VA | U.S. Department of Veterans Affairs

A QUICK REFERENCE GUIDE (2016)

OPIOID USE DISORDER

Identification and Management of Opioid Use Disorder

These pocket cards are intended to aid clinicians in their clinical decision-making and patient management. The Practice Guideline pocket card strives to identify and define clinical decision making junctures that meet the needs of most patients in most circumstances.

Clinical decision-making should involve consideration of the quality and availability of expertise and services in the community wherein care is provided. In circumstances in which the pocket cards are being used as the basis for regulatory or payer decisions, improvement in quality of care should be the goal.

REAL PROVIDER RESOURCES
REAL PATIENT RESULTS

Definitions associated with Substance Abuse[1,2]

Abuse	Harmful use of a specific psychoactive substance Term is considered as a pejorative connotation in the clinical context
Addiction	Primary, chronic disease of brain circuitry characterized by inability to consistently abstain from a substance
Dependence	**Physical:** state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist **Psychological:** subjective sense of need for a specific psychoactive substance, either for its positive effects or to avoid negative effects associated with its abstinence
Tolerance	A decrease in response to a drug dose that occurs with continued use requiring increased doses to achieve the effects originally produced by lower doses
Overdose	Inadvertent or deliberate consumption of a much larger dose than habitually or ordinarily used and likely results in a serious toxic reaction or death
Opioid-induced hyperalgesia	A state of nociceptive sensitization caused by exposure to opioids; a patient receiving opioids for the treatment of pain becomes more sensitive to painful stimuli
Aberrant drug-related behavior	Taking a controlled substance medication in a manner that is not prescribed; behavior outside the boundaries of the agreed-on treatment plan

Opioid withdrawal[1]

- Patients with regular opioid use will have a degree of tolerance and withdrawal
  - Not indicative of addiction; please refer to DSM-5 criteria for OUD
- The Clinical Opioid Withdrawal Scale (COWS) can be used to assess opioid withdrawal symptoms
  - Available in Mental Health Assistant in CPRS

Recognizing key signs of opioid intoxication and withdrawal*[1]

Signs of intoxication

- Drooping eyelids
- Constricted pupils
- Decreased respiratory rate
- Scratching (due to histamine release)
- Head nodding

Signs/symptoms of withdrawal**

- Dysphoric mood
- Nausea or vomiting
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

*Signs/symptoms may vary based on various factors. **Signs/symptoms of withdrawal cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not attributable to another condition, disorder, or non-opioid substance.

Note: DSM-5 criteria for opioid withdrawal requires the presence of either cessation of (or reduction in) opioid use that has been heavy and prolonged (e.g. several weeks or longer) or administration of an opioid antagonist after a period of opioid use and 3 or more signs/symptoms developing within minutes to several days.

Interpreting Urine Drug Tests (UDT)

UDT results[3]

View the following as a "**red flag**," requiring confirmation testing and intervention (see interpreting UDT pocket card #7)

- Negative for opioid(s) prescribed
- Positive for prescription medications not prescribed (benzodiazepines, opioids, stimulants, etc.)
- Positive for illicit drugs (methamphetamine, cocaine or its metabolites, marijuana, etc.)
- Positive for alcohol

If confirmatory drug test substantiates the "**red flag**" (e.g. positive for amphetamines) AND is:

- **Positive for prescribed opioids:** have a discussion with the patient, come up with a plan (consider a controlled taper and consultation with/referral to an addiction treatment program)
- **Negative for prescribed opioids:** have a discussion with the patient, come up with a plan (consider a controlled taper and consultation with/referral to an addiction treatment program)

Urine drug testing specimen validity[4,5]

- Urine samples that are adulterated, substituted, or diluted may avoid detection of drug use[4]
- Urine collected in the early morning is most concentrated and most reliable
- Excessive water intake and diuretic use can lead to diluted urine samples (Creatinine < 20)[3,4]
- THC assays are sensitive to adulterants (e.g. Visine eye drops)

