



California Society of Addiction Medicine

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California Department  
of Health Care Services

# Guidelines for Physicians Working in California Opioid Treatment Programs

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## EDITORS:

- Walter Ling, MD
- Deborah Stephenson, MD, MPH
- Ernest Vasti, MD

This publication made possible through a SAMHSA Opioid State Targeted Response Grant

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575 Market Street, Ste 2125  
San Francisco, CA 94105

[www.csam-asam.org](http://www.csam-asam.org)



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# PREFACE

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By Jara, G. & Ling, W.

These guidelines were developed by the Committee on Opioids of the California Society of Addiction Medicine to provide an overview and discussion of the matters of clinical care that fall under the responsibility of the Opioid Treatment Program (OTP) Medical Director and Program Physicians. They were prepared and distributed first in 1998 and updated first in 2004, and again in 2008. We are now pleased to publish the newest update for 2019 .

In the past decade, much has changed in opioid pharmacotherapy – indeed, even the title for these guidelines required updating to “OTP” (vs. Narcotic Treatment Program). Notably, there are an increasing number of patients receiving buprenorphine treatment and, to a lesser extent, naltrexone. In 2013, [DSM-5](#) was published, replacing DSM IV-TR. Accordingly, this update includes sections on buprenorphine, naltrexone, and management of pain in patients maintained on opioid pharmacotherapy. We have expanded the section on pregnancy and urine toxicology testing; we have updated advancements in treating co-occurring medical illnesses, especially hepatitis, HIV and other infectious diseases, and co-occurring psychiatric disorders. The recent interest in expanding access to difficult-to-reach patients is

highlighted in an overview of the “Hub and Spoke” model.

Equally as notable, however, is how little our treatment protocols, policies, and procedures have advanced — particularly with methadone — since their introduction in the 1960s, despite advances in pharmacological and behavioral sciences. Therefore, the reason for the limited change in practices is likely unrelated to scientific knowledge, but rather a myopic cultural attitude towards addiction. We continue to wage war on patients with substance use disorders that we call a “war on drugs” and although we study addiction as a serious illness, too often people afflicted with it are treated more like criminals than patients. Therefore, in addition to providing guidelines based on the most recent evidence in pharmacology, we also hope to inspire introspective change within ourselves as physicians and healers in our communities. To this end, we have included guidance on general approaches to patients, ethical considerations, and the importance of using non-stigmatizing language.

We thank all the authors who took responsibility for various Chapters.

# INTRODUCTION

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By Stephenson, D., & Ling, W.

The physician in an opioid treatment program (OTP) practices in a uniquely challenging medical environment, responding to a diverse array of medical, psychiatric, and social problems. The past experiences of patients with Substance Use Disorder (SUD) in medical settings often result in mistrust and even aversion to mainstream medical providers, which discourages them from even seeking what limited care may be available. In recent years, OTPs are seeing a growing number of patients who are addicted to prescription opioids rather than, or in addition to, heroin. Many of these patients have chronic pain issues as well as SUD.

Characteristically, people with SUD receive high-cost crisis care in emergency departments and hospitals. After discharge from the hospital there is little to no follow-up, and there is rarely any continuity of care for patients with frequent emergency room visits. The physician in the OTP is often the first medical provider with whom these patients establish a long term therapeutic relationship. The OTP physician can be an important, even lifesaving, resource for patients enrolled in treatment, identifying the multiple medical problems that characterize chemical dependence and providing treatment or referrals to address these problems. The OTP physician

can also improve community safety and public health through screening for and treating communicable diseases, and offering other preventive health services.

## Opioid Treatment Program (OTP) Definition, Accreditation and Management

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Federal regulations require that OTPs be accredited by an agency approved by the Center for Substance Abuse Treatment (CSAT). At this time, in California, the approved agencies are the Joint Commission on Accreditation of Health Organizations (JCAHO) and the Commission on Accreditation of Rehabilitation Facilities (CARF.) The CARF standards say that each OTP must have a medical director who is responsible for:

- a. Administering or supervising all medical services.
- b. Ensuring that the program is in conformance with all applicable local, state, and federal regulations regarding the medical treatment of opioid addiction.

CARF Standards go on to say that, in order to serve as the medical director of an OTP, a physician must have either:

- a. Demonstrated experience in opioid treatment, or
- b. Developed a written plan to attain competence in opioid treatment within twelve months (to include continuing medical education in addiction medicine), and be monitored by the designated authority.

Although the Medical Director of an OTP has administrative responsibilities in addition to the medical/clinical ones, they are separate issues; this guide focuses on the medical piece.

Per federal and state regulation, Opioid Treatment Programs (OTPs) are designed to treat patients who are Opioid Dependent or in more common terminology, addicted to opioids. This does not include patients who are taking opioids as prescribed for pain management and under appropriate medical supervision, meaning patients who have physical dependence on and tolerance to opioids but none of the other features characterizing addiction.

## General Terminology and Regulations

These guidelines use the term “opioid” rather than “opiate,” as “opioid” is the broader term including alkaloids extracted from the resin of the opium poppy, simple chemical derivatives of these (semi-synthetic opiates) and synthetic opioids, which are chemically distinct but bind to the same receptor. OTP is the term used by federal and state regulating agencies to refer to clinics that are specially licensed to provide opioid pharmacotherapy for addiction treatment. OTPs are commonly known as methadone clinics (although other medicines such as buprenorphine or naltrexone may also be used). Both the federal and state governments regulate OTPs. California’s Department of Alcohol and Drug Programs, which was responsible for overseeing OTPs, was moved into California’s Department of Health Care Services. Federal regulations are found

in the Code of Federal Regulations Titles 21 and 42; California’s regulations are found in Title 9 of the California Code. This document refers to these regulations, but it is not designed to summarize all of them. Rather, this guide offers practical clinical information and suggestions for the physician working in an OTP. While this document is intended to assist physicians in making clinical decisions, it does not represent regulations or standards of care. Ultimately clinical decisions are made based on the patient’s situation, the available resources and a physician’s best clinical judgment.

These guidelines are subject to periodic review and revision to incorporate new developments by the CSAM Committee on Opioids. The latest revision is posted on the CSAM website: [www.csam-asam.org](http://www.csam-asam.org)

### *The members of the CSAM Committee on Opioids in 2019:*

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# OBJECTIVE

By Stephenson, D. & Ling, W.

These guidelines are intended to assist Opioid Treatment Program physicians in understanding their role and responsibilities in treatment, including those areas governed by state or federal regulation. These describe the role of the physician in an OTP and the clinical judgment involved in the development of an appropriate treatment plan for the delivery of patient care. These describe responsibilities that should be carried out by the physician or the physician’s designee. These do not prescribe a standard of care, or specific treatment choices. Judgment regarding specific clinical situations must be made on the basis of the clinical information available and on the treatment options available.

# CHAPTER 1

# PATIENT ASSESSMENT AND DIAGNOSIS

**Authors:** Ling, W. & Stephenson, D.

## 1.1. Diagnosis of Substance-Related and Addictive Disorders

### 1.1.1. Diagnosis and Terminology

The regulatory term “opioid dependence” (addiction) is **characterized by compulsive drug seeking and use with loss of the ability to control the drug use despite adverse consequences.** This must be distinguished from the usage of this same term “opioid dependence” in general medical settings, where it often refers only to physical dependence (tolerance, withdrawal). These two uses of the word “dependence” may be confusing. In general medicine, physical dependence with continued use despite adverse consequences is often diagnosed as “addiction.”

### 1.1.2. DSM IV vs. DSM-5

#### Limitations of DSM IV

When these guidelines were last published in 2008, what we now refer to as Substance Use Disorders (SUDs) were designated as Substance-Related Disorders in DSM IV, divided into two groups: Substance Use Disorders and Substance-Induced Disorders. SUDs consisted of Substance Abuse and Substance Dependence; Substance-Induced Disorders included substance intoxication, substance withdrawal, and Substance-Induced Mental Disorders included elsewhere in the Manual, such as anxiety and mood disorders, sexual disorders and dementia, and so on.

The diagnostic criteria for Substance Abuse in DSM-IV consisted of a maladaptive pattern of substance use, within a 12-month period, leading to clinically significant distress or impairment in one or more life domains—physical, social, legal—and failure to fulfill major role obligations <sup>[1]</sup>.

The diagnosis Substance Dependence was meant to correspond with what was previously called addiction, a term thought by then to be pejorative or, more accurately, politically incorrect <sup>[1]</sup>. Its use led to a great deal of confusion between the behavioral disorder of addiction—acting like an “addict” as Alan Leshner, then director of NIDA, put it—and physiological dependence, which is entirely separate from addiction. Most people link dependence with “addiction” when in fact dependence can be no more than physiology.

The basic diagnostic approach taken in DSM-IV was categorical. This method employed a threshold approach that designated an individual as either diagnosed or not diagnosed with a disorder. This “yes/no” approach conferred validity and reliability, and was advantageous for the purpose of communication for researchers, which was a central goal in the early development of the DSM. However, for the members of the American Psychiatric Association (APA) who use the DSM to diagnose and classify mental disorders and who saw patients’ disease manifestation as a continuum, the categorical approach was a problem.

#### DSM-5 – Opioid Use Disorder

The new DSM (DSM-5) <sup>[2]</sup> uses different terminology from the regulations and from the prior edition, combining the DSM IV-TR categories of “Opioid Abuse” and “Opioid Dependence” into a single category called “Opioid Use Disorder” (OUD) with a continuum from mild to severe. OUD is characterized by a

group of behavioral, cognitive and physiological symptoms occurring within a specific time frame (12 months) due to problematic use of opioids.

There are 11 criteria; patients with 2-3 of the criteria have “mild” OUD; 4-5 criteria is “moderate” OUD, and 6 or more is severe OUD. DSM criteria include physical dependence, but also include other behaviors, notably continued use despite adverse consequences. Other specifiers include: in early remission, in sustained remission, in a controlled environment, and for opioid use disorder, being on maintenance therapy (where methadone, buprenorphine, or naltrexone is specified). Please see Table 1.1 – Worksheet for DSM-5 criteria for diagnosis of opioid use disorder.

An extensive body of literature has supported combining abuse and dependence, as both sets of criteria indicate the same underlying condition. The exception is the legal criterion for substance abuse (i.e., arrest or legal problems), which is problematic due to the unfair ways individuals become justice-involved, and so this was removed from DSM-5. Since craving is central to diagnosis and treatment in many areas of the field, and is included in coding definitions for ICD-10, it was added to the list.

### Removal of Polysubstance Dependence Diagnosis

The DSM-5 eliminates poly-substance dependence because of the new threshold to use of each substance. In practice poly-substance use continues. The DSM-5 has added cannabis withdrawal disorder with criteria, specifies criteria for

cannabis use disorder, and aligns tobacco use disorder with criteria for other SUDs, as well as gambling disorder.

Users of the DSM-5 who are familiar with DSM-IV will have little difficulty adjusting to the changes because, except for the deletion of the legal criterion and the addition of craving to the list, the criteria used to make the diagnoses in DSM-5 are the same ones used in DSM-IV. Each specific substance, except for caffeine, receives a separate disorder designation.

### 1.1.3. Treating Patients

The primary purpose of the clinician’s admission assessment is to confirm and document current opioid use disorder and to determine whether the patient is fit for pharmacotherapy through a comprehensive history and physical examination and appropriate laboratory tests. Sample forms for recording the intake history and physical examination can be found [here](#).

### The Effective Clinician’s Approach to Patients

Although healthcare providers understand that examining, diagnosing, and treating patients in a non-judgmental, empathetic way is both morally correct and ethically required, it can be challenging because of the highly stigmatized nature of substance use disorders. Repeated studies have now shown that when terms such as “abuse” or “addict” are used, instead of medically precise terms like “person with opioid use disorder,” a provider is more likely to blame the patient and take an approach involving punishment as opposed to

Figure 1.1

## DSM-IV and DSM-5 Criteria for Substance Use Disorders

	DSM-IV Abuse <sup>a</sup>		DSM-IV Dependence <sup>b</sup>		DSM-5 Substance Use Disorders <sup>c</sup>	
Hazardous use	X	} ≥1 criterion	-	}	X	} ≥2 criteria
Social/interpersonal problems related to use	X		-		X	
Neglected major roles to use	X		-		X	
Legal problems	X		-		-	
Withdrawal <sup>d</sup>	-		X	X		
Tolerance	-		X	X		
Used larger amounts/longer	-		X	X		
Repeated attempts to quit/control use	-		X	X		
Much time spent using	-		X	X		
Physical/psychological problems related to use	-		X	X		
Activities given up to use	-		X	X		
Craving	-		-	X		

- One or more abuse criteria within a 12-month period and no dependence diagnosis; applicable to all substances except nicotine, for which DSM-IV abuse criteria were not given.
- Three or more dependence criteria within a 12-month period.
- Two or more substance use disorder criteria within a 12-month period.
- Withdrawal not included for cannabis, inhalant, and hallucinogen disorders in DSM-IV. Cannabis withdrawal added in DSM-5 <sup>(9)</sup>



Table 1.1

**Worksheet for DSM-5 criteria for diagnosis of opioid use disorder.**

Patient's Name: \_\_\_\_\_

Date of Birth: \_\_\_\_\_

Diagnostic Criteria* (Opioid Use Disorder requires at least 2 within 12-month period)	Meets criteria		Notes/supporting information
	Yes	No	
1. Opioids are often taken in larger amounts or over a longer period of time than intended.			
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.			
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.			
4. Craving, or a strong desire to use opioids.			
5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.			
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.			
7. Important social, occupational or recreational activities are given up or reduced because of opioid use.			
8. Recurrent opioid use in situations in which it is physically hazardous.			
9. Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.			
10. *Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid.			
11. *Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms.			

*\*This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.*

Severity: **Mild:** 2-3 symptoms, **Moderate:** 4-5 symptoms. **Severe:** 6 or more symptoms.

Signed \_\_\_\_\_ Date \_\_\_\_\_

Criteria from American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, Washington, DC, American Psychiatric Association, page 541. It is possible to meet the DSM-5 criteria for an "Opioid Use Disorder" without having tolerance or physical dependence (withdrawal upon abrupt cessation of use.)

invoking the disease model and prescribing treatment. This has led to calls made by professional organizations and leaders in the field to change the language we use when describing the patients we care for <sup>[4-6]</sup>.

These principles are particularly important at the bedside when evaluating a person. We must be aware that our attitudes can greatly influence the quality of information gathered. We must exhibit extra understanding since many individuals struggling with SUD, even when they are willing to be open, may feel shame related to their behavior and obscure parts of the history. Others may also refrain from disclosing all aspect of their history because of fear of losing a job or professional licensure. A warm, non-judgmental attitude encourages self-disclosure and facilitates the establishment of a good working relationship. Using the skills from motivational interviewing can be helpful, including asking open-ended questions, providing the patient with affirmations, using reflective listening, and summarizing the content of the conversation. These practices can help with eliciting a thorough history from the patient. It is also worth noting that there are times in which a full history cannot be obtained because the individual has suffered severe drug effects, co-morbid mental illness, or the possibility that the person is under the influence of a substance.

### Patient Intake and History – Best Practices

**Dedicate your time exclusively and conduct the interview in private.** Put away your phone, electronic devices, etc., and avoid all forms of interruption. Many individuals with a substance use disorder have not received the same consideration we often give to other patients. Giving exclusive attention to your patient shows respect and sensitivity, which are essential for rapport.

**Begin by assuring patients that the information they give is confidential.** Information regarding SUD treatment is protected under federal law (42 CFR Part 2) <sup>[7]</sup> and that information—excluding emergency situations—can only be shared with a signed Release of Information. With widespread use of electronic medical records (EMR), it can be helpful to assure the patient of the separate EMR used in SUD treatment settings.

While the approach needs to be empathetic and supportive, **the questioning itself should be direct and straightforward:**

- Use simple language.
- Ask open-ended questions about the patient's type of substance used, quantity, and mode of use. Because concurrent use of multiple substances is highly prevalent, patients should be screened for all types of substance use. Include questions about prescribed substances such as prescription opioids, benzodiazepines, and buprenorphine.
- **Motivating Events** may be the basis for a person seeking treatment. It is important to elicit that history (i.e., if a woman lost custody of her child), while not making promises to resolve any of these conflicts for the person.
- **Stay neutral.** Do not contradict or endorse their claims. For personal and/or psychosocial reasons, patients may minimize and/or exaggerate the breadth and severity of their actions.

### Patient Assessment – Exhaustive Drug Use History

The cornerstone of patient evaluation is the history. Begin with what brings them to medical attention and explore systematically, one at a time, the common drugs of abuse. Obtaining a complete substance use history will allow the provider to identify patients who need detoxification from another, non-opioid substance, most commonly alcohol and/or benzodiazepine. Knowing this history allows the treatment team to address a patient's recovery from OUD as well as his/her overall health and wellness. Other substances to explore include stimulants (methamphetamine, cocaine, nicotine), sedatives (barbiturates, benzodiazepine, alcohol, muscle relaxants/OTC sleep preparations), cannabis, PCP, designer drugs (e.g., MDMA), other OTC or prescription medications taken inappropriately.

For each drug, determine age of first use, first regular use or use to intoxication, presence of withdrawal on cessation of use, amount of time and money spent, neglect of personal and social responsibilities, and continuous use despite health and social harm. Most substance use disorders begin in adolescence; later adult onset may suggest co-occurring psychiatric disorders, especially affective disorders, or a prescription opioid use disorder that began because of treatment of chronic pain <sup>[8]</sup>.

Explore past periods of abstinence and heavy use, and the surrounding life circumstances; these may suggest motivations to quit, or triggers to relapse. Pay special attention to the pattern of use in recent weeks. The information is crucial to treatment planning, and may help decide whether a period of hospitalization is necessary. Screening tests and questionnaires exist such as the DAST, AUDIT, and CAGE, but they lack the flexibility and rapport-building of a life interview. If needed, a summary of various screening tools can be found on the [National Institute of Drug Abuse \(NIDA\) resource page](#).

### Patient Assessment – Mental Illness

The patient's behavior and responses to questioning during history taking and physical examination usually provide sufficient clues to his or her mental status. Sometimes it may be useful to use a standardized cognitive screening test like the Mini-Mental Status Examination, or the [Mini-Cog](#), but recall that these screening tests may be inaccurate in low-literacy populations. Many patients with opioid use disorder have untreated mental health problems, most commonly major depressive disorder, anxiety-spectrum disorders, and bipolar disorder. If mental health problems are not addressed, a patient may have difficulty achieving and maintaining abstinence from substances of abuse. A mental health history including past and current mental health problems and diagnoses, past and current medications, current symptoms, overdose events, suicide attempts, involuntary commitments ("5150"), and the family history will allow triage and follow-up as appropriate. It is helpful, and sometimes essential, to coordinate with the mental health provider. The patient must sign a release of information prior to communication. Federal regulations governing the confidentiality of patient information when the patient is in treatment for substance use disorders are

found in [42 CFR Part 2](#)<sup>[7]</sup>. A general medical consent form is not adequate. See Table 1.2 or refer to [SAMHSA](#) the specific requirements and a sample consent form. See also Co-Occurring Psychiatric Illness.

### Patient Assessment – Concurrent Medical Conditions

A review of past and current medical diagnoses and current medical concerns/symptoms allows the physician to triage for conditions that need prompt attention and to arrange for evaluation and follow-up prior to or concurrent with opioid use disorder treatment. Questions regarding past hospitalizations, accidents/injuries, surgeries and medications being taken may elucidate conditions the patient does not immediately remember or volunteer. See also Concurrent Medical Conditions.

### Patient Assessment – Physical Examination

Physical examination at admission is a regulatory requirement. California regulations specify inclusion of the following components:

- vital signs
- head, eyes, ears, nose, and throat (HEENT)
- neck (including thyroid)
- chest (including heart, lungs and breasts)
- abdomen
- skin
- extremities
- neurological screening

Observe patients carefully throughout history-taking and conduct a thorough physical examination. Look for fresh needle marks (some needle-related conditions might require urgent care), old scars, thrombosed veins, congested nasal mucosa, abscesses, and enlarged liver and local lymph

nodes. Cardiac arrhythmia and murmur suggest cocaine, methamphetamine, and other stimulant misuse, whereas gynecomastia and spider nevi point to alcoholism.

While it is not a regulatory requirement, including height and weight allows calculation of a body/mass index (BMI), which may be useful in the course of treatment as many patients have problems maintaining ideal body weight. Pelvic exams and rectal exams may be included if the clinic is set up to accommodate them, there is a clear indication to do so, and the patient consents.

### Patient Assessment – Other Important Information.

A brief social history, a review of patient's current living and transportation arrangements, as well as past and present involvement with criminal justice is helpful for identifying barriers to successful treatment.

### Patient Assessment – Verification and Documentation

Supplement the current illness with a careful review of patient records, [Controlled Substance Utilization Review and Evaluation System \(CURES\)](#) database, past medical history, family, social and occupational history. Confirm the information obtained with an independent source whenever possible.

