Opiate Use in Military Veterans
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


Opiate Overdose: Clinical Presentation

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


Management of Opiate Overdose

- Administer naloxone (Evzio®, Narcan®)
  - Preferably IV
    - 0.04 to 0.05 mg initially
    - Titrate until respiratory rate ≥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


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

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

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

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

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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

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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

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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

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Strain E. Pharmacotherapy for opioid use disorder. 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.


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

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

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

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)
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

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


Alcohol Intoxication: Clinical Presentation

<table>
<thead>
<tr>
<th>Blood Alcohol Concentration</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01% - 0.10%</td>
<td>Euphoria, mild deficits in coordination, attention, and cognition</td>
</tr>
<tr>
<td>0.10% - 0.20%</td>
<td>Coordination/psychomotor deficits, ataxia, impaired judgment, slurred speech, mood lability</td>
</tr>
<tr>
<td>0.20% - 0.30%</td>
<td>Loss of coordination, confusion, nausea, vomiting</td>
</tr>
<tr>
<td>&gt;0.30%</td>
<td>Loss of consciousness, coma, respiratory depression, death</td>
</tr>
</tbody>
</table>

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


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


Alcohol Withdrawal: Clinical Presentation

- Minor withdrawal symptoms
  - Usually within 6 hours of alcohol cessation
    - Insomnia
    - Anxiety
    - Tremor
    - Diaphoresis
- 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, or tactile hallucinations
        - Vital signs will usually be normal
    - Delirium tremens
      - Usually within 48 to 96 hours of alcohol cessation
        - Delirium
        - Tachycardia
        - Diaphoresis
        - Fever
        - Agitation

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 foltate
- Monitoring Parameters
  - Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) used to determine dose
  - Richmond Agitation-Sedation Scale (RASS) used in intensive care

Assessment Question #5

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

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
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

Efficacy

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- Patients receiving Vivitrol® 380 mg monthly demonstrated a 25% greater reduction in heavy drinking after 24 weeks compared to placebo

References:

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

References:

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

References:

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

References:
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
  - Titrated to maximum dose of 150 mg twice daily
- Side effects
  - Cognitive impairment
  - Weight loss
  - Fatigue
  - Dizziness
  - Depression

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
    - Longer abstinence period than seen with naltrexone alone

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


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

- 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

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Not found to be useful in treating alcohol dependence in patients who do not have a psychiatric disorder
- May reduce alcohol intake when patient has alcohol dependence and comorbid depression

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

References:
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


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


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

Assessment Question #7
Assessment Question #8

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

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

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
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/

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

References

References


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.


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

References