Normal characteristics of a urine sample[4-6]

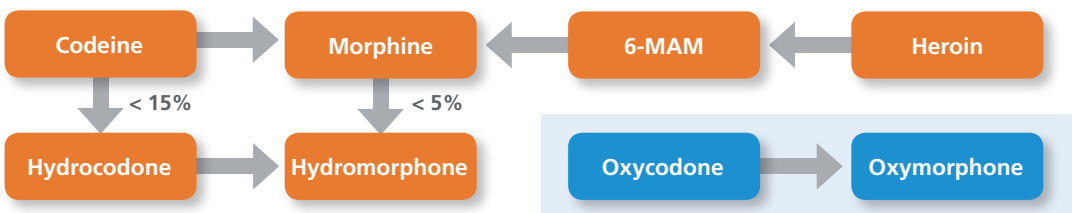
Temperature within 4 minutes of voiding: 90°–100°F
pH: 4.5-8.0
Creatinine: > 20 mg/dL
Specific gravity: > 1.003
Nitrates: < 500 mcg/dL
Volume: ≥ 30mL

UDT = Urine Drug Testing

Interpreting Urine Drug Testing[3-6]

Drug or Class	Expected Results	Considerations
Opioids or "opiates"—Natural (from opium)		
Codeine (Tylenol #2,3,4)	**Opiates Immunoassay:** positive **Confirmatory:** codeine, possibly morphine & hydrocodone	• Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which • Codeine is metabolized to morphine and small quantities of hydrocodone
Morphine (Avinza, Embeda, MS Contin, Kadian)	**Opiates Immunoassay:** positive **Confirmatory:** morphine, possibly hydromorphone	• Immunoassays for "opiates" are responsive to morphine and codeine but do not distinguish which • Morphine (<10%) may be metabolized to hydromorphone
Heroin	**Opiates Immunoassay:** positive **Confirmatory:** heroin (6-MAM), morphine, possibly codeine	• 6-MAM is confirmatory for heroin use, detection 12-24 hrs. • Heroin is metabolized to morphine

Opioid metabolic pathways



Interpreting Urine Drug Testing[3-6]

Drug or Class	Expected Results	Considerations
Opioids—Semisynthetic (derived from opium)		
Hydrocodone (Lorcet, Lortab, Norco, Vicodin)	**Opiates Immunoassay:** positive **Confirmatory:** hydrocodone, possibly hydromorphone	• Opiates" immunoassay may detect semisynthetic opioids – hydrocodone > hydromorphone > oxycodone • Negative result does not exclude use and confirmatory testing (GC/MS) is required • Hydrocodone is metabolized in small amounts to hydromorphone, both may be found in urine • Oxycodone is metabolized to oxymorphone, both may be found in urine • Hydromorphone and oxymorphone use does not result in positive screens for hydrocodone and oxycodone, respectively
Hydromorphone (Dilaudid, Exalgo)	**Opiates Immunoassay:** may be positive **Confirmatory:** hydromorphone	
Oxycodone (Roxicet, OxyCotonin)	**Opiates Immunoassay:** may be positive **Oxycodone Immunoassay:** positive **Confirmatory:** oxycodone possibly oxymorphone	
Oxymorphone (Opana) (NF)	**Oxycodone immunoassay:** positive **Confirmatory:** oxymorphone	
Opioids—Synthetic (man-made)		
Fentanyl	**GC/MS:** fentanyl and norfentanyl	• Current "opiates" immunoassays do not detect synthetic opioids • Confirmatory testing (GC/MS) is needed **Confirmatory testing:** Chromatography (gas chromatography-mass spectrometry (GC/MS) or liquid chromatography-mass spectrometry (LC/MS)) **Note:** Each facility may have its own order sets and lab policies and procedures. Contact your lab for additional details.
Meperidine (Demerol)	**GC/MS:** normeperidine, possibly meperidine	
Methadone (Methadose)	**Methadone Immunoassy:** positive **GC/MS:** methadone, EDDP	
Propoxyphene (Darvon, Darvocet) (NF)	**Propoxyphene Immunoassy:** positive **GC/MS:** propoxyphene & norpropoxyphene	

NF = Not currently on VA National Formulary; consider contacting the lab for help interpreting UDS results.