### Patient Assessment – Screening for Communicable Disease

Screening for symptoms of communicable disease is an important component of this section of the interview. The most commonly encountered communicable diseases are tuberculosis (TB), hepatitis, sexually transmitted diseases and HIV. Several screening tests are required in narcotic treatment programs – commonly, tuberculosis and syphilis, but offering more extensive services is optimal. Ensure

Table 1.2

## Summary of 42 CFR part 2 requirements for release of information forms

### Disclosure under these regulations must include:

- |  |  |
|--|--|
| <ol style="list-style-type: none"> <li>1. The specific name or general designation of the program or person permitted to make the disclosure.</li> <li>2. The name or title of the individual or the name of the organization receiving the disclosure.</li> <li>3. The name of the patient.</li> <li>4. The purpose of the disclosure.</li> <li>5. Scope and type of information to be disclosed.</li> <li>6. The signature of the patient and, when required for a patient who is a minor, the signature of a person authorized to give consent under § 2.14; or, when required for a patient who is incompetent or deceased, the signature of a person authorized to sign under § 2.15 in lieu of the patient.</li> </ol> | <ol style="list-style-type: none"> <li>7. The date of signed consent.</li> <li>8. A statement that the consent is subject to revocation at any time except to the extent that the program or person which is to make the disclosure has already acted in reliance on it.</li> <li>9. The date, event, or condition upon which the consent will expire if not revoked beforehand, to ensure that the consent will last no longer than reasonably necessary to serve the purpose for which it is given.</li> </ol> |
|--|--|

Table 1.3

## Medical syndromes associated with opiate use: Anticipatory, early, and fully-developed symptoms and signs of opiate withdrawal

Syndrome (Onset and Duration)	Characteristics
<b>Opioid intoxication</b>	<ul style="list-style-type: none"> <li>■ Conscious, sedated, “nodding”</li> <li>■ Mood normal to euphoric</li> <li>■ Pinpoint pupils</li> <li>■ Recent history of opioid use</li> </ul>
<b>Acute overdose</b>	<ul style="list-style-type: none"> <li>■ Unconscious</li> <li>■ Pinpoint pupils</li> <li>■ Slow, shallow respirations</li> </ul>
<b>Opiate withdrawal:</b>	
<b>Anticipatory (3-4 hours after last use)*</b>	<ul style="list-style-type: none"> <li>■ Fear of withdrawal</li> <li>■ Drug-seeking behavior</li> <li>■ Anxiety</li> </ul>
<b>Early (8-10 hours after last use)</b>	<ul style="list-style-type: none"> <li>■ Anxiety</li> <li>■ Restlessness</li> <li>■ Yawning</li> <li>■ Nausea</li> <li>■ Sweating</li> <li>■ Nasal stuffiness</li> <li>■ Rhinorrhea</li> <li>■ Lacrimation</li> <li>■ Dilated pupils</li> <li>■ Stomach cramps</li> <li>■ Drug-seeking behavior</li> </ul>
<b>Fully developed (1-3 days after last use)</b>	<ul style="list-style-type: none"> <li>■ Severe anxiety</li> <li>■ Tremor</li> <li>■ Restlessness</li> <li>■ Piloerection**</li> <li>■ Vomiting, diarrhea</li> <li>■ Muscle pain</li> <li>■ Muscle spasm***</li> <li>■ Increased blood pressure</li> <li>■ Tachycardia</li> <li>■ Fever, chills</li> <li>■ Impulsive drug-seeking</li> </ul>
<b>Protracted abstinence (Indefinite duration)</b>	<ul style="list-style-type: none"> <li>■ Hypotension</li> <li>■ Bradycardia</li> <li>■ Insomnia</li> <li>■ Loss of energy, appetite</li> <li>■ Opiate cravings</li> </ul>

\* Anticipatory symptoms occur as the acute effects of opioids begin to subside.

\*\* The piloerection has given rise to the term “cold turkey.”

\*\*\* The sudden muscle spasms in the legs have given rise to the term “kicking the habit.”

patient is current in their vaccinations. It is very helpful, and sometimes essential, that patients sign a release to all treating physicians to allow coordination.

### Patient Assessment – Opioid Withdrawal

The physical examination provides an opportunity to observe for signs of opioid withdrawal (see Table 1.3). The presence of signs of withdrawal establishes the diagnosis of physical dependence. However, it should be noted that symptoms and signs of opioid withdrawal are subject to the effects of environment (less intense in controlled settings) and dependent on the amount and timing of the last use. Severity of withdrawal does not necessarily correlate with high tolerance and does not reliably establish need for a high opioid medication dose. The earliest manifestations of opioid withdrawal are usually subjective, and include anxiety and insomnia. Table 1.3 shows anticipatory, early, and fully-developed symptoms and signs of opioid withdrawal. The physician should expect to see at least

early signs of withdrawal. The Clinical Institute Narcotic Assessment (CINA) Scale (Table 1.4) measures 11 signs and symptoms commonly seen in patients during opioid withdrawal. This can help to gauge the severity of a patient’s withdrawal and to monitor changes in the clinical status over time. The Clinical Opiate Withdrawal Scale (COWS) (Table 1.5) can also be used to document the presence of and to quantify [https://www.naabt.org/documents/cows\\_induction\\_flow\\_sheet.pdf](https://www.naabt.org/documents/cows_induction_flow_sheet.pdf) the severity of opioid withdrawal.

### Patient Assessment – Initial Laboratory Tests

Laboratory evaluation should be individualized, but hepatitis serology, liver function tests, metabolic panel, and screening for STIs, and HIV are highly advisable for all patients in this population. Female patients should be screened for pregnancy. California and Federal regulations require screening for tuberculosis and syphilis.

Table 1.4

## The Clinical Institute Narcotic Assessment (CINA) Scale for Withdrawal Symptoms

### Based on Questions and Observation:

Parameters	Pts.	Findings
<b>1. Abdominal Changes:</b> Do you have any pains in your abdomen?	0	No abdominal complaints; normal bowel sounds
	1	Reports waves of crampy abdominal pain
	2	Crampy abdominal pain; diarrhea; active bowel sounds
<b>2. Changes in Temperature:</b> Do you feel hot or cold?	0	None reported
	1	Reports feeling cold; hands cold and clammy to touch
	2	Uncontrolled shivering
<b>3. Nausea and Vomiting:</b> Do you feel sick to your stomach? Have you vomited?	0	No nausea or vomiting
	2	Mild nausea; no retching or vomiting
	4	Intermittent nausea with dry heaves
	6	Constant nausea; frequent dry heaves and/or vomiting
<b>4. Muscle Aches:</b> Do you have any muscle cramps?	0	No muscle aching reported; arm and neck muscles soft at rest
	1	Mild muscle pains
	3	Reports severe muscle pains; muscles in legs, arms, or neck in constant state of contraction

### Based on Observation Alone:

Parameters	Pts.	Findings
<b>1. Goose Flesh</b>	0	None visible
	1	Occasional goose flesh but not elicited by touch; not permanent
	2	Prominent goose flesh in waves and elicited by touch
	3	Constant goose flesh over face and arms
<b>2. Nasal Congestion</b>	0	No nasal congestion or sniffing
	1	Frequent sniffing
	2	Constant sniffing; watery discharge
<b>3. Restlessness</b>	0	Normal activity
	1	Somewhat more than normal activity; moves legs up and down; shifts position occasionally
	2	Moderately fidgety and restless; shifting position frequently
	3	Gross movement most of the time or constantly thrashes about
<b>4. Tremor</b>	0	None
	1	Not visible but can be felt fingertip to fingertip
	2	Moderate with patient's arm extended
	3	Severe even if arms not extended
<b>5. Lacrimation</b>	0	None
	1	Eyes watering; tears at corners of eyes
	2	Profuse tearing from eyes over face
<b>6. Sweating</b>	0	No sweat visible
	1	Barely perceptible sweating; palms moist
	2	Beads of sweat obvious on forehead
	3	Drenching sweats over face and chest
<b>7. Yawning</b>	0	None
	1	Frequent yawning
	2	Constant uncontrolled yawning
<b>TOTAL SCORE</b>		Percent of maximal withdrawal symptoms = total score/31 x 100% = ____/31 x 100% = Summary: ____%
Date: _____		Number of <b>Absent</b> Signs and Symptoms: ____ out of 11
Time: _____		Number of <b>Maximal</b> Signs and Symptoms: ____ out of 11
		Minimum score = 0, Maximum score = 31. The higher the score, the more severe the withdrawal syndrome.

Patient Name: \_\_\_\_\_

Table 1.5

**The Clinical Opiate Withdrawal Scale (COWS) [11]**

**Instructions:** For each item, circle the number that best describes the patient's signs or symptoms. Rate on just the apparent relationship to opioid withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increased pulse rate would not add to the score.

Patient's Name: \_\_\_\_\_ Date and Time \_\_\_\_/\_\_\_\_/\_\_\_\_ : \_\_\_\_\_

Reason for this assessment: \_\_\_\_\_

**Resting Pulse Rate:** \_\_\_\_\_ beats/min.

Measured after patient is sitting or lying for one minute

- 0 pulse rate 80 or below
- 1 pulse rate 81-100
- 2 pulse rate 101-120
- 4 pulse rate greater than 120

**GI Upset:** over last ½ hour

- 0 no GI symptoms
- 1 stomach cramps
- 2 nausea or loose stool
- 3 vomiting or diarrhea
- 5 Multiple episodes of diarrhea or vomiting

**Sweating:** over past ½ hour not accounted for by room temperature or patient activity.

- 0 no report of chills or flushing
- 1 subjective report of chills or flushing
- 2 flushed or observable moistness on face
- 3 beads of sweat on brow or face
- 4 sweat streaming off face

**Tremor** observation of outstretched hands

- 0 No tremor
- 1 tremor can be felt, but not observed
- 2 slight tremor observable
- 4 gross tremor or muscle twitching

**Restlessness** Observation during assessment

- 0 able to sit still
- 1 reports difficulty sitting still, but is able to do so
- 3 frequent shifting or extraneous movements of legs/arms
- 5 Unable to sit still for more than a few seconds

**Yawning** Observation during assessment

- 0 no yawning
- 1 yawning once or twice during assessment
- 2 yawning three or more times during assessment
- 4 yawning several times/minute

**Pupil size**

- 0 pupils pinned or normal size for room light
- 1 pupils possibly larger than normal for room light
- 2 pupils moderately dilated
- 5 pupils so dilated that only the rim of the iris is visible

**Anxiety or Irritability**

- 0 none
- 1 patient reports increasing irritability or anxiousness
- 2 patient obviously irritable/anxious
- 4 patient so irritable or anxious that participation in the assessment is difficult

**Bone or Joint aches** If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored

- 0 not present
- 1 mild diffuse discomfort
- 2 patient reports severe diffuse aching of joints/ muscles
- 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

**Gooseflesh skin**

- 0 skin is smooth
- 3 piloerection of skin can be felt or hairs standing up on arms
- 5 prominent piloerection

**Runny nose or tearing** Not accounted for by cold symptoms or allergies

- 0 not present
- 1 nasal stuffiness or unusually moist eyes
- 2 nose running or tearing
- 4 nose constantly running or tears streaming down cheeks

**Total Score** \_\_\_\_\_

The total score is the sum of all 11 items

Initials of person completing assessment: \_\_\_\_\_

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal.

# CHAPTER 2

# MEDICATION-ASSISTED TREATMENT

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## 2.1 METHADONE

### 2.1.1. Introduction to Methadone Treatment

#### Clarification of Terms

California and Federal Regulations regarding methadone use the term Opioid Addiction to refer to the condition that is listed in the DSM-5 as Opioid Use Disorder (OUD).

#### Methadone: Description, Properties & Black Box Warning

Methadone is a synthetic opioid that can be taken orally and acts as a full agonist at the mu receptor. It is available in liquid or tablet form. In California, OTPs are required to use the liquid formulation. A state exception request may be submitted if there are special circumstances making the use of liquid methadone problematic.

The bioavailability of oral methadone is high, usually 70-80%, but varies from 36% to 100%. The onset of action is 30-60 minutes, the peak effect of any one dose is usually achieved in 2.5-4 hours, and the half-life is long, about 25

hours in most patients. Methadone undergoes extensive first-pass metabolism in the liver. It binds to albumin and other proteins in the lung, kidney, liver and spleen. Tissue stores in these areas build up over time, and there is a gradual equilibration between tissue stores and methadone in circulation. This buildup of tissue levels produces daily increases in the medication's impact on the patient until steady state is reached, which takes about 5 days.

Methadone's unique pharmacologic properties make it highly effective for management of OUD. The slow onset of action means that there is no rush after ingestion. The long half-life means that craving diminishes and symptoms of withdrawal do not emerge between doses, ending the cycling between being sick, intoxicated and normal and decreasing craving.

However, the long half-life also means that any given dose of methadone will produce a higher blood level each day for the first 5 days of ingestion, so there is a very real risk of overdose during the induction period if the starting dose is too high or the dose is increased too quickly. Hence the admonition to "start low, and go slow".

Because of adverse cardiac events and respiratory deaths during induction, a black box warning was added to the methadone label on 11/27/06. (See Section on Adverse

Events.) Conversion in pain patients from treatment with other opioid agonists to methadone has been particularly problematic as the peak respiratory depressant effects usually occur later and persist longer than the peak analgesic effects, especially in the early dosing period.

## Restrictions in the Use of Methadone for the Treatment of Opioid Use Disorder

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In the United States, the use of methadone for the treatment of OUD is restricted to licensed Opioid Treatment Programs (OTPs). In countries outside the US, methadone maintenance treatment is offered in office-based settings, at the discretion of individual physicians. With rare exception, office based treatment is not permitted in the United States as of this writing.

### 2.1.2. Criteria for Admission to Methadone Treatment

#### Methadone Treatment Options: Detoxification and Maintenance

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Methadone treatment in the United States is regulated, comprehensive treatment, which requires observed dosing, random urine drug testing and participation in counseling. Federal and California Regulations define three treatment options. **Short-term detoxification:** methadone administered in decreasing doses for up to 30 days. **Long-term detoxification:** methadone initiation, stabilization and withdrawal lasting up to 180 days. **Methadone maintenance treatment (MMT):** methadone initiation, stabilization and ongoing treatment with reviews at specified intervals to establish that ongoing treatment is still medically necessary.

Short-term detoxification has been found to be unsuccessful in almost all cases. Methadone Maintenance is much more likely to be effective, but not every patient presenting for treatment meets the regulatory eligibility criteria. Long-term detoxification provides a treatment option for patients who do not want or do not qualify for methadone maintenance. If a patient is unable to stabilize and taper off within 180 days a SAMHSA/CSAT Exception may be requested to allow transfer to MMT. It is best medical practice to document discussion of risks of detoxification including relapse, overdose and death. All patients entering OTP treatment, and especially those choosing detoxification, should be offered Narcan.

#### Criteria for admission to Methadone Treatment – Detoxification

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Any patient who meets DSM 5 criteria for OUD and has been using opioids long enough to develop physical dependence, meaning that they cannot stop using opioids without symptoms of withdrawal, is eligible for admission to Methadone Detoxification Treatment. Because this treatment is so unsuccessful, its use is generally limited

to patients who do not meet criteria for admission to methadone maintenance or who decline methadone maintenance. Strong consideration should be given to offering these patients buprenorphine treatment as they are eligible for buprenorphine maintenance, and detoxification would be more comfortable, if not more successful.

#### Criteria for admission to Methadone Treatment - Maintenance

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Using MMT or other opioid agonist therapy (OAT) has been shown to be more effective than detoxification as initial treatment, and it may be more cost-effective<sup>[12]</sup>. Current federal regulations require that patients meet the diagnostic criteria for OUD and have documentation of at least a one-year history to qualify for admission to MMT<sup>[13]</sup>. Often a failed detoxification attempt provides documentation of the duration of OUD. California regulations require current physical dependence and documentation of at least a two-year history and at least two failed attempts at detoxification.

#### Regulatory Exceptions to Federal and California Admission Criteria

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Federal and California regulations make specific provision for the admission of certain patients who meet DSM 5 criteria for OUD but are not currently physically dependent. Federal and California regulations differ.

**Federal regulations** (42CFR8.12.e.3)<sup>[13]</sup> specify the following exceptions to the general requirement that the patient be “currently addicted to an opioid drug”:

1. Patients released from a penal institution, within 6 months of release,
2. Pregnant patients,
3. Former MMT patients, within 2 years of discharge.

**California’s regulations** (Title 9, section 10270)<sup>[14]</sup> are more restrictive than Federal regulations, but do allow the following exceptions to the requirement for physical dependence at intake:

1. Patients who would have qualified for maintenance before incarceration and who have been incarcerated for at least a month may be admitted within a month of release.
2. Patients who have been on maintenance treatment for at least six months and who voluntarily left treatment may be admitted within six months of discharge.
3. Pregnant patients who are currently physically dependent on opioids and have had a documented history of addiction to opioids in the past may be admitted to maintenance treatment without documentation of a 2-year addiction history or two prior treatment failures, provided the medical director or program physician, in his or her clinical judgment, finds treatment to be medically justified.



## Admission Criteria for Minors

For patients under 18 years of age, Federal regulations require documented parental consent before the patient begins pharmacotherapy at a licensed Opioid Treatment Program <sup>[13]</sup>. In addition, Federal regulations require documentation that the minor has attempted and failed at least two short-term detoxifications or drug-free treatment episodes within the 12 months prior to admission to MMT. No State approval is required in California.

## Program-Wide Exceptions

OTPs can apply to the State for a permanent program-wide exception allowing patients with OUD who meet the federal regulations to be admitted to MMT without meeting California's requirement for a two-year history and two failed detoxification attempts <sup>[15]</sup>.

## Individual Patient Exception

If a program-wide exception is not in place, a physician can apply for an exception for an individual patient when withholding treatment constitutes a life-or health-endangering situation. It is necessary to obtain approval prior to admitting the patient. Public health considerations provide a strong argument in favor of beginning treatment as early as possible in the course of a patient's drug use to reduce the likelihood of HIV and HCV infection and transmission. Clinical experience shows that 80% of people who inject drugs will acquire HCV antibodies within a year of beginning injection drug use. <sup>[16]</sup> Sharing snorting paraphernalia also increases the risk of blood-borne infection.

## MMT for High Relapse Risk Patients

There are patients who are not currently physically dependent, but who have a history of OUD and whose current situation puts them at high risk of relapse. The physician should carefully evaluate and consider these patients for admission to medication assisted treatment to prevent relapse. While buprenorphine maintenance would generally be a better option in this situation, methadone maintenance should be considered if buprenorphine is not available or appropriate for some reason. Prior to admission the physician must carefully review Federal and California regulations and obtain exception waiver(s) if necessary.

## Submitting an Exception Request

Exception requests are made online via the [SMA-168 form](#), which is completely and simultaneously submitted to federal/state authorities. SAMHSA/CSAT is no longer accepting for SMA-168 by mail or fax. Providers can obtain access to online exception requests by registering via the website: <http://otp-extranet.samhsa.gov/request/>. For more information, providers can contact the SAMHSA OTP Exception Request Information Center at 1-866-OTP-CSAT (1-866-687-2728), or by e-mailing [otp-extranet@opioid.samhsa.gov](mailto:otp-extranet@opioid.samhsa.gov). SAMHSA/CSAT decision may be viewed online within one hour of submission. Decisions are typically made within 1 business day. Please clarify this. You may also add that it may take "up to" 2 or 3 days to respond. In the event an exception of high importance is needed, the program may contact their state authority to expedite a decision for federal and California exception.

Table 2.1.1

### Methadone Maintenance Admission Criteria Federal vs. California

	Meet DSM Criteria for Opioid Use Disorder	Current Physical Dependence	Duration of Dependence	Failed Detox Attempts
<b>Federal Regulations</b>	Required	Not required	One year	Only required for minors
<b>California Regulations</b>	Required	Required	Two years	Required; must document failure of two or more attempts
<b>Two + Two Programmatic Exception from California</b>	Required	Required	Six months plus one day or more	Not required

Table 2.1.2

## Exceptions to Requirement for Current SUD at the Time of Admission: Federal vs. California\*

	Incarcerated Patients	Pregnant Patients	Former MMT Patients
<b>Federal Regulations</b>	If admitted within six months of release	If document past history of SUD and current risk of relapse	If admitted within two years of discharge from MMT
<b>California Regulations</b>	If qualified for MMT at the time of incarceration and incarcerated for at least one month provided they are admitted within one month of release	No exception for pregnant patients in California regulations	Patients who were on MMT for at least 6 months and left treatment voluntarily provided they are admitted within 6 months of discharge from MMT

\*Note: Under California regulations, patients must have **physical dependence with documented withdrawal** at the time of admission unless they meet the above criteria or a waiver is obtained from the state.

### Patient Suitability for MMT

MMT is suitable for most adults with a history of OUD of sufficient severity and length who are willing and able to commit to the long term, physical-dependence-sustaining nature of pharmacologic treatment and the encumbrances of opioid maintenance treatment. Patients with **severe** cardiac, hepatic or respiratory conditions may not be candidates for methadone treatment due to safety considerations. Patients with co-occurring sedative use disorders (alcohol, benzodiazepines, etc.) must be evaluated and treatment options carefully considered because they are at increased risk of overdose and death. The non-opioid sedative use disorder must be addressed concurrently to maximize patient safety and treatment efficacy. Patients who are severely mentally ill need to be evaluated to ensure that they are stable enough to function in an outpatient clinic setting and assisted to obtain psychiatric treatment in a timely fashion.

Regulations require that patients enter opioid maintenance treatment voluntarily. Good medical practice requires that patients be advised of the available treatment options, the risks and benefits of each option and be allowed to make an informed decision. The physician should assess the risks and benefits of starting methadone versus the risk of non-treatment or other forms of SUD treatment, especially in cases where there is a medical indication for treatment but uncertainty about the length of time of SUD or when documentation of the patient's history is not readily available. Other treatment options to consider include buprenorphine, vivitrol and non-medication assisted treatment modalities instead of or in addition to MAT.

Patients need to be advised that methadone is considered long-term treatment for a chronic condition, that it includes medication and psychosocial intervention and that retention in treatment is the best predictor for achieving and sustaining abstinence from illicit opioid use. They need to be informed that methadone is an opioid, that it

will perpetuate their physical dependence and that abrupt cessation of dosing will produce symptoms of withdrawal. It is helpful to explain that methadone withdrawal is less intense than withdrawal from heroin or other short-acting opioids, but much longer lasting, 6-8 weeks. They need to be told about the requirement for daily observed dosing in clinic with its attendant restriction on travel, the requirements for counseling, for random urine drug testing and breathalyzer testing. They need to consider the impact of ongoing exposure to a large number of addicted persons congregating at the clinic. The physician should ensure that there is documentation that the patient was informed of these issues and has consented to treatment.

### Summary: The Role of the Physician in Selecting Patients for MMT:

1. To ensure that the patient has a documented history of OUD of sufficient severity and duration.
2. To ensure that the patient is currently addicted and physically dependent on opioids or meets federal and state exception criteria.
3. To establish and document that previous attempts at opioid withdrawal have not been successful and that maintenance treatment is the appropriate treatment option.
4. To ensure that there are no medical, psychological or cognitive contraindications to MMT.
5. To answer patients' questions regarding MMT and obtain informed consent for treatment.
6. To apply for federal and/or state admission waivers if MMT is medically indicated and the patient does not meet regulatory requirements.

### 2.1.3. Methadone – Determining and Adjusting the Dose

At every point during methadone dose determination, from induction onward, the physician, working closely with a well-trained staff, must be mindful of the patient's potential for concomitant use of illicit drugs, alcohol, prescribed and/or over-the-counter medications that can enhance the sedative effects of methadone by additive or synergistic CNS effects, or by increasing methadone's effective plasma level. **Particular caution is needed in patients with medical conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve** such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, and CNS depression. In these patients, even usual therapeutic doses of methadone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

#### Induction

Once a patient has been found medically fit and appropriate for opioid agonist therapy, the physician is responsible for determining the amount and timing of the initial dose of methadone and all subsequent adjustments. California does not allow the use of standing orders for induction. The starting dose and subsequent dose changes must be determined on a case-by-case basis to maximize patient safety. The rationale for all dose changes should be clearly documented in the patient's record.