Drug Addiction Treatment Act of 2000 (DATA 2000) and buprenorphine[7]

In order to prescribe or dispense buprenorphine, qualifying* physicians must:

1. **Qualify for a physician waiver** (which includes completing eight-hours of required training. For information on training options, see: http://www.samhsa.gov/medication-assisted-treatment/training-resources/buprenorphine-physician-training)
2. **Apply for a physician waiver** (Waiver Notification Form SMA-167, available at: http://buprenorphine.samhsa.gov/pls/bwns/waiver)

Veterans Affairs physicians may obtain a DEA X number free of charge (must have a valid state license)

- Physician's official business address and the name and phone number of the certifying official who can verify the physicians' eligibility for this program must be on application
- This DEA registration number may only be used for practice within the federal government installation and may not be used for practice outside this setting

Note: DEA regulations require a DEA X number to be included on all buprenorphine prescriptions for opioid dependency treatment, along with the physician's regular DEA registration number.

*Qualifying physician is specifically defined in DATA 2000 as one who is licensed under state law (excluding physician assistants or nurse practitioners), registered with the Drug Enforcement Administration (DEA) to dispense controlled substances, required to treat no more than 30 patients at a time within the first year, and qualified by training and/or certification.

For more information, contact the SAMHSA Center for Substance Abuse Treatment's (CSAT's) Buprenorphine Information Center at 866-BUP-CSAT (866-287-2728) or send an email to info@buprenorphine.samhsa.gov

Opioid Use Disorder medications in the United States[8]

Available as	Dosage (mg)	Induction dosing (mg)	Recommended dosing range for stabilization/maintenance (mg)
Methadone (HCl oral concentrate, per ml)			
Generic	5, 10	5–10 every 4 hrs. up to 40 in the first 24 hrs.	Gradual titration with close monitoring over 2 weeks to 60–120 daily; rapid metabolizers may require higher dosing
Methadose	10		
Methadose sugar-free	10		
Methadone HCL Intensol	10		
Buprenorphine + naloxone (Sublingual tablet, film, or buccal film)			
Generic (sublingual tablet)	2/0.5, 8/2	2/0.5–4/1; repeat up to 16/4 in the first 24 hrs.	4/1–24/6 daily
Zubsolv (sublingual tablet)	1.4/0.36, 5.7/1.4	1.4/0.36–2.8/0.72; repeat up to 11.4/2.8 in the first 24 hrs.	2.8/0.72–17.1/4.2 daily
Suboxone Film (sublingual film)	2/0.5, 4/1, 8/2, 12/3	2/0.5–4/1; repeat up to 16/4 in the first 24 hrs.	4/1–24/6 daily
Bunavail (buccal film)	2.1/0.3, 4.2/0.7, 6.3/1	2.1/0.3; repeat up to 8.4/1.4 in the first 24 hrs.	2.1/0.3–12.6/2.1 daily
Buprenorphine			
Sublingual tablet (generic only)	2, 8	2–4; up to 16 in the first 24 hrs.	4–24 daily
Naltrexone ER (Used if pretreatment abstinence and no signs of withdrawal and willingness to receive monthly injections)			
Vivitrol	380	380 IM following agonist clearance; oral naltrexone 50 mg daily may precede or supplement initial induction	380 IM every 4 weeks; oral naltrexone may be added to supplement in weeks 3–4 as needed

Buprenorphine and buprenorphine/naloxone contraindications and cautions[9,10]