**California regulations require that the physician observe and document symptoms of opioid withdrawal to ensure that the patient is physically dependent on opioids** prior to administration of the first dose of methadone. (Exceptions to this requirement are listed above under Regulatory Exceptions to Federal and California Admission Criteria.) See DIAGNOSIS OF SUBSTANCE-RELATED AND ADDICTIVE DISORDERS, subsection on Patient Assessment – Opioid Withdrawal for signs and symptoms of opioid withdrawal and assessment tools.

#### The Initial Dose

The physician's determination of the initial dose is based on consideration of the following factors:

1. Regulatory restrictions (Federal & California) limiting the size of the initial dose.
2. Pharmacology of methadone
3. Characteristics of the specific patient, including co-occurring medical conditions, current medications and use of other substances.
4. Current level of opioid dependence (tolerance) of the patient.

**Note:** *There is no direct way to measure tolerance. While the presence of withdrawal confirms the diagnosis of physical dependence, the severity of withdrawal is not*

*correlated with the level of tolerance, meaning that severe withdrawal does not necessitate a higher starting dose.*

Tolerance is assessed indirectly by considering the following factors:

1. The quantity of daily drug use: ¼ gram of heroin or less usually means a low level of tolerance.
2. The route of use: heroin is more efficiently absorbed when injected than when insufflated or smoked.
3. The potency of the opioid being used. Using low potency opioids (codeine, hydrocodone) may produce lower tolerance than using high potency opioids (heroin, oxycodone, fentanyl).
4. Opium smoking. Tolerance may be high or low depending on the amount smoked per day.
5. Time elapsed since daily opioid use. A period of extended abstinence while incarcerated, hospitalized or in residential treatment will produce low tolerance.
6. Recent use of an opioid antagonist (naltrexone) or a partial agonist (buprenorphine) will significantly reduce opioid tolerance.

Selecting a starting dose is particularly challenging when the patient has been using prescription opioids. An opioid equi-analgesic table will provide information about the potency of various opioids compared to morphine, but use to select a starting dose of methadone is not recommended. The conversion table gives the dose of various opioids that will have the same effect as a single, specified dose of morphine, when given in the acute setting for the treatment of pain. It compares the effect of one dose of a given opioid with one dose of morphine without taking into account the effect of accumulation before steady state is reached. As a result, the "equivalent" dose given for methadone in the table will be too high when given as a daily dose.

When a patient's level of tolerance is unclear, or a patient is likely to have a low level of tolerance, an initial dose of 5 - 15 mg methadone maybe safely given. An additional dose may be given every 3 to 5 hours if clinically indicated. Indeed, this is the preferred course for hospitalized patients receiving 24-hour care and for pregnant patients ([See Section on Pregnancy.](#))

By regulation, the maximum initial dose cannot exceed 30 mg. A follow up dose may be given on the same day after observation for a period of time determined by the physician. The total dose administered on the first day may not exceed 40 mg unless the physician clearly documents in the chart why he or she believes that 40 mg will be insufficient to control withdrawal. Typically, patients start at 20-40 mg of methadone on the first day in the outpatient setting.

Ultimately, the right dose of methadone will completely suppress opioid withdrawal between doses. However, the first dose should NOT be expected to do so and is too high if it does. Patients should be advised that suppression of severe physical withdrawal is usually accomplished after the first day or two and complete suppression usually takes a week or two.

## Safety Concerns and Patient Expectations

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The first few days of methadone treatment are critical. Due to increasing blood levels as methadone accumulates and patients' tendency to supplement with outside opioids when feeling uncomfortable, there is a higher risk of overdose during induction than at any other time in treatment. It is important to tell patients that it will take about 4 hours after dosing for them to experience the full effect and to caution them that supplementing with outside opioids or any other sedatives, prescription sedatives, over the counter sedatives or alcohol, is dangerous, putting them at risk of overdose/death. It will also slow the induction process as it will not be possible to know how they would feel if they had taken only methadone, and dose increases will be delayed if they do not present to clinic with signs of withdrawal. Patients should be advised to be careful about driving for the first 4 hours after dosing and to report any sedation.

The physician should inform patients that the methadone dose is expected to allow them to stop outside opioid use completely and encourage patients to avoid people, places and situations where opioids are available because such situations can intensify craving and trigger symptoms of withdrawal.

Careful observation and regular evaluation are imperative until steady state has been achieved, which takes about 5 days. A balance between safety and efficacy concerns is best served by daily evaluation during the induction period as the dose builds to therapeutic levels. Daily evaluation allows the physician to screen for overmedication, to address the patient's discomfort by stabilizing the dose as quickly as is safely possible, and to provide feedback when it is not safe to increase the dose. Daily evaluation is reassuring to the patient, which may help them to avoid or minimize outside supplementation.

## Screening for and Responding to Overmedication During Induction

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Daily screening for overmedication during the first five days of induction is an important safeguard. Patients should be asked whether they experienced any of the following the previous day:

- Feeling sedated, sleepy or unable to stay awake
- Feeling unusually energetic with or without euphoria
- Feeling completely well for 24 hours after the first dose

In the event that any symptom of overmedication is reported, the methadone dose must be decreased promptly. **Failure to reduce the dose when there is sedation or other symptoms of overmedication during induction may result in fatal overdose as tissue stores accumulate.**

Mild sedation (feeling sleepy but able to stay awake) that occurs at the time of the peak and does not last more

than an hour or two may be addressed by decreasing the methadone dose by 20-30%. For example, a 20 mg dose would be lowered to 15 mg, a 30 mg dose would be lowered to 20 mg. Sedation that is severe (patient unable to stay awake after dosing) or long lasting (persisting until bedtime) is best managed by holding the dose for a day and reassessing the following morning. Before establishing a new dose, it is necessary to evaluate carefully to determine whether there are any other factors that would explain the sedation, such as use of another drug or medication.

If the patient is unable to control use of another sedative, such as alcohol or a benzodiazepine, the induction may need to be conducted while patient is in a structured setting/higher level of care. See also Comorbid Polysubstance Use. Provided this is not the case, restarting at a significantly lower dose, about 50% of the original dose, is recommended.

## Establishing Tissue Stores Safely

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Early in induction it is expected that methadone will not provide relief for 24 hours. The first goal is complete suppression of withdrawal 3-4 hours after dosing (at the time of the peak). Once withdrawal is completely suppressed at the peak, the dose will hold a little longer each day as tissue stores accumulate. The next goal is complete suppression of withdrawal between doses.

Before steady state is reached, the patient's response to the previous day's dose serves as a guide to determination of subsequent doses. It is more helpful to ask the patient whether the dose completely controlled symptoms of withdrawal 2 - 4 hours after dosing than whether the dose "held" for the full 24 hours. A new dose that completely suppresses withdrawal 2 - 4 hours after it is taken (at peak plasma level) may cover for the full 24 hours after it has been taken for a few days and a stable blood level has been reached.

Some rules of thumb for dose adjustment during induction include the following:

- If the patient did not experience complete suppression of withdrawal within 2-4 hours of dosing on the preceding day, it is safe and reasonable to increase the dose by 5-10 mg.
- If the patient did experience complete suppression of withdrawal 3-4 hours after dosing on the preceding day, any increase in the dose should be delayed for another day or two even if symptoms re-emerged before 24 hours.
- If the physician does not feel comfortable with the patient's report of response to the dose, the patient may be invited to return to clinic for assessment 3-4 hours after dosing.
- Doses less than 40 or 50 mg are generally increased in 5mg increments; doses of 50mg or more are generally increased in 10mg increments.

Sometimes it is clear on day 2 that the patient's tolerance was markedly underestimated. This is particularly true when

Table 2.1.3

## Methadone Dose Assessment Form

Date: \_\_\_\_\_

Patient Name: \_\_\_\_\_ ID# \_\_\_\_\_

Vitals: BP \_\_\_\_\_ P \_\_\_\_\_ R \_\_\_\_\_ O2 sat \_\_\_\_\_ BAL \_\_\_\_\_ COWS \_\_\_\_\_\*\*

Current Methadone Dose: \_\_\_\_\_ Date of last dose change: \_\_\_\_\_

1. Did you experience any sedation after taking your methadone dose yesterday? \_\_\_\_\_

2. **Four hours after** taking your methadone dose were you feeling completely well? \_\_\_\_\_  
If not, what symptoms were you having?

___ Chills	___ Nausea	___ Yawning
___ Sweats	___ Stomach cramping	___ Sneezing
___ Runny nose	___ Vomiting	___ Body aches
___ Watery eyes	___ Diarrhea	___ Anxiety/irritability

3. Did you use or take anything yesterday? \_\_\_\_\_  
If so, what and when? \_\_\_\_\_

\*\*Note: Scores less than 5 on day 2 need to be brought to the physician's attention.

the patient was started on a dose of 20 mg or less, reports feeling little to no relief after dosing on day 1 and presents to clinic on day 2 with more severe withdrawal than observed on the preceding day. In this situation increasing by 10mg is a logical and reasonable response.

An overly timid approach to induction, which automatically requires patients to wait 3-5 days between dose adjustments, may delay relief to the point that patients become discouraged and continue to use, which puts them at risk of overdose, delays stabilization, and may ultimately increase the level of opioid tolerance.

See Table 2.1.3 for a sample Methadone Dose Assessment Form which may be used by dispensing staff during induction to identify patients requiring a dose adjustment.

### Stabilizing on a Therapeutic Dose

After the initial induction phase when tissues stores have been established, dosage adjustments of 5 - 10 mgs may be made every 3 - 5 days as needed. Using this "start low, go slow" approach, patients generally reach 24-hour coverage of physical symptoms within the first few weeks of treatment. Complete suppression of craving and achieving a sustained abstinence may take longer and may necessitate doses in the 80 - 120 mg range (or higher) as clinically indicated. Daily doses may be lower for patients addicted to prescription opioids or opium.

While a therapeutic dose will take away unwanted thoughts about using and urges to use (cravings), it will be unlikely to prevent the kind of urges that are triggered by associating with people while they are high or using opioids or by having a supply of opioids or drug paraphernalia available. A therapeutic dose should have minimal side effects and produce no sedation. In order to reach stabilization, some patients need a blocking dose, which is a dose that will prevent opioids of abuse from binding to opioid receptors and causing feelings of euphoria.

California regulations require physicians to justify doses above 100 mg in the patient's record. The 180 mg dose cap was removed from the California Health and Safety Code in 2002. Doses above this level are not the norm, but sometimes they are necessary and appropriate.

The objective is to achieve a therapeutic maintenance dose that allows the patient to conduct activities of daily life without sedation or withdrawal. Outcomes are better when a stable, therapeutic dose is achieved. Early in treatment, during stabilization, frequent check-ins with the patient regarding dose adequacy are important. In some OTPs, the counselors are trained to interview the patient about symptoms of withdrawal, craving and adequacy of dose and to pass on information to clinical staff when patients are symptomatic. An integrated care approach, where counselors, dispensing nurses, and physicians work together to ensure that patients stabilize on a therapeutic dose as soon as possible, supports the patient's compliance in treatment.

Some patients report starting to experience sedation after dosing before withdrawal between doses is completely suppressed. Observing the patient before dosing and 4 hours after dosing will allow confirmation. Serum methadone levels, peak and trough are also helpful in this situation.

## Summary: Definition of a Therapeutic Dose of Methadone

A therapeutic dose of methadone is one that:

1. Suppresses physical signs and symptoms of opioid withdrawal between doses
2. Minimizes intrusive thoughts/dreams about opioids and urges to use (craving)
3. Allows clear mentation and function without sedation
4. Minimizes side effects, such as sweating, constipation and decreased libido
5. Blocks the usual “high” or euphoric effects of opioids (not necessary for all patients)

## Methadone Blood Levels

Serum levels of methadone, peak and trough, may be utilized as an adjunct to clinical evaluation, to evaluate the safety and adequacy of a patient’s dose and to identify patients requiring aspl divided dose to stabilize. Methadone is an enantiomer, and only the R isomer is active for the treatment of OUD. Unfortunately, serum levels do not distinguish active and inactive isomers of methadone. The amount of the methadone dose has been found to be significantly correlated with serum blood level (TIP 43); the correlation was much stronger in patients with no drug use when compared with patients who were using. As with all lab data, the entire clinical picture must be considered. Some clinicians routinely obtain serum methadone levels when a patient’s dose reaches 100mg per day.

## Obtaining and Interpreting Blood Levels

Serum methadone levels are generally obtained when a patient has reached steady state, that is after 5-7 consecutive days at the same dose. The trough level is drawn before the daily dose is taken and about 24 hours after the previous dose. The peak level is drawn 3-4 hours after ingestion of the daily dose. The patient may be asked to remain at the clinic while waiting for the peak to be drawn to preclude outside methadone ingestion in the interim.

Methadone levels should not replace good clinical judgment, but they can provide a point of reference. Thomas Payte notes that adequate trough levels in the highly tolerant opioid dependent patient are in the 400 to 600 ng/mL range. However, there are patients who stabilize with trough levels of 100 to 200 ng/mL. Payte<sup>[17]</sup> notes that absolute numbers in evaluating trough levels are less useful than a comparison of peak and trough levels. The

ratio of the peak to trough level indicates a patient’s rate of methadone metabolism. A patient with a normal metabolic rate will have a peak to trough ratio that is less than two. A peak to trough ratio that is more than two suggests a rapid rate of methadone metabolism.

## Dividing the Dose

While most patients can be stabilized on a single daily dose, patients who are rapid metabolizers of methadone may require split dosing to alleviate withdrawal between doses. A patient’s perception of stability is based on the relative rate of decline of the methadone blood level. As methadone peak to trough ratios increase, say from 2:1 to 4:1, the patient is more likely to feel the more rapid serum methadone decline as symptoms of withdrawal.

Split dosing usually requires that the patient be given a daily take-home dose to be taken in the evening. The physician must weigh the risk of diversion against the benefit to the patient and determine whether the patient meets regulatory criteria for a daily take-home dose. In cases where the patient has not been in treatment long enough for the regulations to allow seven take-homes per week (270 days), or when other criteria have not been met, a waiver from CSAT/CA is needed prior to initiating split dosing. California regulations specifically allow a daily take-home for patients needing a split dose provided they meet all other eligibility criteria for take-home doses. California regulations pertaining to Split Doses and Take-Home Medication state: “ After determining medical necessity, the medical director or program physician may order that a patient receive his or her daily dose of medication split in two. The portion of a split dose removed from the program shall be considered take-home medication, and adherence to federal and California step level scheduled shall be implemented. For purposes of calculating the take-home supply of medication a split dose shall be considered a one day take-home supply.

Split doses are recommended in pregnancy. See the Section on Treatment of Pregnant Women. Split dosing may be helpful for patients with pain because methadone provides some analgesia for four to six hours after dosing.

When patients report sedation shortly after dosing and withdrawal before the next dose, some confirmation of rapid metabolism is prudent. Some patients will report these symptoms and specifically request a split dose with a daily take-home. In many cases, the report is accurate, but there are patients who want a daily take-home as a revenue source. The street value of methadone is currently \$.50 - \$1.00 per mg. Serum methadone levels and/or observation of the patient prior to dosing and again 4 hours after dosing allows clinical confirmation. Often split dosing is initiated after the daily dose has been increased to the point that the last increase produced sedation. In this situation, reducing the AM dose to the amount that did not produce sedation and providing the remainder as a PM dose is a reasonable place to begin. After this, 5-10 mg may be transferred from the AM to the PM dose or the PM dose may be increased by 5-10 mg every few days until symptoms of withdrawal are controlled. This approach has the advantage of

minimizing the amount of methadone that needs to be sent home and offering the patient a solution that will allow them to immediately feel better. An alternative approach is to start by dividing the dose in half. This may put the patient in the position of not experiencing complete relief after the AM dose and spending the day trying to decide when to take the PM dose or taking sips of it throughout the day.

While some patients may stabilize on an even split of their methadone dose, many patients feel better when a larger dose is taken in the AM. Patients who work swing or graveyard shifts may feel better when the larger dose is taken in the PM. Patients should be advised to take their PM dose at roughly the same time every day, usually 10-12 hours after the AM dose, so they do not spend the day trying to decide when they feel badly enough to take it. Patients should be advised to let clinic staff know if and when they are feeling withdrawal, so the dose may be adjusted.

It is important to keep in mind that if split dosing must be discontinued at some point, the patient may not tolerate taking the entire dose in the AM. The physician will need to evaluate the situation carefully to determine the best exit strategy. One approach is to transfer 5-10 mg from the PM to the AM every few days, while monitoring for sedation at the time of the peak. If/when sedation occurs, the AM dose should be decreased to the last tolerated dose, and the PM dose tapered and discontinued. Discontinuing the split dose in a rapid metabolizer will make it impossible to achieve a therapeutic dose. Many times the split must be discontinued because the patient is no longer eligible for a daily take out dose of methadone because of relapse to another substance (methamphetamine, alcohol, etc). In this situation, referring the patient to a higher level of care (residential treatment) where the split dose may be continued is a better option.

## Re-evaluating the dose in the event of clinical change

After stabilizing on a therapeutic dose, some patients will continue on the same dose for years. More commonly, the dose will need to be adjusted from time to time. Changes in a patient's health, medication regimen, schedule, life circumstances, level of stress and exposure to triggers may result in the emergence of symptoms of withdrawal or overmedication or may make a patient more sensitive to methadone's side effects. In these situations, adjusting the methadone dose may be helpful. Other times, the patient may be experiencing symptoms that feel like withdrawal, but are not dose-related.

Patients have a tendency to attribute any or all new symptoms or discomforts to a problem with the methadone dose. However, there are many other conditions that feel like opioid withdrawal, so the physician needs to assess the situation to determine whether the methadone dose should be adjusted or other interventions recommended. Input from nursing and counseling staff may be helpful. When there is no clear explanation for a patient's symptoms, the physician should meet with the patient.

## Common reasons for destabilization

Relapse should always be ruled out as a reason for loss of stability. Continued or resumed use of short-acting opioids during methadone maintenance treatment may increase tolerance and render the current dose inadequate. A methadone dose increase may be necessary to suppress withdrawal between doses and to help control drug cravings. If the short-acting opioid of abuse is still producing euphoria, the dose may be adjusted until this effect is blocked. Counselors and medical staff should work with patients to identify and address lifestyle choices that are barriers to abstinence and encourage participation in activities that support recovery. Coordination with prescribing physicians to limit the number of short-acting opioids obtained by prescription may also be helpful. (See Section on Chronic Pain.)

Use of sedating drugs, such as alcohol and/or benzodiazepine, may require methadone dose reductions to counter over-sedation and decrease the risk of potentially fatal overdose. While withholding or reducing the methadone dose may help prevent over-sedation, it will not solve this difficult problem. Dose reduction may significantly interfere with adequate control of opioid craving. If the patient is using a sedative known to produce a medically significant withdrawal syndrome, such as benzodiazepine or alcohol, the physician will need to determine whether a medically supervised withdrawal from the sedative is necessary and where and how such detoxification treatment is to be accomplished. (See Section on Management of Co-Morbid Poly Substance Use.) Continued abuse of non-opioid substances should be addressed vigorously in counseling sessions and referral to a higher level of care offered if available, where methadone dosing may be continued. Discharge from treatment should be avoided if at all possible.

Stress can result in patients experiencing withdrawal symptoms. Patients with OUD may suffer from deficits in the stress response system. In the event of re-emergence of withdrawal due to increased life stressors, an increase in the daily methadone dose may be indicated. Conversely, when patients achieve stability in their life and are no longer confronted with daily "triggers," they may no longer need a "blocking" dose and may do well at a lower dose than that which was previously indicated.

## Drug Interactions with Methadone

As with all medications, methadone has the potential to interact with other medications. These interactions can put the patient at risk of discomfort from under-medication or of life threatening respiratory depression and sedation from overmedication. Methadone is metabolized in the liver by the cytochrome P450 system of enzymes. Some medications induce these enzymes, increasing the rate of breakdown of methadone and decreasing the serum methadone level. Some medications inhibit these enzymes, decreasing the rate of breakdown of methadone and increasing the serum methadone level. Some medications compete with methadone for these enzymes, so that

one drug prevents the other from being metabolized. In addition medications that alkalinize the urine (bicarbonate) decrease the rate of methadone excretion. Medications that acidify the urine (vitamin C) increase the rate of methadone excretion.

Most of these interactions are possibilities or potentials for interactions and not absolute contraindications to co-administration. The clinical response to co-administration varies widely from patient to patient and from drug to drug. Many patients will not develop problems. Many drugs that could potentially increase or decrease the methadone blood level do not result in clinically significant symptoms. Careful clinical monitoring is necessary, so that adjustments may be made to the dose if the interaction causes clinically significant symptoms. When cytochrome P450 enzymes are inhibited, symptoms of overmedication may emerge over a few days. When cytochrome P450 enzymes are induced, symptoms of withdrawal may emerge over about a week.

It is essential that a complete list of prescribed, OTC and herbal preparations be obtained and reviewed prior to starting methadone treatment. Patients must be informed that other medications may interact with methadone and that these interactions can be serious, so they need to alert prescribing physicians that they are taking methadone. They also need to let methadone clinic staff know about any new medications they are taking. Patients should be encouraged to ask the pharmacist about the possibility of interaction with methadone before starting any new medication.

There are some medications that frequently induce withdrawal. These include medications such as anti-convulsants (carbamazepine, phenytoin, etc.), some antibiotics (rifampin, etc.) and some anti-virals. These medications can increase methadone metabolism reducing the effective blood level of methadone. In some cases, especially with anti-convulsants and rifampin (Rifadin®, Rimactane®), an incremental dose increase may not be adequate to resolve this problem. In these situations, patients may need a split dose to re-stabilize. Split dosing is discussed in the Section on Determining and Adjusting the Dose.

Partial opioid agonists or antagonists will acutely precipitate withdrawal in patients maintained on methadone. Precipitated withdrawal has a sudden onset and is more severe than naturally occurring withdrawal, and may be hazardous in some cases. Patients should be educated and warned about the more common of these drugs, such as pentazocine (Talwin®), naloxone (Narcan®), naltrexone (ReVia®), nalbuphine (Nubain®) or buprenorphine (Suboxone®). Some programs list these drugs, with a warning, on patient identification cards. While not an opioid per se, Tramadol (Ultram®) interacts with the mu receptor and may precipitate withdrawal symptoms in patients on MMT.

Other drugs (such as macrolide antibiotics, Luvox® fluvoxamine, etc.) may decrease metabolism and require a decrease in the methadone dose. Ciprofloxacin can significantly increase the methadone blood level, resulting in severe sedation and/or respiratory failure. The combination of methadone and a tricyclic antidepressant may increase tricyclic toxicity. Medications used to treat HIV infections

may affect methadone. The U.S. Department of Health and Human Services provides an excellent reference for HIV medication interactions at the interactive database [AIDSinfo](#). Underlying medical conditions such as cirrhosis, pregnancy, chronic pain and psychiatric disorders must be considered when assessing dose adjustments and safety. Consultation with a pharmacist is recommended for new medications taken alongside methadone. The National Library of Medicine's [MedlinePlus](#) provides a list of medications that may interact with methadone <sup>[18]</sup>.

Alcohol will slow methadone metabolism when consumed intermittently (competition for Cyt P450) and will hasten it when consumed regularly (induction of Cyt P450).

## Comorbid Medical or Psychiatric Conditions

Comorbid medical or psychiatric conditions can sometimes explain new onset of withdrawal in a previously stable patient. Some conditions may change the metabolic rate of methadone, produce symptoms that mimic withdrawal, or carry a burden of stress and worry that triggers craving. Minor colds and flu often produce symptoms that feel like withdrawal; patients need reassurance and suggestions for symptomatic relief. Pregnancy may significantly increase the rate of methadone metabolism, lowering methadone blood levels. Split dosing is usually necessary to completely suppress withdrawal between doses.

Although withdrawal affects mood, and mood is improved with adequate dosing, anxiety that is related to depression or an underlying anxiety disorder will not respond to a higher dose of methadone. The underlying condition must be treated with appropriate psychotropic medications or counseling.

In the case of insomnia, it may be hard to tell whether the dose should go up, down or stay the same. Use of stimulants or alcohol should be ruled out. Depression should also be ruled out. Many opioid dependent patients have sleep disorders that need non-opioid specific treatment. On the other hand, if the maintenance dose is too low, methadone blood levels may be dropping to sub-therapeutic values during the night, producing withdrawal-mediated insomnia. In a case where the patient has been unable to rest during the night because of withdrawal, he or she may fall asleep during the daytime when blood levels are adequate and thus may appear to be over-sedated by his or her dose, when, in fact, the dose is actually too low to maintain steady blood levels through the night. Careful interviewing and monitoring is necessary to distinguish the proper clinical choice in these cases.

In a patient who has been in treatment beyond the induction phase, changes of 5 or 10 mg at a time are generally used to adjust the dose up or down when indicated. A five milligram change may be adequate if the current dose is 40 mg or less. For patients on doses greater than 40 mg, it is reasonable to change the dose by 10 mg and re-evaluate after a few days. Payte notes that it takes 4 to 5 half-lives to achieve a new steady state, which could



be 4 to 5 days. Further changes in 5-10 mg increments every 4-5 days may be made until the symptoms resolve.

This review of maintaining stability is not intended to be exhaustive, but rather to address some of the more common issues. Carefully and respectfully listening to the patient's specific concern often helps to clarify the nature of the problem, so that the discomfort can be addressed whether it involves changing the methadone dose or some other intervention.

## Management of Pain with MMT Patients

This topic can be found in the Chapter on Pain Management for Patients in Medication Assisted Treatment.

## Summary:

Some of the more common reasons for a change in the clinical picture include:

1. Relapse
2. Stress
3. Medication Changes
4. Medical Conditions, such as pregnancy
5. Psychiatric Conditions
6. Insomnia

Table 2.1.4

### Studies testing effects of methadone on the QT interval

- The mechanism for methadone's effect on the QT interval was studied by Katchman et al. in 2002<sup>[21]</sup>. Methadone blocks the HERG gene, resulting in a blockage of the HERG ion channel. This is a reversible effect (see Ehret below). It is the current dose of methadone that effects the QT interval, not the duration of methadone treatment.
- Martell et al. (2005) assessed QTc intervals prior to induction and 6 and 12 months after induction<sup>[22]</sup>. QTc interval increased significantly from baseline at both 6 and 12 months; there was no significant difference in the interval between 6 months and 12 months. Serum methadone level was positively correlated with magnitude of QTc interval change. Studies by Kornick et al. (2003)<sup>[23]</sup> and Krantz et al. (2003)<sup>[24]</sup> also found a positive correlation between daily methadone dose and QTc prolongation.
- Maremmani et al. (2005)<sup>[25]</sup> and Peles et al. (2006)<sup>[26]</sup> found that patients on methadone had longer QTc intervals than patients not on methadone, but that the methadone dose and serum levels did not correlate with the QTc. Because of these inconsistent findings, the jury is still out on this issue. Studies by Kornick et al. (2003)<sup>[23]</sup> and Krantz et al. (2003)<sup>[24]</sup> also found a positive correlation between daily methadone dose and QTc prolongation.
- Ehret et al. (2006)<sup>[27]</sup> studied patients with a history of injection drug use (IDU) who were hospitalized in a tertiary care center and compared the QTc interval in those receiving and not receiving methadone. They found that 16.2% of those on methadone and 0% of those not receiving methadone had a QTc of 500 milliseconds or longer. A QTc interval of more than 500 milliseconds is considered a definite risk for TdP. QTcs of 500 milliseconds or longer were less common at methadone doses less than 40 mg, and episodes of TdP were less common at doses below 70 mg. QTc interval prolongation was more likely in patients taking a medication that inhibited CYP3A4, patients with decreased prothrombin (a marker for decreased liver function) and hypokalemia. This study also showed that discontinuation of methadone was associated with a shorter QTc interval.
- Fanoie et al. (2007)<sup>[28]</sup> studied syncopal episodes amongst patients in Copenhagen on methadone or buprenorphine for the treatment of heroin addiction. Patients were asked whether they had experienced syncope (sudden unexpected loss of consciousness) not associated with prior injection or inhalation of drugs. ECGs were performed and QTc intervals measured. Methadone dose was associated with the QTc in both women and men. Incidence of syncope increased with higher doses of methadone and higher odds for reporting syncope with longer QTc intervals. Opioid use decreased as methadone dose increased, making it unlikely that the increased syncope in the methadone patients on higher doses was due to opioid use. The duration of methadone treatment was not associated with QTc length, and discontinuing methadone decreased the QTc. There was no association between the buprenorphine dose and QTc. The probability of participants reporting syncope was the lowest in patients on buprenorphine.
- Chugh et al. (2008)<sup>[29]</sup> conducted a prospective study over a 4 year period of patients with sudden cardiac death in the Portland area, comparing patients with a therapeutic level of methadone to patients with no methadone. Just over half (55%) of the methadone patients were pain patients. They found that among patients on methadone, only 23% had sudden-death-associated cardiac abnormalities, meaning that there was no clear cause of sudden cardiac death in 77%. Among patients with no methadone, 60% had sudden-death-associated cardiac abnormalities; 40% did not. Lower prevalence of cardiac disease in the patients on methadone suggests that there may be an association between methadone and sudden cardiac death, but it is possible that some of the methadone patients died due to suppression of breathing, especially while asleep.

## 2.1.4. Adverse Reactions

When properly used for the treatment of OUD, methadone is a medication with an excellent safety record. However, because cardiac events and respiratory deaths have occurred during induction, a black box warning was added to the methadone label on 11/27/06.

### Black Box Warnings

The black box warnings include the following topics: appropriate use, addiction, abuse and misuse, respiratory depression, accidental ingestion, QT prolongation, neonatal opioid withdrawal syndrome, CYP450 interactions, risks from concomitant use with benzodiazepines, CNS depressants, and opioid addiction treatment. An excellent summary may be found at: <https://online.epocrates.com/u/10b53/methadone/Black+Box+Warnings>

### Potential Cardiotoxicity

Manufacturers' package inserts have always included possible cardiac-related side effects such as bradycardia, palpitations, faintness and syncope. In November of 2006, the black box warning included a statement that notes "QT interval prolongation and serious arrhythmia (torsades de pointes (TdP) have been observed during treatment with methadone." While most cases have occurred in patients being treated for pain with large multiple daily doses, there have also been cases in patients receiving doses used for MMT, more commonly, but not exclusively, with higher dose treatment (greater than 200 mg/day).

A prolonged QT interval means prolonged cardiac ventricular repolarization, which can increase the risk of the occurrence of torsades de pointes (TdP). The QT interval is inversely correlated with heart rate. Generally QT intervals are corrected for heart rate. The corrected QT is called the QTc. The definition of prolonged QT interval varies. Prolonged QTc interval has been defined as > 450 milliseconds for men and > 460 – 470 milliseconds for women<sup>[19]</sup>. Current recommendations for tapering methadone treatment is a QT > 470 ms<sup>[19,20]</sup>. Cases of prolonged QT interval and TdP have been associated with a number of factors including family history, patient history of heart disease (especially CAD or CHF), hereditary prolonged QT (LQTS), use of medication(s) that prolong the QT, electrolyte instability (especially decreased potassium and magnesium), use of cardiotoxic drugs (cocaine, methamphetamine, alcohol, etc.), or signs/symptoms suggesting cardiac disease or arrhythmia. When cocaine and alcohol are consumed concurrently, the liver creates a pseudocondensate cocaethylene, which increases the risk of cardiac arrhythmias.

In response to the literature indicating that methadone can cause QT prolongation and the known cases of TdP in patients on methadone maintenance, CSAT convened a consensus panel in December of 2007. The guidelines are reported in the [Journal of Addictive Diseases](#) and are summarized below<sup>[19]</sup>. Every OTP should have a cardiac risk management plan, which should include:

1. The arrhythmia risk related to methadone should be disclosed in the informed consent document signed by patients at intake.
2. The medical inventory at intake should include personal and family history of structural heart disease, MI, heart failure, arrhythmias and syncope.
3. A screening ECG to measure the QTc should be performed at admission. A follow-up ECG should be scheduled when the patient is stabilized (or no more than 30 days following admission). An additional ECG should be performed if the methadone dose exceeds 100 mg/day, or if unexplained symptoms of syncope or seizures emerge.
4. For patients whose QTc is more than 450 but less than 500, methadone can be initiated, accompanied by a risk-benefit discussion and stepped-up monitoring. For methadone-maintained patients with marked QTc prolongation (> 500 msec) strong consideration should be given to (1) reducing the methadone dose, (2) eliminating other contributing factors, (3) employing an alternative treatment modality, or (4) discontinuing methadone therapy.
5. Attention to potential interactions between methadone and other medications that also have QT-prolonging properties, or between methadone and medications that slow the elimination of methadone.

The CSAT consensus panel guidelines offer specific suggestions about how to address the potential for adverse cardiac events for patients on methadone maintenance.

**Informing** patients about this risk, carefully **screening** patients for cardiac disease/cardiac risk factors/family history of cardiac disease, **monitoring** for overmedication with methadone, for syncope/seizures/new cardiac risk factors/cardiac events and for drug interactions with potential to increase the risk are straightforward suggestions that are readily implemented. Offering and obtaining ECG screenings poses some real challenges for programs/patients where there are barriers to accessing or paying for ECGs.

OTP physicians sometimes find themselves confronted with a patient who cannot or will not undergo the ECG screening recommended by the guidelines. It is helpful for OTP physicians who work together, either within a clinic or a group of clinics to discuss these situations and arrive at a consensus as to the best way to manage them, so that there is consistency in the way patients are managed and a documented rationale. It is helpful for patients to be told prior to induction that there may be a time when an ECG or even evaluation and medical clearance by an internist or cardiologist is necessary and required to continue methadone treatment.

ECG screening and medical evaluation/clearance is necessary if a patient on methadone reports symptoms suggestive of an acute cardiac event or of new or progressing cardiac disease. ECG screening is recommended for patients taking a medication in addition to methadone with the potential for QTc prolongation (such as quetiapine, trazodone, etc.), for patients on higher doses of methadone (> 100 mg), or with higher serum methadone levels (> 500 ng/mL). There may be some discussion about

what constitutes higher doses of methadone and a higher serum level. Patients with chronic diseases that increase the risk of heart disease/heart attack should be under the care of a primary care physician. Coordination of care with that physician is helpful to discuss and determine who will order screening ECGs, how often and how the results will be shared.

Patients with identified cardiac risk factors, for whom ECG screening is inaccessible, may be better candidates for buprenorphine. Methadone is generally long term treatment for a chronic disease; patients who are marginal candidates for methadone at the time of admission are apt to be at increased risk over time as their underlying disease progresses. Transitioning from methadone to buprenorphine is difficult, so anticipating and avoiding the need is prudent.

Another challenge OTP physicians encounter is in interpreting ambiguous ECG findings. In light of the inevitability of this situation, it is best to ensure that there is a knowledgeable internist or cardiologist available for consultation and/or referral before ordering an ECG.

## Sedation

Although opioids in general may be stimulating, sedating or both, and some patients may find methadone to be more sedating than their opioid of abuse, patients generally develop tolerance to sedation. Dose reductions may be needed until tolerance to sedation occurs. Interaction of methadone and other CNS depressants (i.e., alcohol, narcotic analgesics, tranquilizers and tricyclics, etc.) is of particular concern since this can lead to hypotension, profound sedation, coma or death. Patients with respiratory, cardiovascular, or other compromising conditions are particularly vulnerable to these mishaps. Naloxone (Narcan®) is the usual choice for the immediate treatment of the respiratory depression that may accompany the profound sedation. Patients should be provided with a Naloxone kit and instructions about use at the time of admission to MMT. They should be encouraged to let family and friends know where the kit is located and how to use it. A dramatic reaction to naloxone injection should be anticipated in any methadone patient, so treatment should be started with a low dose of naloxone, watching for vomiting, aspiration and agitation. If naloxone is administered, emergency transport to a hospital is mandatory. Repeated administration of naloxone may be necessary. Medical surveillance may be necessary for 24 hours or more, due to methadone's long half-life and naloxone's short duration of action. Consideration of repeated dose administration is particularly necessary if the patient has concurrently ingested another long-acting sedative.

## Most Frequently Observed Adverse Reactions

The most frequently observed adverse reactions in methadone maintenance patients are sweating, constipation, sedation (see above) and decreased libido. Many patients gain weight when they achieve abstinence

from heroin use and attribute it to methadone. Often patients' eating habits change dramatically when they stop using heroin, so it is unclear how much of a role methadone plays in the weight gain.

Tolerance to sweating and constipation is not likely to occur, but can be managed clinically. Anticholinergics, such as Methscopolamine 2.5 mg three times per day may be used as a 'drying' agent in cases of severe sweating, but are not useful if patients have high blood pressure or urinary retention. Patients should be encouraged to eat a healthy diet including plenty of fruits, vegetables, high fiber grains and to stay active and well hydrated to help avoid constipation. Fiber supplements such as Metamucil or Benefiber or osmotic cathartics, such as Miralax, may be used if necessary to treat constipation.

Methadone commonly causes decreased libido in men. This may be due to lower testosterone levels. In some cases, it improves in time without treatment. Although not extensively studied, case reports suggest that testosterone deficiency in methadone treatment is dose related and less severe than with heroin. Lowering the dose of methadone may help, but is not a good solution for patients who are still using illicit opioids or experiencing craving. Methadone-related impotence in males can be successfully treated with phosphodiesterase type 5 inhibitors, such as sildenafil (Viagra®), tadalafil (Cialis®) or vardenafil (Levitra®). Cigarette smoking, diabetes and anti-hypertensive medications are other common co-occurring causes of impotence that may complicate the picture.

Edema of the extremities is not uncommon. Most patients continue the medication (perhaps with salt restriction and increased ambulation). A few patients become so uncomfortable that they choose to taper to a lower dose of methadone or to discontinue MMT.

## Endocrine Issues

Research and clinical evidence suggest opioids, including methadone, impact gonadal function in both male and female patients.

### Male Patients:

Naturally occurring opiates (endorphins) decrease testosterone levels by inhibiting both hypothalamic gonadotrophin releasing hormone (GnRH) production and testicular testosterone synthesis. (Daniell 2002) Methadone maintained male patients frequently develop low luteinizing hormone (LH) and total testosterone levels. The effect on gonadal hormones is greater with higher methadone doses. These low LH and total testosterone levels are found in men using other opioids as well.

The functional implications of low testosterone levels include decreased libido, erectile dysfunction and fertility problems. Potential implications of chronic low testosterone levels include risks of decreased bone mineral density, low energy, anergia and depression-like symptoms. For symptomatic male patients, a medical work-up is recommended. The workup may include laboratory testing

Table 2.1.5

## Adverse Reactions as listed in the 2006 Methadone Label

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating.

<b>Body as a Whole</b>	Asthenia (weakness), edema, headache
<b>Central Nervous System</b>	Agitation, confusion, disorientation, dysphoria, euphoria, insomnia, seizures
<b>Urogenital</b>	Amenorrhea, antidiuretic effect, reduced libido and/or potency, urinary retention or hesitancy
<b>Digestive</b>	Abdominal pain, anorexia, biliary tract spasm, constipation, dry mouth, glossitis
<b>Cardiovascular</b>	Arrhythmias, bigeminal rhythms, bradycardia, cardiomyopathy, ECG abnormalities, extrasystoles, flushing, heart failure, hypotension, palpitations, phlebitis, QT interval prolongation, syncope, T-wave inversion, tachycardia, torsades de pointes, ventricular fibrillation, ventricular tachycardia
<b>Hematologic and Lymphatic</b>	Reversible thrombocytopenia has been described in opioid addicts with chronic hepatitis
<b>Metabolic and Nutritional</b>	Hypokalemia, hypomagnesemia, weight gain
<b>Respiratory</b>	Pulmonary edema, respiratory depression
<b>Skin and Appendages</b>	Pruritis, urticaria, other skin rashes, and rarely, hemorrhagic urticaria
<b>Special Senses</b>	Hallucinations, visual disturbances

*Note: During prolonged administration of methadone, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.*

for luteinizing hormone (LH), follicular stimulating hormone (FSH), total testosterone (TT), free testosterone (FT), estradiol (E2) and dihydrotestosterone (DHT). Referral to an endocrinologist may be indicated for additional diagnostic and treatment recommendations including testosterone replacement.

When compared with methadone, buprenorphine seems to have less of an impact on lowering testosterone levels and causing sexual dysfunction. (Bliesener <https://www.ncbi.nlm.nih.gov/pubmed/15483091>)

### Female Patients:

The gonadal function problems experienced by women maintained on methadone or other opioids include luteal and follicular phase disruptions. (Santin 1975) These abnormalities are likely due to opioid-induced impairment of hypothalamic gonadotrophin releasing hormone (GnRH) production and impaired ovarian and adrenal steroidogenesis. Clinically, women experience decreased libido and menstrual irregularities, amenorrhea and

oligomenorrhea. Due to irregular menses, some women mistakenly believe they cannot become pregnant; others suspect they are pregnant when they are not. (Daniell 2007)

For symptomatic female patients, a medical work-up is recommended. The patient's reproductive history and menstrual cycle history, both prior to and after the administration of methadone, are important. The work-up may include laboratory testing for luteinizing hormone (LH), follicular stimulating hormone (FSH), estradiol, progesterone and allopregnenolol. Correlation with the menstrual cycle is necessary to interpret these tests. Referral to an endocrinologist or gynecologist may be indicated to identify or rule out other medical conditions that can cause amenorrhea or oligomenorrhea and/or for treatment recommendations.

In view of the frequency of irregular menses in this population and the possibility of becoming pregnant without regular menses, discussions regarding the use of birth control and the necessity of prompt identification of pregnancy are important. For a summary of the adverse reactions associated with methadone please see Table 2.1.5.

## 2.1.5. Managing Methadone Maintenance Treatment

After admission to MMT and stabilization of the patient's methadone dose, physicians provide ongoing medical oversight of the patient's overall treatment. Key responsibilities are described below.

### Treatment Planning

By California regulation, the physician reviews and signs each patient's treatment plan every 90 days to assure that treatment is appropriate to the patient's needs. California regulations are very detailed in describing what must be in the treatment plan. In addition, accrediting bodies such as JCAHO and CARF have their own standards for treatment planning. Treatment planning in the OTP is multidisciplinary; the treatment plan is usually written by the patient's counselor. California regulations require that current medications, including the methadone dose, be listed on the treatment plan and that the frequency of clinic attendance for dosing (i.e., the take-home step), and the frequency of urine testing and counseling be specified. OTP physicians work with counselors to include medical problems on the treatment plan, as a mechanism to assist patients to follow through with referrals for evaluation and treatment of new medical problems and routine follow-up of chronic medical problems.

### Counseling Services

By Federal regulation, it is the physician's responsibility to ensure that patients receive adequate counseling. Current Federal and California regulations require documentation of at least 50 minutes of counseling per month. This is minimal, and often insufficient, given the myriad life changes that are needed for patients to achieve and sustain abstinence.

Numerous studies have confirmed that psychosocial treatment is a vital component of MMT. Studies in the 1990s showed that while methadone alone produced some improvement in drug use and employment, methadone plus counseling by a rehabilitation specialist showed significantly more improvement in drug use and most areas of life [30-32]. Methadone plus counseling and enhanced services including family therapy, employment, medical and psychiatric services showed even more improvement. However, MMT plus counseling was shown to be the most cost-effective care 6 months out. A study by Avants et al. (1999) showed that MMT plus weekly group and referrals were as effective as MMT plus a 25 hr/week day program in term of outcomes at 3 and 6 months. For both groups, drug use decreased significantly as did drug-related problems and HIV risk behaviors. Although part of the goal of counseling is to help medication adherence and getting the maximal benefit out of the medication, more importantly, counseling serves to support patients in achieving a meaningful and purposeful life. This entails both emotional support and a supporting strategy to becoming a self-sufficient and contributing member of the community.

### Dose Determination

OTP physicians, or their designees, evaluate patients who appear sick or intoxicated when they present for dosing and patients who have missed multiple doses to determine whether they may be safely dosed and to adjust the dose as necessary. If a patient is unfit to be dosed in clinic, they determine where and how a patient is to be transported and coordinate care if a patient will need to be dosed by a hospital or emergency room. They evaluate patients returning to clinic after hospitalization, outpatient surgery, ER treatment or incarceration and adjust the methadone dose as necessary to maximize safety and efficacy.

They review the patient's chart, including methadone dose and urine drug screen results every 90 days when the treatment plan is signed. Patients who are testing positive for illicit opioids or for other sedatives need to have their methadone dose evaluated. The physician may consult with the patient's counselor or dispensing staff or may request to meet with the patient to determine whether the dose should be adjusted, methadone blood levels checked and/or a higher level of care offered.