Contraindication/Cautions	Recommendations
Demonstrated allergy/hypersensitivity	• Do not prescribe
Compromised respiratory function (e.g., COPD, decreased respiratory reserve, hypoxia, hypercapnia, preexisting respiratory depression)	• Prescribe with caution; monitor closely • Warn patients about the risk of using benzodiazepines or other depressants while taking buprenorphine
Hepatic impairment Moderate to severe liver impairment results in decreased clearance, increasing overall exposure to both medications, and resulting in higher risk of buprenorphine toxicity and precipitated withdrawal from naloxone	• **Mild impairment** (Child-Pugh score of 5–6): No dose adjustment needed • **Moderate impairment** (Child-Pugh score of 7–9): – Combination products not recommended for induction with patients with moderate hepatic impairment as they may precipitate withdrawal* – With careful monitoring, combination products may be used with caution for maintenance treatment in moderate hepatic impairment who have been inducted with mono-product • **Severe impairment** (Child- Pugh score of 10–15) – Do not use the combination product – With a mono-product, reduce the starting and titration doses by half; monitor for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine

*Moderate to severe hepatic impairment results in reduced clearance of naloxone much greater than clearance of buprenorphine. Nasser et al.[11] found that moderate hepatic impairment led to 2 to 3 times the exposure (compared with subjects with no or mild impairment) for both naloxone and buprenorphine. In subjects with severe hepatic impairment, buprenorphine exposure was also 2 to 3 times higher; however, naloxone exposure increased more than tenfold.

Methadone contraindications and cautions[12,13]

Contraindication/Cautions	Management
Demonstrated allergy/hypersensitivity	• Do not prescribe
Compromised respiratory function (e.g., COPD, decreased respiratory reserve, hypoxia, hypercapnia, preexisting respiratory depression)	• Prescribe with caution; monitor closely • Warn about risk of concomitant benzodiazepines or other depressants
Cardiac Prolonged QT interval QT interval prolongation and serious arrhythmia (torsades de pointes) reported and appear associated with, but not limited to, higher dose treatment (> 200 mg/day)	• Closely monitor patients with: – Risk factors for prolonged QT interval (e.g., cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia) – history of cardiac conduction abnormalities – other medications affecting cardiac conduction • QT prolongation has been reported with no prior cardiac history with high doses • Evaluate patients developing QT prolongation on methadone for modifiable risk factors (i.e., concomitant medications with cardiac effects, drugs that cause electrolyte abnormalities and drugs that inhibit methadone metabolism) • Use with already known prolonged QT interval has not been systematically studied
Hepatic impairment Methadone is not hepatotoxic; but, the liver has key role in metabolism, clearance, and drug storage	• Methadone has not been extensively evaluated with hepatic insufficiency • Liver impairment may risk increased systemic exposure after multiple dosing • Start on lower doses, titrate slowly, monitor for respiratory and CNS depression
Renal impairment Up to 45% eliminated through feces, suggesting it may be used safely in renal disease	• Recommend caution when dosing methadone in a low GFR population, and to start with lower doses titrating up. (GFR<10, start with 50%-75% of original dosing)

Naltrexone IM contraindications and cautions[14]

Contraindication/Cautions	Management
Demonstrated allergy/hypersensitivity	• Do not prescribe
Vulnerability to Opioid Overdose	• Counsel about opioid sensitivity after treatment completion (overdose risk)
Injection site reactions • Pain, tenderness, induration, swelling, erythema • Some reactions may be very severe	• Consider alternate treatment if body habitus precludes an IM gluteal injection • Monitor for injection site reactions; evaluate signs of abscess, cellulitis, necrosis, or extensive swelling
Precipitation of Opioid Withdrawal • Withdrawal symptoms are uncomfortable, usually don't require hospitalization • Precipitated withdrawal with naltrexone may result in severe withdrawal/hospitalization	• Patients should be opioid-free before starting treatment • Opioid-free interval of 7–10 days if previously dependent on short-acting opioids • Transitioning from buprenorphine or methadone; risk of withdrawal for up to 2 weeks • If rapid transition from agonist to antagonist therapy is necessary, monitor closely in a medical setting to manage precipitated withdrawal
Hepatotoxicity Extensive hepatic metabolism; may cause further hepatic injury in patients with liver dysfunction	• Warn of hepatic injury risk; advise to see provider if symptoms of acute hepatitis occur* • Discontinue naltrexone if symptoms and/or signs of acute hepatitis • No dosage adjustment required with mild or moderate liver dysfunction
Depression and Suicidality	• Monitor for depression or suicidal thinking; inform caregivers of risk and report if present
Hepatic impairment Undergoes extensive hepatic metabolism	• No dose adjustment with mild or moderate hepatic impairment (Child-Pugh A and B) • Pharmacokinetics were not evaluated in subjects with severe hepatic impairment
Renal impairment Urinary excretion primary route for metabolites	• No dosage adjustment required with mild renal dysfunction (CrCl 50 to 80 mL/min) • No data in patients with moderate to severe renal dysfunction (CrCl < than 50 mL/min)