Patients may request to taper their methadone dose; it is the physician's responsibility to review the taper request and to intervene if a taper appears premature or too rapid. Methadone treatment is voluntary, so patients cannot be maintained when they wish to taper off. However, it is the physician's responsibility to provide information about the rate of taper likely to be tolerated given the patient's current dose and to ensure that the patient understand the risks of tapering too soon or too rapidly and of discontinuation of methadone treatment. The physician should encourage patients to request to stop tapering in the event they become uncomfortable, start to crave illicit opioids or relapse.

When patients provide the clinic with a list of the medications they are taking or alert clinic staff to medication changes, it is the physician's responsibility to review the medications and to determine whether the patient's methadone dose needs to be re-evaluated. The physician will need to meet with patients when significant interactions may occur and/or to coordinate with prescribing physicians.

When patients move into the 6<sup>th</sup> and 7<sup>th</sup> decade of life, the rate that they metabolize methadone slows down. Checking a methadone trough annually and gradually tapering the methadone dose if the trough has gone up will prevent the patient from experiencing side effects from too high of a methadone dose.

Patients may need or choose to relocate to a place where methadone treatment is not available. It is the physician's responsibility to meet with these patients to discuss the situation, to counsel them regarding the risks of discontinuation of methadone treatment, to explore the possibility that alternative treatment (buprenorphine) may be available and to work with the patient on a methadone taper or transition plan if necessary and appropriate.

## 2.1.5. Take-Home Privileges

### Perspectives

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Treatment staff, state regulatory staff, federal drug enforcement agencies and patients often view take-home medications differently. Balancing these perspectives and complying with regulations is the responsibility of the physician in developing the take-home policy of each clinic.

Treatment staff may view take-home privileges as a reward for patient compliance with program rules or reduction in drug use. Controlled clinical trials provide evidence that granting take-home privileges contingent upon drug-free urine is effective in reducing drug use – in other words, as part of a therapeutic structure to support behavior change through contingency management<sup>[33, 34]</sup>. Conversely, restriction or revocation of take-home privileges may be used to discourage patients' illicit drug use or failure to comply with clinic rules.

Drug enforcement agencies view take-home doses as a potential hazard because patients may sell or otherwise divert part or all of their medication to the illicit drug market. Many patients feel that the requirements and restrictions on take-home medication are unreasonable and interfere with their ability to work, travel and participate in other activities.

### Regulatory Requirements

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Because of concerns about diversion and overdose, Federal and California regulations are strict on who is eligible for take-home privileges. See Tables 5 and 6 for specific requirements. The regulatory system tries to support and encourage abstinence by allowing patients with favorable drug tests and adherence to clinic rules to move through a graduated take-home schedule from Step 1 (one take-home per week if it is a holiday) to Step 6 (30 take-homes per month). Federal and California regulatory requirements concerning take-home medication are more closely aligned now, but California's regulatory requirements for Step-level 1 continue to be more stringent than federal regulations. Table 2.1.6 lists the 8-point criteria to be considered before granting take-out doses. Table 2.1.7 provides the time in treatment Requirements for take-home Medication: Federal vs. California.

In addition to negative drug screens and compliance with clinic rules, both Federal and California regulations tie take-home privileges to stability in the patient's home environment. To qualify for take-home medication, California regulations ([Title 9 Section 10370](#)) specifically require that patients be participating in educational, vocational and/or responsible homemaking activity, and that daily attendance at the program would be incompatible with such activity<sup>[35]</sup>. [Title 9 Section 10385](#) also specifies that a medical director or program physician can provide an exception to take-home medication for persons with physical disability, severe illness, or exceptional circumstances preventing them from attending their MMT program daily<sup>[36]</sup>.

A drug test positive for an illicit drug, a positive breathalyzer test or coming to the clinic intoxicated, require a reduction of take-home privileges. Failure to comply with counseling requirements or clinic rules also requires restriction of take-home privileges. The regulations also specify criteria for regaining take-home privileges.

In some situations, a federal or California exception is required because the patient's time in treatment is not long enough for them to be eligible for the number of take-out doses needed for work, necessary travel, vacation or acute medical problems (surgeries limiting ambulation). For newly admitted patients who have been in treatment less than three months, a federal and/or California exception must be on file before take-home medication is granted. For vacations or other out-of-town travel, California regulations require that the OTP attempt to arrange courtesy dosing by another OTP before considering take-home medication. The exception request and the patient's record must document the reason that courtesy dosing could not be arranged.

Regulations concerning take-home medication are subject to revision and should be reviewed carefully prior to granting take-home medication. The physician should be familiar with regulatory criteria for take-homes. The physician specifically authorizes take-home medication and specifically requests or designates someone to request exceptions when federal or California regulatory requirements are not met, but a patient seems able to safely handle the take out doses and needs them to ensure continuity of dosing during necessary travel or logistical barriers to dosing in clinic. Most of the documentation will be gathered and recorded by the counseling staff, but the physician must review the record and feel confident that the information is accurate before making a decision.

It is the OTP Program's responsibility to ensure that policies and procedures incorporate the most current federal and California regulations. Nothing in the federal or California regulations prevents a program from establishing in its individual protocol take-home medication requirements which are more stringent than those specified in the regulation step-level schedule.

### Determining if Take-home is Appropriate

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All relevant members of the patient's treatment team including counselors and management staff should be included in the approval/denial decision process. However, the physician must make the final decision about take home doses. It is the physician's responsibility to view take-home medication from a safety perspective, considering the patient's ability to safely transport, store, and take the medication as prescribed. Take-home medication poses a risk of accidental overdose if the patient takes other sedating medications with methadone, or if the patient inadvertently takes multiple daily doses of methadone on the same day.

Table 2.1.6

## Federal Criteria for Considering Eligibility for Take-Home Privileges

### 42 CFR Chapter 1, Part 8.12 (i) (2) (i)-(viii)

1. Absence of recent abuse of drugs (opioids or other) including alcohol
2. Regularity of clinic attendance
3. Absence of serious behavioral problems at clinic
4. Absence of known recent criminal activity, e.g. drug dealing
5. Stability of the patient's home environment and social relationships
6. Length of time in comprehensive maintenance treatment
7. Assurance that take-home medication can be safely stored within the patient's home
8. Determination that the rehabilitative benefit to the patient derived from the decreased frequency of clinic attendance outweighs the potential risk of diversion.

Table 2.1.7

## Federal vs. California Time in Treatment Requirements for Take-Home Medication

Time in Treatment	Federal Regulations*	California Regulations**
First 90 days of treatment	One dose/week allowed	Not permitted, unless a patient meets the criteria for a holiday or Sunday closure
Second 90 days of treatment	Two doses/week allowed	Two doses/week allowed
Third 90 days of treatment	Three doses/week allowed	Three doses/week allowed
Remaining months of first year	Six-day supply allowed	Six-day supply allowed
After one year of continuous treatment	Fourteen-day supply allowed	Fourteen-day supply allowed
After two years of continuous treatment	One-month supply allowed; monthly clinic visits required	One-month supply allowed; monthly clinic visits required

\*Federal Regulations: 42 CFR Chapter 1, Part 8.12 I

\*\*California Regulations: CCR, Title 9 Division 4, Chapter 4, Subchapter 5, Article 4

One public health concern with take-home medication is the potential for accidental overdose of someone other than the patient. If inadvertently ingested, the daily dose of methadone dispensed for the treatment of opioid dependence could be lethal to a child or a non-opioid tolerant adult. In addition to confirming that a patient meets regulatory requirements for take-home medication, the physician should assess the level of responsibility of the patient and the stability of the home environment prior to granting take-home privileges. The patient must have the ability to safeguard take-home medication from theft or accidental ingestion by a child or other non-opioid dependent person.

Due to these concerns, it is important to ensure that patients are well educated about their responsibilities in handling take-home medication. Before any take-home doses are granted, a clinician should meet with the patient, thoroughly review a written agreement outlining the specific responsibilities, policies, rules, and regulations when take-home medication is in a patient's possession, obtain a signature and provide the patient with a copy of the agreement. Educating patients empowers them to safeguard their medication and makes them aware of the steps they need to take should an unforeseen circumstance occur. An Example of a Take-Home Agreement is [here](#).

Table 2.1.8

## Other Federal vs. California Regulations of Take-Home Medication

	Federal Regulation*	California Regulation**
<b>Days clinic is closed for business: Sundays &amp; Federal or State Holidays</b>	One dose allowed for all patients	One dose allowed for patients that are determined responsible in handling medication
<b>Dosing Conflict</b>	Not specified	Patient must be participating in gainful vocational, educational or responsible homemaking which conflicts with daily dosing in clinic
<b>Toxicology Test Results</b>	Must meet requirement in the eight-point criteria for absence of recent abuse of drugs (opioid or other) including alcohol	Meet Federal criteria for urine toxicology. In the month take-home is granted, must be negative for illicit drugs and positive for methadone and its metabolite <sup>[35]</sup>
<b>Short-term detoxification patients</b>	No take-home medication allowed	No take-home medication allowed
<b>Interim maintenance patients</b>	No take-home medication allowed	No take-home medication allowed
<b>Long-term detoxification patients</b>	Same as for patients in MMT	Same as for patients in MMT
<b>Requirements for take-home bottle label</b>	OTP's name, address and phone number	Federal requirements <ul style="list-style-type: none"> <li>■ 24-hour emergency telephone number</li> <li>■ Medication name</li> <li>■ Name of prescribing medical director/ MD</li> <li>■ Patient's name</li> <li>■ Date issued</li> </ul> <p>WARNING: poison, may be fatal to adult or child, keep out of reach of children</p>
<b>Packaging for take-home doses</b>	Designed to reduce the risk of accidental ingestion (e.g., childproof containers)	Same as Federal
<b>Methadone formulation</b>	Oral form that reduces potential for parenteral abuse	Liquid formulation required
<b>Emergency Disaster</b>	Unknown	California may grant exceptions to take-home medication in the case of an emergency or natural disaster, such as fire, flood, or earthquake

\*Federal Regulations: 42 CFR Chapter 1, Part 8.12 I

\*\*California Regulations: CCR, Title 9 Division 4, Chapter 4, Subchapter 5, Article 4

Table 2.1.9

## Protocol Elements Required by California Programs for Take-Homes beyond Six Days per Week

- Patients must have been on a once/week clinic attendance schedule successfully for at least 6 months.
- The patient's last 6 months of toxicology testing must have been negative for illicit drugs and positive for methadone and metabolite of methadone.
- The program must have a call back procedure in place, such as bottle counts, to check on compliance with medications and monitor for possible diversion.
- The patient must have a working, updated phone number and must agree to comply with call back procedures designed to check on proper use of medications.
- The program must have procedures for collecting at least eight samples for toxicology testing per year.
- The program must have proper procedures for handling and labeling take-home bottles of medication.
- The program must have procedures in place to restrict the take-homes of patients who relapse.



## Take Home Doses and Terminal Illness

When a patient is terminally ill and is admitted to hospice care, OUD is no longer the primary diagnosis. Provision of methadone and management of the dose should be transferred to the hospice provider. Comfort and pain control become the primary concerns, so methadone will be generally be given in divided doses. Doses may need to be adjusted in amount and frequency as the patient's ability to metabolize medications changes. Careful documentation of the particulars of the situation should be included in the patient's chart before it is closed. The OTP physician is not in a position to oversee methadone use for the management of pain in a terminally ill patient under the care of hospice or palliative care providers.

## Extended Take-Homes

While California does allow up to a 30-day supply of methadone for patients who have been in treatment for two continuous years or more, programs must first submit a protocol to the state for approval. See Table 2.1.9 for elements the protocol must include.

In addition to the requirements above, programs need to consider carefully how they will handle some of the issues frequently encountered. What about patients on a split dose? Sixty bottles would be required for a 30-day supply. Dispensing this number of doses is time consuming for staff, and transporting this number of bottles would make a patient conspicuous when arriving at or leaving the clinic. Which patients should be considered good candidates for extended take-outs? Would any patient who meets the time in treatment and negative urine drug screen criteria be a candidate or only patients where weekly dosing in clinic poses an unusual logistical conflict at work? Would patients who are medically fragile be appropriate, or is more frequent contact with the clinic necessary to allow regular observation by medical staff? Finally, having an exit plan is essential to ensure that patients may be returned to more frequent clinic visits if more observation is needed for safety reasons. The criteria for participation in the extended take-out program and for discontinuation of participation need to be made clear at the outset to avoid difficulties later on.

## Courtesy Dosing

The OTP physician is responsible for reviewing courtesy dosing requests: outgoing, for home clinic patients wanting to dose at an outside clinic, and incoming, for patients from outside clinics. For outgoing requests, the physician must review the patient's record and determine whether the patient is medically stable to travel to the location and for the duration specified. For patients with serious illnesses, consultation with the treating MD may be helpful. For patients who are using illicit drugs or alcohol, the risks

and benefits must be weighed. Patients who are unable to dose daily at the home clinic because they have a history of presenting to the dosing window while using alcohol or other drugs, or who routinely miss doses, presumably because they are too intoxicated to come to clinic, or who have recent ER visits/hospitalizations for overdose or altered mental status are not appropriate candidates. Patients testing positive for sedatives, benzodiazepine, soma, etc. require careful consideration of the risks and benefits of the travel proposed. Patients with severe and unstable mental health diagnoses, particularly those who are not on mental health medication and/or have a history of recent and frequent EPS visits, may not be good candidates. If a decision is made to sign the courtesy dosing request, the accepting MD must be alerted to any medical concerns or issues such as those above. When accepting an incoming patient for courtesy dosing, the OTP MD should consider what information he or she would like the outside program to provide for consideration. If necessary, the OTP MD from the requesting clinic may be contacted for further information.

## Discontinuation of MMT

MMT must be viewed as a long-term treatment commitment that will include medication and psychosocial intervention. Misusing opioids can cause multiple medical problems, including accidental overdose and death. Injection drug use poses further risk of exposure to hepatitis, HIV, clostridium botulinum, staphylococcus and streptococcus. Evidence to date has shown that the benefit of treatment is directly proportionate to the length of treatment and the adequacy of the maintenance dose. Every effort should be made to stabilize the patient on a therapeutic dose and to offer the intensity of treatment services needed to support abstinence. In view of the potential for adverse events associated with ongoing opioid use or relapse to opioid use, it is better for patients to remain in MMT and delay consideration of withdrawal from methadone until they are at lower risk of relapse to opioid use. It is important to stress to incoming patients the benefits of long-term opioid maintenance treatment. At the same time, participation in MMT is voluntary, so patients must be free to choose the length of time they will remain in MMT.

## Regulations in Flux

Federal and state regulations differ and each have changed over time. Future changes are likely. Recent updates have resulted in the state having a better alignment with federal regulation, and more interrelated take-out rules that will help to simplify the determination of when and if a patient meets the criteria for take-home medication. Additionally, the Department of Health Care Services "DHCS" has drafted additional revisions to Title 9 California Code of Regulations (CCR) that provide clarification and additional alignment with federal regulations as it relates to take-home medication.

## When OUD Patients are Hospitalized

Opioid Treatment Programs (OTPs) should have policies and procedures that allow them to provide the information needed for the hospital to provide appropriate care for the patient and to avoid interruptions in OAT when the patient is hospitalized. Every patient should have a signed consent for the OTP to release their treatment information to hospital physicians providing care. Such information should include, but not be limited to, the last visit to the clinic specifying whether patient picked up any take-home doses, other medications known to be taking that are prescribed by the clinic or other physicians, and any other information deemed necessary for optimal patient care.

The initial contact between clinic and hospital physician should also serve to establish a collaborative care strategy for maintaining the patient's OUD treatment during the patient's hospital stay, and to plan a similar strategy to transition the patient out of hospital and back to the OTP.

## 2.2 BUPRENORPHINE

### 2.2.1. Introduction to Buprenorphine Treatment – Medication and Mindset

The availability of buprenorphine for opioid pharmacotherapy is the most significant event in addiction medicine since the introduction of methadone maintenance in the 1960s (Fiellin, 2007; Green, 2010). Its true significance is that, for the first time in nearly a century, physicians in the U.S. can treat opioid use disorders (OUD) using an opioid medication in their usual and customary practice settings, i.e., in the same way patients receive treatment for a range of chronic illnesses.

For most of the last century opioid use disorder was treated as a criminal matter. In reaction to a troublesome opioid epidemic in the late 1800s and early 1900s, the U.S. Congress passed the Harrison Narcotic Act, the subsequent interpretation of which led to prohibition of physicians from prescribing opioid medications to treat OUDs. Consequently, generations of physicians were indoctrinated with the societal attitude that treatment for people suffering from OUD was best managed by the criminal justice system with the underlying implication that these individuals deserve to suffer because they had, by their drug use, brought upon themselves their own suffering. Even with introduction of methadone and the more recent embrace of the notion of addiction as being a medical illness and recognition of the failure of the criminal justice system to resolve opioid addiction, physicians continue to be ambiguous about how best to treat people suffering from opioid use disorders. We know that they are sick and need treatment. But there remain strong attitudes among many that while these patients may deserve treatment, we should not treat them too well. It could well

be all right if some element of suffering persists as part of the treatment.

While buprenorphine has yet to realize its full clinical potential, it is the case that a new day has dawned for both physicians and patients in office-based treatment of OUD. Demands are placed on physicians to get to know patients in a new way, which are a direct result of the increasing recognition of substance use disorder (SUD) as a chronic, relapsing health condition. This shift calls for a restoration of the fundamental relationship between doctors and patients in treatment—sincerity based on trust. Recognition that addiction is a medical disorder reframes drug use as a symptom, not as a failure of a patient's morals or character. Physicians (and physician extenders) are now in a role similar to their role when treating patients with any other chronic condition: a position of power in the relationship with patients and an obligation to shift understanding of their patients as having a medical disorder much like many others. The change in understanding shifts the perception of patients away from being undesirables to that of being the babies we delivered and brought into this world, as the children we gave vaccinations and allergy shots to, as the students for whom we filled out school health questionnaires. More, the change in understanding recognizes that primary care physicians have a key role in addressing the problem from untreated OUD—unnecessary early deaths and disability across the population. For the first time, life expectancy in the U.S. has declined—a shift attributed to the tens of thousands of Americans who die unexpectedly due to untreated or undertreated OUD and corresponding overdoses of opioids and other drugs<sup>[37, 38]</sup>. Wide scale use of buprenorphine by primary care providers represents a vital step toward the normalizing treatment of OUD—without ambiguity or ambivalence—and the promoting of health in a group of patients who have been neglected traditionally.

## Chemistry of Buprenorphine Preparations Used to Treat OUD

The most widely used formulation of buprenorphine to treat OUD in the U. S. is the combination of buprenorphine hydrochloride with naloxone for sublingual administration. Buprenorphine hydrochloride is weakly acidic with limited solubility in water (17 mg/mL). Naloxone hydrochloride is soluble in water, in dilute acids, and in strong alkali. Combination tablets contain buprenorphine HCl and naloxone HCl in a ratio of 4:1 buprenorphine:naloxone, with the naloxone tag being a deterrent to injection use. The combination product is available in tablet and film formulations. A mono-product containing only buprenorphine HCl is available for patients who have adverse reactions to the combination product, though risks for injection use are inherent. This mono-product is also preferred for women during pregnancy. As well, recently marketed, extended-release and implant formulations of buprenorphine are available. Transmucosal mono and combination buprenorphine products come in many different forms and from several manufacturers, from pills to films, proprietary and generic. (See Table 2.2.1)

## Pharmacokinetics and Metabolism

Buprenorphine is not well absorbed when orally ingested (10% of injected), and much of what is absorbed is destroyed in the liver. Alternatively, it is well absorbed through the lining of the oral cavity, and when given sublingually, it reaches 60-70% of the plasma concentration achieved by the parenteral route. After absorption, buprenorphine is widely distributed throughout the body with peak plasma concentration reached at approximately 60-90 minutes and with a half-life of 2-3 hours. Plasma levels of buprenorphine increase with sublingual doses of the mono-product and of the buprenorphine/naloxone combination product, and plasma levels of naloxone increase with sublingual doses of the combination. A wide inter-subject variability exists with regard to sublingual absorption of both buprenorphine and naloxone. Both maximum concentration of drug in serum ( $C_{max}$ ) and the area under the concentration-time curve (AUC) of buprenorphine appear to increase in a linear fashion with an increase in dose (in the 4-16 mg range), although the increase is not directly dose-proportional<sup>[9]</sup>. The bioavailability of sublingual buprenorphine after a single administration is about 40 percent; with repeated dosing

Table 2.2.1

### Buprenorphine Transmucosal Products for OUD Treatment

Product Name/Active Ingredient	Route of Administration	Available Strengths	Recommended Once-Daily Maintenance Dose
Bunavail ■ Buprenorphine hydrochloride ■ Naloxone hydrochloride	Buccal Film	1.2 mg/0.3 mg 4.2 mg/0.7 mg 6.3 mg/1 mg	Target: 8.4/1.4 mg Range: 2.1 mg/0.3 mg to 12.6 mg/2.1 mg
Generic combination product ■ Buprenorphine hydrochloride ■ Naloxone hydrochloride	Sublingual tablet	2 mg 8 mg	Target: 16 mg Range: 4 mg to 24 mg*
Generic monoprodukt ■ Buprenorphine hydrochloride	Sublingual tablet	2 mg 8 mg	Target: 16 mg Range: 4 mg to 24 mg*
Suboxone ■ Buprenorphine hydrochloride ■ Naloxone hydrochloride	Sublingual film	2 mg/0.5 mg 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg	Target: 16 mg/4 mg Range: 4 mg/1 mg to 24 mg/6 mg*
Zubsolv ■ Buprenorphine hydrochloride ■ Naloxone hydrochloride	Sublingual tablet	0.7 mg/0.18 mg 1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg	Target: 11.4 mg/2.9 mg Range: 2.9 mg/ 0.71 mg to 17.2 mg/ 4.2 mg

\*Dosages above 24 mg buprenorphine or 24 mg/6 mg buprenorphine/naloxone per day have shown no clinical advantage (Adapted from material in the public domain)

the bioavailability increases. Naloxone does not affect the pharmacokinetics of buprenorphine; the buprenorphine mono-product and the combination product deliver similar buprenorphine plasma concentrations.

The metabolites of buprenorphine include norbuprenorphine, buprenorphine-3-glucuronide, and norbuprenorphine-3-glucuronide and are excreted mainly via the fecal route. In urine, most of the buprenorphine and norbuprenorphine (its major metabolite) are conjugated.

## Pharmacodynamics

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Buprenorphine is a partial agonist at the  $\mu$  opioid receptor and an antagonist at the kappa-receptor. Pharmacologically, buprenorphine acts as an agonist opioid, like morphine and methadone, when the background opioid activity is low, but when there is a high level of background opioid activity, buprenorphine will act like an antagonist. This partial agonist effect gives buprenorphine a ceiling effect on respiratory depression, which lessens its likelihood of overdose and makes it relatively safe clinically. Buprenorphine can precipitate an acute opioid withdrawal in the presence of high opioid activities. This has caused concerns about its induction, and is the reason physicians try to give the first dose of buprenorphine to patients when they are in some degree of withdrawal, that is, having a low level of background opioid activity. See also Buprenorphine Induction.

Administered at the clinically appropriate dose and by the usual sublingual route, buprenorphine does not produce the familiar opioid ‘rush’ effect, but it does have a reinforcing effect that renders it acceptable to people who use opioids. In clinical studies, daily sublingual buprenorphine doses suppress heroin self-administration; a mild abstinence occurs following abrupt discontinuation. Buprenorphine’s ceiling effect on respiratory suppression renders it safe with only very remote potential for overdose. Buprenorphine is an excellent medication for patients to abstain from opioid drugs, but builds a similar level of physical dependence to other opioids that presents similar challenges when trying to discontinue the medication. In practice, discontinuation of all opioid pharmacotherapies predispose patients to relapse, which reinforces the importance of patients’ stability in their access to medical care, social support, and occupation prior to starting a taper, leading to MAT discontinuation.

## History: Buprenorphine’s Development

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Dr. Donald Jasinski, recognizing that buprenorphine has properties like those of methadone that patients like, and properties like those of naltrexone that patients hate but clinicians like, believed it would be just the thing to treat opioid use disorder. Patients would take something like methadone and in time have something in them that acts like naltrexone. He conducted a series of studies in the 1970s and published the results in the Archives of General Psychiatry in 1978. A series of NIDA-sponsored trials compared buprenorphine to methadone, buprenorphine

to placebo, and buprenorphine in various doses<sup>[40-42]</sup>, and established buprenorphine as safe and effective (see Clinical Implications below), leading to its approval by the FDA, along with the passage in 2000 of the Drug Addiction Treatment Act (DATA). It became clinically available to clinicians in 2002 with some special requirements of physician training and provision of certain ancillary clinical services. Today, buprenorphine is an established pharmacotherapy in MAT. Development of extended-release formulations further extends buprenorphine’s clinical usefulness<sup>[43]</sup>.

## Clinical Implications

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For the clinician, two important pharmacological characteristics of buprenorphine are its ceiling effect on respiratory depression and its tight binding to the  $\mu$  opioid receptor. The former makes it a very safe medication in clinical practice, as it greatly reduces risks of overdose for patients and others if diverted. The latter, coupled with its long half-life provides effective coverage against withdrawal symptoms, making it possible for a wide range of dosing options. In consultation with patients, these properties facilitate dosing regimens from once daily to several times a day, which allows flexibility for patients to successfully manage their subjective experiences attributed to opioid withdrawal and/or to upset from psychological, social and other sources of distress. As well, the flexibility allows for less than daily dosing for patients who successfully reduce the severity of their OUD. As with all opioid medications, discontinuation from buprenorphine can be done, usually using a taper over a period of time. Yet for many patients, withdrawal from buprenorphine leads to relapse and increased risks for overdose. As yet, there are no firm guidelines on optimal procedures for buprenorphine discontinuation. Best practices would emphasize conducting a careful risk-to-benefit analysis with patients before starting a taper off of buprenorphine and using a taper schedule that is based on patient’s comfort and stability in recovery.

## FDA Approval and Requirement to Prescribe Buprenorphine

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Because of its safety profile, the Drug Addiction Treatment Act of 2000 permits physicians to treat patients suffering from OUD using Schedule III, IV or V narcotic medications without filing a waiver with the Drug Enforcement Agency to establish a narcotic treatment program.

Despite its high safety profile and its ability to be prescribed for patients in the physician’s place of normal practice, buprenorphine’s clinical availability comes with a number of restrictions and requirements. In California, physicians can only treat a limited number of patients and must, after undergoing an approved course of training, obtain an official waiver and provide, directly or by referral, psychosocial treatment. Physicians interested in prescribing buprenorphine in their practice must familiarize themselves with these requirements and obtain the appropriate waiver.

## Requirements for Physicians to Prescribe Buprenorphine

The requirements for acquiring this waiver include a commitment from the physician to keep records and file reports, to maintain records, reports and inventories, to maintain security, to monitor thefts involving controlled substances, and to dispose of controlled substances appropriately. In addition, a physician must first obtain a waiver from the [Drug Enforcement Administration \(DEA\)](#) after meeting certain specific requirements, including an eight-hour approved training or having specific board certifications. In 2016, the waiver was made available to nurse practitioners and physician assistants after completion of 24 hours of approved training. During the first year, the waived physician is limited to treating 30 patients at any given time. After the first year, physicians may submit a second notification of need and intent to treat up to 100 patients. After the second year, physicians may submit another notification and intent to treat up to 275 patients. SAMHSA provides the information on the requirements to obtain the waivers [here](#).

## Buprenorphine Induction

The partial agonist property of buprenorphine causes concern for clinicians because it can cause a precipitated withdrawal in some patients during induction. In practice, the risk can be mitigated by following certain protocols. Precipitated withdrawal rarely occurs except in patients habitually taking long-acting opioids like methadone, sustained-release morphine, or oxycodone; a few cautionary steps can minimize the risk in those cases <sup>[44]</sup>.

The basis for precipitated withdrawal is buprenorphine displacing other opioids when these are present at high levels. The key to avoiding a precipitated withdrawal is to make certain that the background opioid activity is low – so low that the patient shows mild to moderate signs of withdrawal, such as having a Clinical Opioid Withdrawal Scale (COWS) score <sup>[45]</sup> of 8 or even 10 or 12 <sup>[11]</sup>. COWS scores will provide information about potential for acute withdrawal during induction for those with recent opioid use. Persons who have been off opioids for days or weeks (e.g., returning to the community from criminal justice settings) may have COWS of 0, with no or low background opioid activity, but still should be considered for treatment using buprenorphine—particularly before the patient returns to active opioid use and concomitant risk for precipitated withdrawal during induction. First steps for induction include the following:

1. Begin induction by explaining to the patient the principle of precipitated withdrawal, stressing the importance of honestly reporting any recent opioid use.
2. Examine carefully, looking for needle marks from recent use.
3. Conduct an onsite urine test for opioids, paying attention to recent and local fads that are not part of the routine tests.

4. Look carefully, ensuring there are no signs of intoxication—slow speech, small pupils, slow and shallow breathing.
5. Look for physical signs of moderate opioid withdrawal, observing for restlessness, dilated pupils, yawning, sweatiness, goose bumps, rapid pulse, elevated blood pressure, signs of achy discomfort.
6. In a reassuring manner, ask the patient to recall their worst experience of cold turkey and rate it on a 1-10 scale, 10 being the worst ever.
7. Tell the patient to wait until they are experiencing at least 5-6/10; which usually means 12-24 hours after the last use of heroin or short-acting prescription opioids, and 48-72 hours for methadone and sustained-release long acting opioids.
8. After reaching 5-6/10, encourage them to wait another 10 minutes, before giving them the first dose of 4-8 mg buprenorphine. (Many experienced clinicians use an initial dose of 8 mg.)
9. Observe the patient over the next 30-60 minutes.
10. If symptoms improve, send the patient home with two additional 4 mg doses and instructions to take the additional doses later if needed to manage emerging symptoms of withdrawal.
11. If symptoms do not improve or worsen in the hour following initial dosing, give an additional 4 mg dose and repeat the observation.
12. Keep increasing doses by 4 mg until the patient reports feeling better before sending him/her home.

During induction, patients may use over-the-counter medications like acetaminophen (Tylenol) or NSAIDs (Ibuprofen) for aches and pains, Loperamine (Immodium) for diarrhea, and Diphenhydramine (Benadryl) for sleep. Encourage patients to call if they have problems or questions before resorting to using illicit opioids. Contact the patient by phone later on the first day. See the patient the next day, total up the first day's doses, make any adjustments needed, and instruct the patient to take the total amount in 2-3 divided doses. See the patient the following day if the patient is not clinically stable and needs further dose adjustment. Most patients are stable by the second or third day and can assume a weekly visit schedule. Needless to say, individualize according to the patient and how well he/she is known.

## Tips for Monitoring Patients during Inductions

Some things are best learned by observing and practicing. Consistent with all medical training procedures, the best way to learn buprenorphine induction is to watch an experienced colleague perform a few and have them do a few with you. There are no complicated techniques or special skills, only confidence and composure; reassure the patient that you know what you are doing and will not let them down. **When rating COWS, try to rely on observable physical signs: pulse rate, blood pressure, pupil size, skin moisture, goose bumps, yawning, etc.**

## Home Induction

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Many experienced clinicians perform home buprenorphine induction; it can be done safely if a protocol is methodically followed. This protocol is the one used at the UCLA Department of Family Medicine Addiction Medicine Clinic (thanks to Drs. Heinzerling, Shoptaw and colleagues):

*We have learned over time that a reasonably safe time to initiate buprenorphine is when the patient goes from “mild withdrawal” into “moderate withdrawal”, which is why the original suggestion was a COWS score of 12—end of mild withdrawal and beginning of moderate withdrawal. A COWS score of 8 seemed to separate those who did well from those who did not do as well. We also found that after the initial 4 mg. dose, we almost always had to give another 4 mg., and began to give 8 mg. as the first dose.*

*For home induction, also vary the COWS scores according to the patient. For example, in an obsessive patient who sticks to the rules, a COWS score of 8 is fine, but in a patient who is likely to fudge, the patient should wait until they get past 10-12 (give them the actual signs to look for) and then wait another 10 minutes. (They usually do not, but they have a better chance to go past 8.)*

## Use of Ancillary Medications during Induction and Early in Buprenorphine Treatment

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The use of ancillary medications during buprenorphine induction and early treatment, except over-the-counter preparations for aches and pains, insomnia and diarrhea, remains controversial, with views varying from “never” to “always.” In practice, there are no hard and fast rules. Not surprisingly, the regulatory position appears to discourage their use, or use as little as possible. The use of benzodiazepines is especially discouraged. Other medications that are sometimes used include clonidine, gabapentin, and phenobarbital. Some patients find it impossible to deal with the withdrawal symptoms while waiting for their COWS score to reach a level where they can be safely dosed. Some physicians use ancillary medications to keep the buprenorphine low, for induction and later treatment, believing it is better for patients to be using a lower dose that facilitates its discontinuation. Treatment ultimately depends on physicians’ personal philosophy about medications and recovery, and on the relationship between physicians and patients. To some extent, success depends less on what is done clinically and more on how much trust and confidence patients have in their physicians.

## Dosing Across the Course of Treatment

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The initial daily stabilization dose of buprenorphine ranges from 4-24 mg. It is important to recognize the distinction between pharmacological stabilization and clinical stabilization. Pharmacologically stabilization means a steady blood level, which takes approximately 5 half-lives,

or 5-7 days for buprenorphine. Thus, seven days of a steady daily dose that prevents between-dose symptoms of withdrawal, without symptoms of over-medication such as sedation, will likely be the adequate daily dose to continue treatment. However, this is not clinical stabilization, which encompasses a broader range of treatment goals: staying off drugs and getting a life.

## Dose Adjustment

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Dose adjustment is one of the most frequent topics of discussion in opioid pharmacotherapy, in part because the medication is always on the patient’s mind, and in turn, on the mind of the physician. This is often an issue when treatment is not going particularly well, or worse, when there is an indication of continued drug use, reports of intense craving, and unmanaged withdrawal symptoms. However, these problems do not always relate to insufficient dose; dose increase is not always the answer. Craving, in essence, can be a forerunner of substance use. And drug use in the course of treatment, provided that the patient is taking the medications as prescribed, is the downstream expression of upstream problems, which can comprise many things: exposure to drugs and cues, psychological and social stressors, other chronic health problems, etc. See Counseling and Support Groups [below](#).

## Discontinuing Buprenorphine Treatment (or any form of MAT)

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Patients with OUD have a chronic disease, and our aim is to help patients manage it. There is much more to recovery than medication assisted therapy (MAT). The patient’s decision to begin treatment is fickle and unpredictable. Their psychological crisis needing management is ambivalence (i.e., the patient’s simultaneously held beliefs about their opioid use that “I have a problem” and “I don’t have a problem.”) The strengths of these ever-present ambivalent beliefs shifts, sometimes rapidly. When the “I have a problem” belief is far stronger than the “I don’t have a problem” with opioids, patients are more likely to seek MAT. Once treatment starts, MAT helps patients who wish to abstain from opioids to manage their withdrawals and risk of overdose so they can achieve greater life stability and self-efficacy. Thus, the time to stop administering medication is when patients are living a life characterized by recovery: not using illicit drugs, having good health, taking personal responsibility, and positive community involvement. Yet even with sustained recovery, the ambivalence about having or not having a problem plays in the mind. Indeed, lapse and relapse occur when patients’ ambivalence shifts so far as to facilitate the belief they do not have a problem with opioids and can successfully cope with an exception to use opioids and relive that euphoria.

Some people, including some doctors, believe that taking a medication is being addicted to it, and they argue that being on MAT is substituting one addiction for another. The scientific evidence is clear: SUD and MAT may both be facilitated by regular use of pharmacological substances that produce physical dependence, but the outcomes

are far different. Consistent and compulsive use of illicit opioids or misuse of prescribed opioids results in the physical and behavioral consequences that constitute the DSM-5 definition of addiction. Regular use of prescribed buprenorphine supports patients as they meet their needs and fulfill their roles as individuals, as family members, and as members of communities. This difference underscores the truth that while opioids can be used in the setting of addiction or in the setting of treatment, the outcomes on the behaviors facilitated by these closely related compounds in dramatically different settings render the “swapping one addiction for another” argument to being a simple polemic. More, the decision to use an opioid compound like buprenorphine to treat opioid addiction is the patient’s right.

## Counseling, Support Groups, and Recovery

Remember that medications work to correct brain chemistry; their primary effect is to stabilize the brain physiology. Medications contribute overwhelmingly to the patient’s ability to abstain from substance use. Abstinence is one component of remission, which is defined by a life characterized by the absence of SUD criteria per the DSM-5, with the exception of possible cravings. Needless to say, abstaining from substance use alone is not synonymous with recovery, but it is necessary for recovery.

Attending support groups such as Narcotics Anonymous and seeing a counselor are the most common follow-up strategies offered to patients to assist maintaining their recovery. The emphasis of many support group programs is on maintaining abstinence. Unfortunately, few programs offer practical assistance beyond this to help patients repair the many other parts of their lives. Many patients have life events, trauma, mental illness and other comorbidities that present real challenges to living without turning to drugs to find some relief. While the first and most essential step to recovery is to stop the compulsive use of opioids (e.g., by entering MAT), counseling and/or psychotherapy can aid in preventing return to opioid use as a coping skill – and increase chances for sustained recovery.

## Extended-release Buprenorphine Preparations

A very promising advancement in MAT is the development of extended-release buprenorphine. The advantage of this product is its ability to directly address the strength of ambivalent thoughts regarding one’s opioid addiction. By having an extended-release product onboard, patients avoid regular daily dosing and the ways that a lapse can occur if the dose was missed, delayed or skipped. Injectables and implants are products that help facilitate long-term recovery by reducing the option for an occasional lapse, which could risk full relapse.

## Buprenorphine Sub-dermal Implant

The basic medication unit of the sub-dermal buprenorphine implant is a small, match-sized solid rod containing a mixture of ethylene vinyl acetate and approximately 80 mg. buprenorphine. The FDA approved the product in 2016 for treatment of OUD in patients stabilized on low to moderate doses of sub-mucosal buprenorphine. Each treatment consists of four rods implanted sub-dermally in the upper arm during a brief office procedure. The rods are similarly removed at the end of the 6-month treatment period. A second implant with four rods can be placed in the opposite arm to continue treatment. Only buprenorphine-waivered physicians can prescribe the product and the physician undertaking the implant procedure must have certified appropriate training. The product is available through a restricted distribution system with an FDA-approved [Risk Evaluation and Mitigation Strategies](#) (REMS) <sup>[46]</sup>.

The buprenorphine implant provides a sustained, constant blood level of buprenorphine lasting through six months. It not only reduces or eliminates illicit opioid use, but also removes the risk of street diversion, loss, and accidental poisoning. More importantly, patients are no longer preoccupied with daily medication intake, freeing patients to focus on activities that promote recovery.

## Extended-release Injectable Buprenorphine

A monthly injection of buprenorphine incorporated into the biodegradable ATRIGEL delivery system received FDA approval, in November 2017, for treatment of patients with moderate to severe OUD, who had initiated treatment and early stabilization of at least 7 days with sub-mucosal buprenorphine <sup>[47]</sup>. The product is injected subcutaneously into the abdominal area. Two treatment regimens are available: a monthly 300 mg injection for 6 months or two monthly injections of 300 mg followed by four monthly 100 mg injections.

Awaiting FDA approval is the CAM 2038 product. A single 24-mg weekly injection or 96-mg monthly injection delivers an approximate dose equivalent to 16-mg/d of sublingual or sub-mucosal buprenorphine during these treatment intervals. (JAMA Internal Medicine May 14, 2018)

The injectable preparation also has all the advantages of the buprenorphine implant over sub-mucosal products, with the added advantage of not needing removal later <sup>[47]</sup>. The product also appears to rapidly produce a clinically effective buprenorphine blood level, and offers additional flexibility in dosing intervals compared to the 6-month implant. The terminal half-life of the product is long, and it remains unclear what this means clinically after a six-month injection. A new rationale underlying the product’s approval is its high degree of receptor blockade, which is presumably beneficial in reducing drug cravings and misuse <sup>[47, 48]</sup>. How this will translate into a clinically relevant message for the patient, and how it will affect treatment adherence and acceptance is unclear.

## Additional Information

Physicians authorized to prescribe buprenorphine should have acquired from their required training certain basic information about the clinical pharmacology and clinical applications of buprenorphine in treating OUDs. These guidelines are not, therefore, exhaustive; some topics are regulated and specified by Federal and State authorities, such as the REMS, the drug labeling, which list indications and contraindications, side effects, adverse reactions, and cautions <sup>[46]</sup>. Other topics are

too large or changing too quickly to be suitable for inclusion in this type of guide, such as buprenorphine drug interactions; still others are covered under other chapters of this guidelines; see also the Chapters on Pain and Pregnancy. More detail and regulatory information can be found here:

- CSAM
- SAMHSA
- NIDA
- ASAM

## 2.3 NALTREXONE

### 2.3.1. Introduction to Naltrexone Treatment

Patients who are highly motivated, do not want or fail treatment with methadone or buprenorphine, and are willing to undergo opioid withdrawal, may receive antagonist pharmacotherapy with naltrexone as a third option. Patients must be totally withdrawn from all opioids before starting naltrexone to avoid the risk of precipitated opioid withdrawal. The theoretical mechanism by which naltrexone works as a pharmacotherapy is simple—naltrexone occupies the  $\mu$ -opioid receptor and blocks it. If the patient uses an opioid while on naltrexone, the opioid will have no effect <sup>[49]</sup>. In other words, once in place, naltrexone has a receptor attachment that is much stronger than most opioids, but has negligible opioid effect of its own. Long acting injectable naltrexone can be an effective treatment for opioid use disorder in some patients, but oral naltrexone is rarely an ideal choice. Furthermore, a naloxone challenge test as described below can be used to ascertain abstinence from opioids.

### 2.3.2. Naltrexone Pharmacology

Naltrexone comes in two formulations, 50 mg oral tablets or 380 mg extended release intramuscular injection. The tablets have been FDA approved for treatment of opioid use since 1984. The extended release injection received FDA approval for treatment of opioid use disorder in 2010 after findings from a double-blind, placebo controlled trial conducted in Russia demonstrated reduced illicit opioid use and enhanced treatment retention in those receiving this medication <sup>[50]</sup>. In the extended release formulation, naltrexone microspheres are encapsulated in a biodegradable polylactide-coglycolid polymer that slowly degrades and releases naltrexone into the surrounding tissue following deep intramuscular injection <sup>[51]</sup>. Experimental formulations of naltrexone as a subcutaneous implant that releases active medication over a two-month or longer interval, while still undergoing evaluation, appear safe and efficacious <sup>[52, 53]</sup>.

### 2.3.3. Naltrexone Pharmacokinetics

#### Absorption of Naltrexone

Absorption occurs rapidly and completely after oral ingestion of Naltrexone with 80%-95% of the oral dose undergoing first pass hepatic metabolism <sup>[51, 54]</sup>. Because naltrexone acts as an antagonist, initial subjective or objective effects are negligible in the opioid-free individual. Peak plasma levels are achieved on average about 1 hour after ingestion <sup>[51, 54]</sup>. Oral naltrexone displays an estimated average terminal half-life of 4 hours <sup>[51, 54]</sup>. Protein binding is estimated at 20 percent <sup>[54]</sup>.

Absorption also occurs reasonably quickly with the long acting injectable formulation. Naltrexone situated at or near the surface of the microspheres is rapidly released, giving an initial peak in plasma concentrations 1 to 2 hours after administration <sup>[51]</sup>.

#### Distribution of Naltrexone

Concentrations begin to decline 12 hours following administration but increase again 1 day after administration as naltrexone embedded deeper in the microspheres is released, resulting in a second and higher peak about 2 days after administration <sup>[51]</sup>. At approximately day 14 after administration, plasma naltrexone concentrations begin a gradual decline <sup>[51]</sup>. Concentrations are detectable for longer than 35 days <sup>[51]</sup> and should provide pharmacological blockade for that period of time, though the duration of blockage varies from patient to patient. After sequential dosing, the average half-life of naltrexone with the long acting injection is approximately 5 days <sup>[51]</sup>.