* Symptoms: fever, rash, itching, anorexia, nausea, vomiting, fatigue, malaise, right upper quadrant pain, dark urine, pale stools, and jaundice

The injection route use (intravenous or even intramuscular) of opioids or other drugs increases the risk of being exposed to HIV, viral hepatitis, and other infectious agents.

Opioid Use Disorder and HIV / HCV[1,15-18]

Injection drug use problems

HIV and HCV linked to injectable drug use

- Majority of injection drug users are addicted to heroin or other opiates
- 25% of new HIV cases in the U.S. secondary to injection drug use
- 50% of new HCV cases secondary to injection drug use
- Prevalence of HCV infection in opioid dependent patients range from 36%–95%

High risk practices of injectable drug users

- Sharing of needles and syringes
- Sharing of paraphernalia
- Sexual exposure

Management

HIV and HCV linked to injectable drug use

- Opioid Agonist Treatment to Decrease HIV / HCV Transmission in Injection Drug Users
- Routine HCV antibody testing
  - With HCV infection 3 – 5 times more common in the U.S. than HIV/AIDS—and more deadly—CDC recommends routine HCV antibody testing (screening) for all current or former injection drug users

Drug interactions between methadone or buprenorphine and HIV medications[19,20]

HIV Medication	Type	Methadone	Buprenorphine
AZT (Zidovudine)	NRTI	• Increase in AZT concentration; possible AZT toxicity	• No clinically significant interaction
Atazanavir	PI	• No clinically relevant PK interactions	• Significant increase in buprenorphine; may cause cognitive impairment or over sedation • Consider slow titration or dose reduction of buprenorphine
Darunavir–ritonavir (NF)	PI	• Methadone levels are decreased • Opiate withdrawal may occur • May need to increase methadone dose	• Some PK effect • Dose adjustments unlikely needed but recommend monitoring
Delavirdine	NNRTI	• Increased methadone (and LAAM) concentrations; no cognitive impairment	• Significant increases buprenorphine concentration, no cognitive impairment • Dose adjustments unlikely to be needed. Use caution, as long-term effects (more than 7 days) are unknown
Didanosine	NRTI	• Significant decreases in didanosine concentration • Effect on methadone not studied	• No information
Efavirenz	NNRTI	• Methadone levels are decreased • Opiate withdrawal may occur • May need to increase methadone dose	• Some PK effect; no clinically significant interaction • Dose adjustments unlikely to be needed
Fosamprenavir	PI	• Methadone levels are decreased • Opiate withdrawal may occur	• Some PK effect • Dose adjustments unlikely needed

HIV Medication	Type	Methadone	Buprenorphine
Nelfinavir	PI	• Methadone levels are decreased • Opiate withdrawal may occur • May need to increase methadone dose	• No clinically significant interaction • Dose adjustments unlikely to be needed
Nevirapine	NNRTI	• Methadone levels are decreased • Opiate withdrawal may occur	• Some PK effect; no clinically significant interaction • No dose adjustments needed
Lopinavir / ritonavir	PI / NNRTI	• Methadone levels are decreased • Opiate withdrawal may occur	• No clinically significant reaction
Ritonavir	NNRTI	• May decrease methadone effects (eg, withdrawal) • Monitor for signs and symptoms of methadone withdrawal; some patients may need an increase in the methadone dose	• Some PK effect; no dose adjustments needed
Stavudine	NNRTI	• Significant decrease in stavudine concentrations	• No information
Tipranavir	NNRTI	• Decreased methadone effects (eg, withdrawal); Monitor for signs and symptoms of methadone withdrawal; some patients need an increase in the methadone dose	• No clinically significant reaction