## Metabolism of Naltrexone

The metabolism of naltrexone is not catalyzed by CYP 450 enzymes but by aldo-keto reductase enzymes AKR1C1, AKR1C2, and AKR1C4, previously designated as dihydrodiol dehydrogenase enzymes (DD1, 2, and 4) [56]. Naltrexone undergoes reduction via these enzymes to the active metabolite 6- $\beta$ -naltrexol. Both parent and metabolite can also undergo glucuronidation [56]. 2-Hydroxy-3-O-methyl-6- $\beta$ -naltrexol is a minor metabolite found in trace amounts. The main route of elimination for both parent drug and metabolites is renal, with much lower amounts in the feces [57]. After oral dosing 6- $\beta$ -naltrexol levels peak at one hour, and the half-life is about 13 hours [51]. After the long acting injection, 6- $\beta$ -naltrexol levels peak at 3 days, and after repeated dosing the half-life is about 5 days [51]. Ratios of plasma levels of metabolite and parent drug are quite different between oral dosing and injection because of decreased first pass metabolism with the injection. For oral dosing the ratio of 6- $\beta$ -naltrexol to naltrexone is 10:1, but for injection it is 1:1 [51]. The extended release injection of 380 mg displays an area under the curve of naltrexone exposure over 28 days 4 times the area under the curve for the oral form given at 50 mg per day for 28 days [51].

## Naltrexone Pharmacodynamics

Although naltrexone is believed to function as a non-specific opioid antagonist and have some capacity to block  $\delta$ - and  $\kappa$ -opioid receptors [58, 59], it exerts its clinical effects primarily by acting as an antagonist at the  $\mu$ -opioid receptor [60]. 6- $\beta$ -naltrexol has weaker antagonist effects than the parent drug [61].

### 2.3.4. Clinical Use of Naltrexone

In order to be started on naltrexone, the patient must be completely withdrawn from opioids and have no signs or symptoms of opioid withdrawal. This process usually takes from 3-6 days for short-acting opioids and up to 10 days for methadone or buprenorphine. If any opioids remain on the receptor at the time of naltrexone administration, it will precipitate severe opioid withdrawal by displacing the opioid from the receptors. Therefore, a procedure called a naloxone challenge test is often performed prior to administration of naltrexone for opioid use disorder [49].

Because of the relatively long half-lives of naltrexone and its active metabolite, any withdrawal precipitated by naltrexone would last many hours. Naloxone has a short half-life. Precipitated withdrawal caused by naloxone lasts only 1-3 hours. A negative urine drug screen for all opioids including oxycodone, fentanyl, methadone, and buprenorphine can be a helpful indicator that the patient has been fully withdrawn from all opioids. In addition, a detailed history from the patient about last opioid use, obtained after informing the patient about the risk of precipitated withdrawal if recent opioid use has occurred, can help to confirm that sufficient time since last use has elapsed.

## Naloxone Challenge and Initiation of Naltrexone

Once the clinician is satisfied that the patient is fully withdrawn from opioids and opioid-free, and baseline vital signs are checked, naloxone is administered parenterally (subcutaneous, intramuscular, or intravenous) to a total dose of 0.8 mg. The patient is observed for emerging symptoms or signs of opioid withdrawal or elevations in heart rate or blood pressure. If any indication of even mild withdrawal is observed, the induction onto naltrexone is postponed at least 24 hours, and the naloxone challenge is repeated.

If withdrawal is no longer observed, naltrexone can then be administered orally in a dosage of 25 to 50 mg (one-half to one tablet) or the extended release injection can be administered directly without a trial of oral medication if desired. If precipitated withdrawal occurs from either naloxone or naltrexone, it often manifests as the abrupt appearance of very severe withdrawal signs and symptoms. Precipitated withdrawal can be managed symptomatically using clonidine or lofexidine (latter not yet approved in the U.S.) for autonomic nervous system signs and symptoms, benzodiazepines for muscle cramping, agitation, and insomnia, and anti-emetics and anti-diarrheals for gastrointestinal signs and symptoms.

The usual oral naltrexone dose is 50 mg daily. It is also possible to use a three-day-per-week schedule of 100 mg on Mondays and Wednesdays and 150 mg on Fridays. However, now that the extended release form is available, it makes sense to use the extended release preparation for most patients to avoid the relapses that could occur with oral medication non-adherence. Since the extended release preparation maintains therapeutic blood levels for more than 30 days, it can be given as a deep intramuscular gluteal injection of 380 mg every 28 or 30 days using opposite sides of the buttocks for every other injection. Once the patient is stabilized on naltrexone, either oral or intramuscular, the dose is simply maintained unless side effects supervene. No studies have examined patients taking naltrexone for periods beyond 6-12 months. There is no conclusive evidence that long-term use of naltrexone is harmful. Therefore, in most instances patients can be continued on naltrexone for as long as it appears to be clinically helpful without serious side effects and as long as the patient is willing to take it.

### 2.3.5. Naltrexone Drug Interactions

Because naltrexone metabolism does not depend upon the CYP 450 system, it does not affect the metabolism of other medications, and the only important interactions are with opioids. Clearly, naltrexone will block the effects of other opioids. This interaction presents a potential challenge if a patient on naltrexone unexpectedly needs treatment with opioid analgesics, for example, after serious physical trauma or an emergent medical or surgical condition such as acute pancreatitis or cholecystitis. In such an event

the patient must be admitted to the hospital for pain control. Regional anesthesia and strong non-opioid pain medications, such as ketamine, may be ideal in these patients. If those are insufficient or unavailable, the patient should be treated with high intravenous doses of a potent opioid such as fentanyl, hydromorphone, or morphine until the blockade is overcome. In this scenario there is the theoretical potential of an opioid overdose with respiratory depression so the patient must be closely monitored, possibly in an ICU setting, and hospital staff need to be prepared to rescue the patient with intubation and mechanical ventilation.

Patients at risk to use large quantities of illicit opioids intravenously need to be warned of this theoretical risk of overdose. In addition, patients need to be warned of the risk of overdose after stopping naltrexone. Since opioid tolerance dramatically decreases during the time patients take naltrexone, a high risk for opioid overdose is present after the medication is discontinued<sup>[62]</sup>. Because of this known risk, it is reasonable to consider advising patients to carry a wallet card or have a medi-alert bracelet indicating that they are on naltrexone, although such notifying methods are by no means required.

### 2.3.6. Naltrexone Side Effects

Common side effects of naltrexone include nausea, diarrhea, dizziness, headache, and insomnia. Typically, these annoying but not dangerous side effects appear early in treatment and tend to dissipate, so that often patients can be coached through them. If necessary, ancillary medications, such as anti-emetics, can be prescribed. It is important to note that oral naltrexone has a boxed warning for hepatic injury. However, in practice no serious or lethal hepatic toxicity has been observed. The extended release naltrexone does not have this boxed warning. Nevertheless, it is standard practice to obtain liver function tests prior to and during treatment. Should liver transaminases show a marked upward trend (5-10 times the upper limit of normal) in the absence of other potential etiologies, the provider should consider whether or not to continue naltrexone.

Depression and suicidal ideation have also been reported. These psychiatric adverse events should be handled as they would for any other psychiatric patient by initiating antidepressants and/or psychotherapy for depression and potential hospitalization for suicidal ideation. If naltrexone is deemed causative, it clearly should be discontinued.

The extended release preparation has the additional potential side effect of injection site reactions. Mild injection site reactions can usually be managed with palliative measures like hot compresses and over-the-counter analgesics. In rare severe cases, antibiotics or minor surgical intervention might be necessary. Injection site reactions appear to be related to injection technique. The injection formulation comes as a kit containing a syringe, needles, medication in a powder form, and diluent. Once the powder is reconstituted in the diluent, it is intended for deep intramuscular injection. If the medication is inadvertently injected in the subcutaneous fat rather than in the gluteal muscle, injection site reactions are more likely.

### 2.3.7. Efficacy of Naltrexone for Opioid Use Disorder

Despite its seemingly ideal pharmacologic characteristics, oral naltrexone has not been particularly effective in treating opioid use disorder. Because patients need to taper off opioids before initiation, patients have difficulty starting the medication. Even when they do start successfully, drop-out rates are high and medication adherence low. A meta-analysis of 10 randomized placebo-controlled trials of oral naltrexone for OUD with 696 participants pooled naltrexone vs placebo studies with naltrexone vs placebo plus psychosocial treatment. The analysis found that despite a slight statistically significant reduction in opioid use among naltrexone recipients, drop-out rates for oral naltrexone therapy were unacceptably high, comparable to placebo groups<sup>[63]</sup>. A separate meta-analysis of 15 randomized, controlled trials including 1,071 participants came to a roughly analogous conclusion noting that retention moderated illicit opioid use, and that participants with high retention who received naltrexone showed reduced opioid use<sup>[64]</sup>. Studies which used contingency management with naltrexone included in that meta-analysis had better results<sup>[64]</sup>.

It does appear that oral naltrexone performs well in clinical situations that involve external sanctions. For example, a study of federal probationers or parolees who could be returned to incarceration for drug use randomly assigned participants to naltrexone or no medication in open label fashion. Retention rates at 6 months were 52% for naltrexone-treated participants vs. 33% for participants with no medications, and rates of illicit opioid use were 8% versus 30% respectively<sup>[65]</sup>. A study of oral naltrexone in Russia, where methadone and buprenorphine are not available and where participants tend to live with their family of origin and hence are under external motivation from parents, randomized 52 participants to naltrexone versus placebo in double blind fashion.<sup>[66]</sup> Naltrexone showed superiority in outcomes of both retention and relapse prevention.

The few placebo-controlled randomized trials done with extended release naltrexone show that the active medication improves treatment retention and illicit opioid use<sup>[50, 67]</sup>. An open label randomized trial that compared extended release naltrexone to treatment as usual among individuals with opioid use disorder who had criminal justice involvement showed that the active medication reduced rates of relapse to illicit opioid use to a greater extent than did treatment as usual (20).

Two randomized open label trials compared extended release naltrexone to buprenorphine among patients who were initially receiving inpatient care for opioid withdrawal and were subsequently followed in the outpatient setting. One study found equivalent benefits for both medications as regards retention in treatment but superiority of extended release naltrexone as regards illicit heroin use (21). It should be noted that the mean buprenorphine dose used in that study was only 11.2 mg per day. This dosage is typically inadequate to suppress illicit opioid use, so the comparison of the two medications in this study may not have been completely fair. The other study comparing these two medications found a substantial barrier for

participants to withdraw successfully from opioids and be inducted on extended release naltrexone compared to being inducted on buprenorphine (22). Thus, overall participants randomized to buprenorphine fared better. However, among participants who were successfully inducted onto medication, relapse rates were similar across both medications. Taken together, the available information suggests that it can be difficult for patients to complete the opioid withdrawal process and be successfully inducted onto extended release naltrexone. The limited individuals who can complete this process and begin extended release naltrexone are those most likely to benefit from this medication in their treatment of OUD.

### 2.3.8. Naltrexone – An Editor’s Epilogue

The idea for using opioid antagonists to treat Opioid Use Disorder (OUD) is rooted in behavioral experiments showing that animals trained to self-administer opioids would, when given an opioid antagonist, learn to stop drug self-administration because the antagonist blocks the rewarding effects of opioids. The phenomenon is known as extinction and it was believed that humans would behave similarly. In this scenario naltrexone, a potent opioid antagonist derived from oxymorphone, was an ideal agent: it completely blocks the effects of opioids, has no reinforcing properties of its own, and was relatively safe with few side effects.

One of its great virtues, it was said, is that people who take it feel as if they have taken nothing; however it is evidently for this reason that patients do not keep taking it and

then relapse. Still, four years after its synthesis in 1967, Congress designated it a high priority and gave specific funding for Nixon’s Special Action Office for Drug Abuse Prevention (SAODAP) to develop its use in treating opioid dependence; as its director put it, SAODAP really had no choice in the matter.

Early clinical trials with oral naltrexone proved to have very poor medication adherence<sup>[68-70]</sup> and low patient acceptance except among a few “highly motivated” groups: physicians, other licensed health care personnel, and attorneys, who shared a common threat of losing their livelihood, and prisoners on work release. As long as people took the medication, they mostly did not use opioids. But given the opportunity, almost everyone stopped taking the medication and relapsed. That did not deter governmental encouragement to continue developing an antagonist and, based almost entirely on its pharmacological blockade with little clinical data, the FDA approved an oral naltrexone to treat OUD in 1984. It was not a commercial success. Still, efforts to develop an extended-release formulation that would last for weeks once given, continued. A sustained-release formulation of naltrexone for opioid addiction received FDA approval in October 2010. Ironically, the pivotal study<sup>[71]</sup> was conducted in Russia where patients had no access to agonists. Thus a product made in the U.S. proved highly effective in Russia, and the data made in Russia facilitated its approval in the U.S.

Our infatuation with naltrexone, in all its formulations, can be traced to our social and political preoccupation with detoxification, our ambivalence about methadone, and by extension, buprenorphine, and long-held irrational belief that OUD recovery means taking no opioids.

# CHAPTER 3

# MANAGING PAIN IN PATIENTS WITH OPIOID USE DISORDER

**Author:** Compton, P.

## 3.1 General Principles of Pain and OUD

Pain is a common condition in patients on medication-assisted therapy (MAT) for opioid use disorder (OUD). Reported rates of chronic pain hover between 50%-60% in patients receiving methadone or buprenorphine treatment [72, 73], and they are likely to suffer acute painful conditions (i.e., dental, infections, trauma), that may or may not be related to the general health consequences associated with addiction behaviors, which may require acute pain care. For those on full and partial opioid agonist therapy (OAT), patients present with opioid tolerance and hyperalgesia [74, 75], thus will require higher doses of opioids to manage acute pain and/or provide anesthesia than that required by the opioid-naïve patient. Because opioid withdrawal is likely to aggravate hyperalgesia, it is important that the maintenance OAT dose be continued during pain treatment.

Although both methadone and buprenorphine have intrinsic analgesic properties, the daily dosing regimen for OUD is intended to treat the symptoms of withdrawal and craving, and thus should not be considered to provide sufficient pain relief. For patients on naltrexone therapy, it can be expected that they will receive little to no opioid analgesia while opioid receptors are fully occupied; however, as the half-life approaches (4 hours for the oral formulation and 5-10 days for the injectable), pain relief can be appreciated, and patients may even be super-sensitive to opioid effects related to receptor resetting with antagonist treatment [76]. In all these cases, immediate-release (IR) opioids should be used in addition to MAT opioids, titrated to analgesic effect, while remaining vigilant for signs of toxicity and with naloxone readily available should these emerge. There is no evidence that opioids provided for pain exacerbate or worsen OUD outcomes, however there is concern that untreated pain may precipitate return to use.

Fortunately, for acute, chronic and surgical pain, treatment approaches are increasingly utilizing effective multimodal non-opioid or opioid-sparing regimens, which should be heavily relied upon to provide analgesia for those on MAT. In general, these include utilization of non-pharmacologic interventions including heat, cold, massage, bracing and stretching, and behavioral interventions such as distraction, graded exercise, and relaxation or mindful meditation. Non-opioid pharmacotherapies focus on around-the-clock use of acetaminophen or NSAIDs, with more specific medication adjuvants utilized for specific pain indications (see below). In some cases, regional procedures with lidocaine or steroid injections can be an important component of the pain management plan.

## 3.2. Manifestations of Pain and Opioid Treatment

### 3.2.1 Acute Pain

Acute pain exposure has been negatively correlated to OUD treatment retention related in part to insufficient pain relief, underscoring the need to aggressively manage acute pain in patients on MAT [77]. To avoid the risk of withdrawal and return to use, it is important to continue the maintenance MAT dose, which should be verified with the MAT provider. The state prescription drug monitoring program (PDMP) must also be consulted to determine if non-MAT opioids are being consumed according to the [Controlled Substance Utilization Review and Evaluation System \(CURES\)](#). This regulation specifically addresses non-MAT opioid use, and does not adequately address evaluation of patients receiving MAT in an OTP setting. Multimodal opioid-sparing techniques should be emphasized.

In addition to acetaminophen or NSAIDs, ketamine administered in a low dose as a continuous intravenous or subcutaneous infusion has been demonstrated to treat acute pain in the ambulatory setting, emergency room, or hospital for patients on MAT. Anesthesiologists typically recommend ketamine dosing regimens of a starting dose of 100–200 mg 24/hr, using a mixture of 200 mg ketamine and 5 mg midazolam made up to a total volume of 48 ml with normal saline and a rate of infusion of 1–2 ml/hr or 0.1 mg/kg/hr [76, 78]. A regional anesthetic blockade may also be implemented where possible [79].

If opioids are required for patients on methadone, IR opioids can be utilized, ideally administered via PCA to enable self-titration and minimize perceived drug-seeking behaviors [80]. Although the same approach can be utilized for patients on buprenorphine therapy, some clinicians report that giving the total daily dose divided three or four times daily (i.e., 4–8 mg every 6–8 hours) can be useful in treating moderate pain; the ceiling effect of buprenorphine suggests that this strategy will be less effective in cases of severe acute pain [78]. Early recommendations that patients on buprenorphine be rotated to methadone or other full agonists (fentanyl or morphine) to enable more predictable IR opioid analgesic response appear unnecessary, and may expose the patient to greater risk of withdrawal or return to use than continuing the usual buprenorphine dose. Patients on naltrexone therapy may require general anesthesia in cases of severe pain if IR opioid administration cannot override the receptor blockade.

### 3.2.2. Peri-operative Pain

Because opioids have been a peri-operative mainstay, utilized pre-operatively, intra-operatively and post-operatively, providing pain care for patients on MAT undergoing surgical procedures requires mention. Although no specific practice guidelines exist to address surgical pain-relief interventions in this population, the general principles outlined for acute pain can be implemented.

### 3.2.3. Pre-operative Management

Pre-operative opioid use assessment is critical to effective anesthesia and post-operative analgesia. In preparation, MAT dose and formulation should be verified with the provider and the PDMP consulted. It is also important to determine if the patient is regularly using benzodiazepines or alcohol to avoid these dangerous withdrawal syndromes [81]. The patient and family should be included in the management plan (admission to discharge), and liaisons with other healthcare professionals (i.e., pain medicine, psychiatry, nursing, social work) should be initiated.

If the patient will be NPO for greater than 24 hours post-surgery, plans to convert the patient from oral methadone or buprenorphine to IV equivalent should be instituted. Methadone can be administered parenterally; doses of half to two-thirds of the total daily oral dose can be given in three to four divided doses by intermittent intramuscular or subcutaneous injection or by continuous infusion [82, 83]. Some clinicians opt to convert to morphine or another full agonist first, and when performing an opioid rotation, it is recommended to reduce the calculated equianalgesic dose by 30–50% due to the possibility of incomplete cross-tolerance [84].

Although it has been suggested that patients on buprenorphine be rotated to methadone prior to surgery [85], there is no evidence that this improves pain management as opposed to continuing their usual OAT. Others recommend that patients on higher dose buprenorphine maintenance (i.e., 16 mg - 32 mg/day) be titrated down to 12 mg/day prior to surgery to minimize potential dose-dependent opioid antagonism effects. If possible, it is recommended that oral naltrexone be discontinued 72 hours prior to surgery so that opioids can be utilized if necessary [82], however this becomes impractical for patients on naltrexone XR or for unplanned procedures. In these cases, non-opioid approaches become essential.

### 3.2.4. Intra-operative Management

As noted, baseline opioid requirements should be met, and if possible, the usual prescribed OAT dose is taken on the day of surgery using a take-home dose provided by the MAT provider. Effective multi-modal opioid-sparing anesthetic techniques, which differ across surgical procedures [86], are highly recommended, and may include pre-emptive administration of acetaminophen, celecoxib or pregabalin; preloading the incision sites with local anesthetic before incision; and placement of an epidural catheter for intraoperative and postoperative use. Local and regional analgesia techniques are preferred when suitable. If opioids are used, higher opioid requirements can be anticipated; in spontaneously breathing patients, maintaining a respiratory rate of 12–14 can be used as a guide [81]. Instillation of long-acting lidocaine in the surgical wound prior to closure has been shown to significantly decrease pain and opioid requirement for several days following surgery. Local anesthetic techniques including wound infiltration, regional, or neuraxial block with spinal or epidural anesthesia. Local anesthetic catheters can prolong the benefits of regional anesthesia into the postoperative period [85].

### 3.2.5. Post-operative Management

Post-operative pain management should proceed as outlined for acute pain, with the goals of providing effective analgesia while maintaining opioid coverage for OUD treatment, and relying on multimodal, opioid-sparing approaches whenever possible. Non-opioid analgesics, including around-the-clock NSAIDs, acetaminophen, COX-2 inhibitors (coxibs), or ketorolac administration [79, 82], can be utilized; these are available in parenteral and other forms of administration, and associated with a reduction in postoperative opioid use and improved analgesia. Less well-tested agents include clonidine and dexmedetomidine, which elicit analgesia by agonism of the  $\alpha$ -adrenergic receptor, and gabapentin and pregabalin, which inhibit pain transmission via blocking sodium-channels [87].

Regional blockade with local anesthetics can be useful in the early postoperative period as it theoretically removes the need for additional systemic analgesia. Although neuraxial opioids allow for lower doses of opioid exposure, these may not prevent opioid withdrawal and additional systemic opioids are often required [87]; further, it may be difficult to estimate an appropriate or safe dose.

When regional analgesia is not applicable and/or IR opioids are indicated, an intravenous PCA administration system is highly recommended, as it allows for individual dose titration and reduces workload for staff. Because patients on OAT

develop opioid tolerance, they often require higher doses than those usually prescribed opioids for the first time or in the short term (including higher PCA bolus doses). Similarly, it can be anticipated their pain severity scores will be higher and decrease more slowly, and that review and adjustment of dosing will be required more frequently.

Several studies indicate that after a variety of surgical procedures, first 24-hour PCA morphine requirements were, on average, three times greater in the opioid-tolerant versus opioid-naïve patients. Determining the appropriate setting of bolus size and lockout interval may be challenging. One recommended method is to begin with the patient's usual 24-hr opioid requirement, and base the size of the bolus dose at 50% of the hourly background infusion rate with a 5-minute lockout. Concerns that IR opioid provision may result in respiratory depression in OAT patients are not supported by clinical experience, likely related to the development of cross-tolerance; however, evidence of opioid toxicity should be carefully monitored for, and naloxone made readily available.

Patients on naltrexone therapy should be managed with multi-modal opioid sparing approaches to the degree possible. Competitive blockade of naltrexone can be overcome with opioid agonists, but the required doses are on the order of 10–20 times the usual doses by weight [78]. This becomes particularly hazardous as naltrexone dissociates from the opioid receptor and subsequent receptor super-sensitivity puts the patient at risk for opioid toxicity. Close monitoring and availability of naloxone become paramount when opioids are provided to those receiving naltrexone treatment for OUD.

As post-operative pain subsides, it is important to bring the patient on methadone or buprenorphine therapy back to the usual OAT dose as soon as possible. Ideally, naltrexone can be re-induced prior to hospital discharge.