PK = Pharmacokinetic; PI = Protease Inhibitor; NRTI = Nucleoside Reverse Transcriptase Inhibitor; NNRTI = Non-nucleoside Reverse Transcriptase Inhibitor;
NF = not currently on VA National Formulary

- Some HIV antiretroviral (ARV) medications induce CYP 450 3A4 which metabolized methadone. This associated with opiate withdrawal due to decreasing methadone levels.
- Interestingly, these medications when given to buprenorphine-maintained individuals were not associated with opiate withdrawal despite reductions in buprenorphine. This may be due to an active metabolite, norbuprenorphine, and due to the slow dissociation and high affinity for mu receptors of buprenorphine.
- To date, none of the adverse drug interactions that have been observed between methadone and ARVs have been observed in buprenorphine-maintained individuals.
- Buprenorphine has not been shown to significantly alter plasma concentrations of ARVs.
- No significant drug interactions between OAT and HCV medications known at this time.[19]

Physical exam findings in substance abuse disorders (prescription or illicit, i.e., heroin)[1,21]

System	Findings
Dermatologic	Abscesses, rashes, cellulitis, thrombosed veins, jaundice, scars, track marks, pock marks from skin popping
Ear, nose, throat and eyes	Pupils pinpoint or dilated, yellow sclera, conjunctivitis, rhinorrhea, rhinitis, excoriation or perforation of nasal septum, epistaxis, sinusitis, hoarseness or laryngitis
Mouth	Poor dentition, gum disease, abscesses
Cardiovascular	Murmurs, arrhythmias
Respiratory	Asthma, dyspnea, rales, chronic cough, hematemesis
Musculoskeletal and extremities	Pitting edema, broken bones, traumatic amputations, burns on fingers
Gastrointestinal	Hepatomegaly, hernias

Extended-release naltrexone and special considerations[1,22-24]

Managing pain in patients on naltrexone

- Emergency situations: use regional analgesia, conscious sedation with a benzodiazepine, and/or use of non-opioid analgesics or general anesthesia
- For opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged
- A rapidly acting opioid analgesic is preferred, titrating dose to the needs of the patient. Non-opioid receptor mediated actions (presumably histamine release) may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction)

Switching from naltrexone to OAT (methadone or buprenorphine)

- It may be necessary to wait ~30 days after last extended-release injectable naltrexone to switch to OAT
  - 2 peak blood levels occur after injection of the IM formulation: a transient initial peak ~2 hrs. after injection and a second peak ~2-3 days later
  - ~14 days after injection, the blood level slowly begins to decline in a linear fashion
- Initial doses of methadone or buprenorphine should be low

Patients on naltrexone should be educated that they are at increased risk for overdose and death if they discontinue naltrexone and resume opioid use (decreased tolerance)

Addiction-focused medical management*[9]

*Session structure varies according to the patient's substance use status and treatment compliance.

BAM = Brief Addiction Monitor

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VA Academic Detailing Service

REAL PROVIDER RESOURCES
REAL PATIENT RESULTS

U.S. Department of Veterans Affairs

This reference guide was created to be used as a tool for VA providers and is available to use from the Academic Detailing SharePoint. These are general recommendations only; specific clinical decisions should be made by treating provider based on an individual patient's clinical conditions.

VA PBM Academic Detailing Service Email Group:
PharmacyAcademicDetailingProgram@va.gov

VA PBM Academic Detailing Service SharePoint Site:
https://vaww.portal2.va.gov/sites/ad

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