### 3.2.6. Chronic Pain

As promulgated by the recent [CDC Guidelines](#) [88], it is increasingly appreciated that opioids should not play a primary role in the management of chronic pain, and that in some cases, functionality improves when opioids are tapered. Conceptualized as chronic illness for which complete remission is not expected, non-pharmacologic approaches become central, and include such evidence-based interventions as acupuncture, physical therapy, graded exercise, weight loss, cognitive behavioral/acceptance therapy, mindful meditation, and yoga. Non-opioid pharmacotherapies with demonstrated efficacy are the NSAIDs and acetaminophen; the anticonvulsants gabapentin and pregabalin; and the SNRIs duloxetine and venlafaxine. Certain tricyclic antidepressants have also been recommended, but are typically less useful due to associated adverse side effects. These same strategies are indicated for chronic pain patients on MAT. In fact, several of these (acupuncture, cognitive behavioral therapy, mindfulness meditation, antidepressants) are likely to provide benefit for the treatment of both pain and OUD [89–92].

However, there is a subpopulation of patients with chronic pain whose functionality and quality of life are maximized with ongoing opioid therapy, which may include patients on OAT and in stable recovery. Risk monitoring strategies utilized for all chronic pain patients on opioid therapy can include the use of treatment agreements, urine toxicology, and monitoring of PDMPs. Because patients with a history of a substance use

disorder are at higher risk for return to use, opioid prescribing for chronic pain to patients on buprenorphine or methadone for the treatment of OUD requires expansion of the chronic pain treatment plan. The plan should include the integration of relapse prevention strategies, frequent assessment for evidence of aberrant drug use behaviors, and the expectation that they maintain good standing and engagement in addiction treatment [93]. Due to ongoing opioid blockade, opioid provision is not an option for patients on naltrexone MAT.

## 3.3. Managing Addiction in the Context of Pain

Critical to managing pain in patients on MAT is the understanding that the chronic disease of addiction requires continuous management; a single-minded focus on treating pain may allow the addiction to progress unchecked. The presence of pain, be it acute or chronic, is a stressor, and even if opioids are not prescribed for its management, the associated anxiety, functional losses, sleep disturbances, and general discomfort can set the patient up for a return to use of the drug which, in the past, had reliably provided psychic relief. Most important to ensuring that an exacerbation of substance use disorder does not occur is the establishment of a collaborative treatment relationship between the addiction treatment provider and the pain care provider, with regular communication about the patient's response to each. Obtaining the patient's permission to allow such communication should be part of the treatment plan.

There are specific strategies the addiction treatment provider can utilize to support recovery goals of in the context of pain treatment. Continued and active engagement in addiction treatment should be encouraged; even if the patient is hospitalized, virtual 12-step meetings, on-site mutual support group meetings, visits from sponsors or the MAT provider, or access to readings or web-based programming can be facilitated. It is necessary to continuously evaluate the presence and severity of stressors that might precipitate return to use (such as unrelieved pain, sleep issues, withdrawal symptoms, psychiatric symptoms, interpersonal conflicts, craving), as well as identify protective factors that promote recovery, and to support/strengthen these to the extent possible. If it becomes apparent that a return to use has occurred, it is critical that the MAT provider notify the pain treatment provider as soon as possible to reassess pain management strategies, minimize the extent of the exacerbation, and reinforce recovery efforts.

### Summary guidelines for managing pain in patients on medication-assisted treatment:

- Continue usual MAT dose
- Utilize non-pharmacologic and non-opioid pain management strategies
- If necessary, use immediate release opioids, titrate to effect and monitor for toxicity
- Expect that larger doses of opioids will be required to manage pain
- Establish collaborative treatment relationship with MAT treatment provider

# CHAPTER 4

# PREGNANCY AND NEONATAL WITHDRAWAL

**Authors:** McCarthy, J. J.; Stephenson, D.

## 4.1. Introduction

### 4.1.1. Pregnant Patients Need Treatment

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Few areas of addiction medicine are as challenging and rewarding as helping a pregnant women recover from opioid use disorder (OUD) through medication assisted treatment (MAT) and having them deliver healthy, drug-free babies. Many physicians have received little to no training in the management of pregnancy complicated by OUD, which makes them understandably reticent to treat this population; they may feel uncertain about the physiologic needs of the fetus and the fetal response to methadone or buprenorphine. Is the fetus dependent? Are medications needed or not? Are the medications beneficial or harmful? Is one medication better than the other? MAT is often misunderstood, and potentially viewed as THE cause of Neonatal Abstinence Syndrome (NAS). However, most women are already physically dependent on an opioid before MAT is started, so the fetus was already at risk of opioid-related NAS. The exception is women who conceive on methadone or buprenorphine. In this situation, the question becomes, "Given that a woman is opioid dependent when she learns she is pregnant, does MAT raise or lower the risk of NAS or other adverse outcomes?"

Decades of research support the safety and efficacy of methadone use in pregnancy in facilitating maternal recovery; maternal recovery rates of over 90% have been reported [94]. Buprenorphine has been implemented for a much shorter time, but the research supports similar

efficacy [95]. Methadone and buprenorphine significantly improve perinatal outcomes, reducing maternal and neonatal complications.

There are many treatment issues unique to pregnancy and the postpartum period that will be discussed, but the most important issue when treating a pregnant patient on MAT is understanding adequate and appropriate medication use during pregnancy. Two overriding issues influence all treatment interventions:

1. The fact of fetal dependence with the risk for Neonatal Abstinence Syndrome (NAS);
2. The profound maternal pharmacokinetic changes that occur throughout pregnancy and the perinatal period, which complicate medication use, especially methadone use [96].

These guidelines provide information specific to the medical management of OUD during pregnancy and the postpartum period, focusing on the use of methadone or buprenorphine to optimize treatment of maternal/fetal dependence given the altered physiology and pharmacokinetics associated with the perinatal period. Optimized treatment increases the likelihood of term delivery of a drug-free baby and decreases the risk of NAS.

### 4.1.2. Pharmacokinetic Changes during Pregnancy

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It is not uncommon for mothers maintained on methadone to experience opioid withdrawal between doses soon after conception. For most women, this process of

increased methadone clearance and metabolically-induced withdrawal continues throughout the pregnancy, with significant individual differences in intensity [96]. Increased clearance of buprenorphine is less likely to occur and less pronounced when it does.

Pharmacokinetic science has documented major alterations in drug metabolism secondary to induction of the Cytochrome P450 (CYP) enzyme system by the hormones of pregnancy. Methadone and buprenorphine are both CYP450 substrates whose metabolism is accelerated by pregnancy. However

- Methadone is quickly converted to an inactive metabolite; whereas
- Buprenorphine is a pro-drug, which is converted to three active metabolites.

Pregnancy specifically induces CYP enzymes 3A4 [97], 2D6 [98], and 2B6 [99]. Methadone is primarily metabolized by CYP 3A4, 2B6, and by lesser and variable contributions from 2D6, 2C19, and 1A2. The parent molecule is demethylated into inactive EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine) [100, 101]. Changes in pregnancy can shorten the effective half-life of methadone from its usual 24-hour range to 12 hours, and at times to as short as 4-6 hours [94]. There is a 17-fold variation in methadone serum concentration for a given dosage [102] in large part due to CYP genetic polymorphism.

Alteration in the half-life means that methadone is rarely a once a day medication in pregnancy. Pregnancy changes methadone from a long-acting drug, which can be given once a day, to a short-acting drug that must be given in multiple (divided) doses to maintain stability of maternal/fetal opioid activity and avoid withdrawal. The significant variability in the rate of metabolism during pregnancy creates significant challenges to safe and effective perinatal management. Using divided doses to compensate for the reduced half-life has been associated with a reduced rate of NAS requiring treatment (29% compared to the published rates of 60-80%) [94]. On rare occasions, rapid clearance of methadone may cause the urine drug screen to become negative for methadone or methadone metabolite. The physician must review the situation to determine whether the most likely explanation is a low methadone blood level or diversion of the PM dose.

Despite buprenorphine's accelerated metabolism during pregnancy, once per day dosing is feasible because it is converted to active metabolites, but there is evidence that twice per day may be preferable [103].

Clearly, dose amount and scheduled regimen must be individualized regardless of whether a pregnant woman is prescribed methadone or buprenorphine. Basing the dosing regimen on pharmacokinetics maximizes the desired pharmacodynamic effect, which is stability of mu receptor occupancy by the medication in the maternal and fetal brain. The stability of the opioid system during pregnancy is presumed to be very important for promoting normal fetal brain development.

### 4.1.3. Medication Selection Considerations: Methadone vs. Buprenorphine

The most important point about the treatment of pregnant women with OUD is that withdrawal puts the woman, the pregnancy and the baby at risk for adverse outcomes. In view of this risk, methadone maintenance is often the treatment of choice. Methadone induction does not require a woman to be in withdrawal at the time of the first dose and poses no risk of precipitated withdrawal. Treatment retention rates are higher with methadone maintenance, and treatment retention correlates strongly with abstinence. The longer a woman remains in treatment, the more likely she is to become and remain drug-free, increasing the likelihood of term delivery of a healthy, drug-free baby that remains in the patient's custody.

There are some cases where buprenorphine may be a better choice:

- Women who meet DSM-5 criteria for OUD, are seeking treatment because they are fearful of relapse, but are **not physically dependent** at the time of presentation for treatment.
- Women who **present for treatment in moderate to severe withdrawal**, because of the time elapsed since the most recent opioid use.

When buprenorphine is used in pregnancy, the mono-product, Subutex, is the recommended formulation. Buprenorphine has several advantages: stabilization on a therapeutic dose may be accomplished in two or three days vs. the weeks or months it takes with methadone. There are no regulatory constraints limiting divided doses. The rate of metabolism of buprenorphine over the course of a pregnancy and post-partum is less variable, so that fewer dose adjustments are required to maintain a therapeutic dose.

Women should be provided with information about both medications and asked which medication they would prefer. Their preference should be honored to the extent possible. They should be informed that the goal of MAT is stabilization on a therapeutic dose to ensure complete suppression of opioid withdrawal. **They should be advised that it is easy to transition from buprenorphine to methadone at any point, but that transition from methadone to buprenorphine is significantly more difficult and should not be attempted in pregnancy.**

A critical question is whether there are differences between methadone and buprenorphine on outcomes, especially NAS severity. A study was done by NIDA (the MOTHER Study) to try to answer this question.

#### The MOTHER Study (Maternal Opioid Treatment: Human Experimental Research)

The MOTHER Study is the most comprehensive research effort to date on the use of methadone versus buprenorphine for the treatment of OUD in pregnancy. This study examines the safety and efficacy of methadone versus buprenorphine for mothers and babies. The study is well known and widely quoted, so it is important for



physicians treating pregnant women with OUD to be aware of it. The data from this study continues to be analyzed, new questions explored and new articles written to share the findings. There are many important findings from this study. Unfortunately, it did not resolve the question about whether methadone or buprenorphine is more likely to cause NAS.

Perhaps the most important finding is that buprenorphine is a safe and effective alternative to methadone for treating OUD in pregnancy. The rates of pregnancy complications were similar for methadone and buprenorphine. The key indicators of neonatal health and development were also similar. (NIDA Notes 7/6/2012)

There are two reasons that the MOTHER study did not resolve the NAS question. First, during the MOTHER study, methadone was always given as a single daily dose, which means that the women on methadone were not stabilized on a therapeutic dose. A single daily dose of buprenorphine is less problematic because buprenorphine breaks down to active metabolites.

A second reason has to do with different findings at the sites. One of the six study sites, Johns Hopkins Medical Center (an urban U.S. site) found buprenorphine-exposed neonates to have shorter treatment durations for NAS and lower medication (morphine) requirements than methadone-exposed neonates<sup>[104]</sup>. None of the other sites showed this, but the findings at this site were so pronounced that cumulative scores (from all the sites) favored buprenorphine. Furthermore, morphine use at the Johns Hopkins site was 7 times greater, and the number of days of medication use was 2-3 times longer than at the rural U.S. or European sites<sup>[105]</sup>. This would suggest that the treatment location, and other non-pharmacologic variables, seem to be more significant determinants of outcome than medication used.

One important difference between sites was that the Vienna site, which found no medication differences in NAS severity and used significantly lower mean morphine doses for both medications, was the only site to use a rooming-in model of post-natal care. This suggests that methadone-exposed neonates who are separated from the mother may be more

vulnerable to increased NAS severity, but methadone-exposed neonates that are not separated are not.

The drop-out rate due to medication dissatisfaction was significantly greater for buprenorphine than for methadone, indicating that a mixed partial agonist/antagonist medication is not optimal for many pregnant women.

### Methadone vs. Buprenorphine – Other Considerations

The major known differences between the two medications are pharmacokinetic (see Table 4.1). However, there are no studies comparing methadone and buprenorphine using dosing based on pregnancy pharmacokinetics. Therefore, it is not clear if there is an advantage to one or the other medication in terms of neonatal outcomes. However, the major known differences between the two medications are pharmacokinetic (see Table 4.1). Metabolic clearance is the major determinant of fetal exposure and a source of potential differences in outcomes.

As Grossman et al. (2017) stated<sup>[106]</sup>: “None of the published articles on NAS comparing different drug therapies control for non-pharmacologic interventions, nor are these interventions routinely documented. When a child has a [Finnegan] score of 8 or greater, we do not make sure that the mother is at the bedside or review other non-pharmacologic interventions to ensure they are maximized. We just give morphine.”

Whatever the actual differences are between medications, they appear to be relatively minor compared to recent studies demonstrating that the standard policy of separating mothers and babies to monitor or treat NAS in newborn intensive care units (NICUs) actually worsens the NAS symptoms. Four studies of increasing sophistication have demonstrated that a rooming-in model that relies on intensive maternal care (prolonged skin to skin contact, nursing, other normal maternal soothing) to minimize NAS symptoms was associated with dramatic reductions in the need for treatment, shorter length of stay, and major cost reductions vs. traditional management in a NICU<sup>[106-109]</sup>.

Table 4.1

### Advantages of Buprenorphine vs. Methadone

Buprenorphine	Methadone
<ul style="list-style-type: none"> <li>■ More rapid stabilization on a therapeutic dose and a narrower dosing range (2mg-24mg)</li> <li>■ Relative ease of medication management with less frequent episodes of withdrawal requiring dose increases</li> <li>■ No regulatory restrictions on divided dosing regimens</li> <li>■ Availability of medication through regular MD offices/ pharmacies, allowing for treatment of patients who need to travel or relocate to a remote area</li> </ul>	<ul style="list-style-type: none"> <li>■ Safety of induction with no risk of precipitated withdrawal</li> <li>■ Greater rates of retention in treatment, the best marker of treatment success</li> </ul>

#### 4.1.4. Risks of Withdrawal vs. MAT During Pregnancy

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With the epidemic of opioid dependence nationally, the rate of women delivering babies with NAS requiring treatment has risen dramatically <sup>[110]</sup>. In response, there has been public pressure to withdraw mothers from opioids during pregnancy. However, this is not a good solution because the risk of relapse to illicit opioid use is very high when MAT is discontinued. NAS that is related to withdrawal from multiple substances (alcohol, benzodiazepine, marijuana, cigarettes, etc.) may have different long-term outcomes than that related to methadone or buprenorphine alone. There is a growing literature that raises concern about long-term neurodevelopmental problems for babies treated for NAS. The MOTHER Study and the Developmental Follow-up Study is the only randomized controlled trial of infants and children who were exposed in utero to methadone or buprenorphine with minimal to no concomitant illicit drug use. The findings from this study are encouraging. “Children exposed to methadone or buprenorphine before birth followed a three-year path of normal physical and mental development. Children who required treatment for NAS did not differ in developmental outcome from children who did not require treatment.” (Addiction Treatment Forum 4/17/2018, Jones 2012, Kaltenbach 2017)

In light of this study, NAS appears to be a short-term problem that does not pose a long-term risk; babies treated generally do not differ in long-term outcomes from babies not treated. If NAS does occur, it is far safer to treat significant NAS in a fully grown, term baby with an appropriate pharmacologic agent (methadone, buprenorphine or morphine) than to allow a small, incompletely developed baby to withdraw under blind conditions in utero by trying to taper the pregnant mother. Long-term safety should be the critical determinant of approach to dependence and pregnancy.

The most documented risk of maternal opioid withdrawal is miscarriage in the first trimester. After the first trimester, fetal mu opioid receptors are fully functional, so maternal withdrawal is associated with fetal withdrawal. Mothers in withdrawal often feel uterine cramping and fetal hyperactivity. Risks from maternal opioid withdrawal during the second trimester and after are less visible but may have significant consequences.

Withdrawal causes a physiologic stress reaction in maternal and fetal brains. An intrauterine abstinence syndrome (IAS) has been described, supported by clinical studies and animal model research <sup>[111, 112]</sup>. Gross measures of fetal distress may not accompany withdrawal because routine clinical measures are not sensitive to fetal stress symptoms unless they are life-threatening. Although it is not possible to use routine fetal monitoring to clinically diagnose fetal withdrawal or to quantify short- and long-term consequences of fetal withdrawal stress, there is an expanding literature on the adverse effects of in-utero stress on fetal development. The effect of maternal withdrawal stress carries an adrenergically-mediated risk for fetal hypoxia, as well as a corticosteroid-mediated risk of epigenetic alterations of the fetal genome and the potential for long-term developmental problems.

#### 4.1.5 Admission Criteria

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Under current federal and California regulations, any pregnant woman with a past history of OUD who is determined by the admitting physician to be physically dependent on opioids is qualified for methadone maintenance treatment (MMT). Federal regulations allow for MMT for a pregnant woman who is not currently physically dependent, if she has a past history of OUD and is at risk for relapse. In California, an exception request must be submitted to and approved by the Department of Alcohol and Drug Programs (ADP) prior to admitting a pregnant woman who is not currently physically dependent.

A history, physical examination and records documenting prior treatment episodes or opioid dependence while hospitalized or incarcerated are sufficient to comply with these regulations. Observation of signs of opioid withdrawal is the usual way of documenting physical dependence. However, withdrawal should be minimized during pregnancy because of the risk of fetal stress and the potential for precipitating premature labor. Women should be told to time their last opioid use so that the earliest stages of withdrawal will begin within a few hours of presentation to the clinic. They should be cautioned that if they come to clinic when intoxicated, it will not be safe to start medication.

#### 4.1.6. Pregnant Patients and Polysubstance Abuse

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Pregnant women who are physically dependent on alcohol, benzodiazepine, barbiturates or other sedatives, in addition to opioids, must be evaluated by the admitting physician to determine whether inpatient detoxification with fetal monitoring is necessary. Methadone treatment should be initiated prior to hospitalization, so opioid withdrawal does not complicate the sedative detoxification.

A DSM-5 diagnosis of OUD and a [waiver](#) to prescribe or dispense buprenorphine is needed to qualify for admission to buprenorphine treatment. For pregnant women who are physically dependent on opioids, induction must be delayed until the patient is in moderate opioid withdrawal. Initiating treatment before this poses the risk of precipitated withdrawal.

#### 4.1.7. Pregnancy and Patient Assessment

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The most important task during the admission interview is to establish nonjudgmental rapport with the patient on the mutual, primary issue of fetal safety. If this is not accomplished, the patient may decline treatment altogether, provide an incomplete history or drop out of treatment. As the pregnancy progresses, she may be reluctant to request dose increases or for a higher level of care when/if needed.

In addition to the usual patient history queries, prior pregnancies should be noted, specifying whether patient

was opioid dependent at the time, whether treatment was received, the outcome of the pregnancy, and the current status of the child. If the patient received treatment during a prior pregnancy, it is helpful to understand whether she had a positive or negative experience with treatment in general and with treatment around delivery in particular. If the experience was a negative one, an effort should be made to address the issue(s) raised, in an effort to ensure that patient's experience during the current pregnancy will be a positive one.

Review of the patient's non-opioid substance use history is essential, including other illicit drugs, alcohol, marijuana, nicotine, prescription and over-the-counter medications. If another physician is prescribing medication(s), the OTP physician should confirm that the medication(s) are still indicated and are compatible with pregnancy and with methadone/buprenorphine treatment. For example, lithium and valproate are contraindicated in pregnancy because of the risks of birth defects. Certain TB medications (e.g. Dilantin, Phenobarbital, Tegretol, Rifampin) will severely complicate methadone stabilization by inducing CYP450 metabolism of both methadone and potentially buprenorphine (see sections on Dosing and [Pharmacokinetics](#)). Sedating medications like benzodiazepines pose risk of maternal/fetal dependence. Written authorization should be obtained to allow coordination of care with the prescribing physician to ensure the baby's safety.

An obstetrical history including complications during prior pregnancies/deliveries should be recorded. Equally important are the patient's feelings about the current pregnancy, whether the father is involved and whether the father and patient's family are supportive of patient, the pregnancy, treatment and recovery, especially recovery with MAT. Conjoint sessions with the father or other concerned family members may be critical to patient participation. Asking whether the father is using alcohol or drugs will allow the program to assist and expedite getting him into treatment if desired.

Mental health problems are a particularly important area for inquiry, as mental illness can adversely affects neonatal and long-term outcomes. Women with OUD have a very high incidence of both childhood and adult traumas, including molestations, rapes, and physical violence. PTSD and other anxiety disorders are common, as are mood disorders (depression and bipolar disorder). Patients should be asked if they feel safe in their current living situation and whether there is a history of domestic violence with the baby's father or current partner; they should be advised and assisted accordingly.

#### 4.1.8. Pregnancy and Initial Testing

Routine laboratory testing including a metabolic panel, hemogram, confirmation of pregnancy, medical urinalysis, liver function tests and screens for syphilis, hepatitis B and C should be included in the record. All women should receive HIV counseling and be offered testing. The physician should encourage all pregnant women with known risk factors (e.g. IV drug use, multiple sexual

partners) to be tested for HIV in view of the data that treatment has been shown to reduce the risk of perinatal HIV transmission <sup>[113-115]</sup>. If the patient has risk factors within the preceding year, the HIV test and/or syphilis screening should be repeated in each trimester and at delivery. Many of these tests will be offered by the prenatal care provider, so it is reasonable to check to see what has already been done to avoid unnecessary phlebotomy.

A PPD (tuberculosis) skin testing should be done unless the patient has a history of a prior positive result, in which case the physician should conduct a symptom review and investigate whether a chest X-Ray (CXR) was done. If there was no CXR, or no copy may be obtained, referral for a CXR should be considered. If the patient is asymptomatic and low risk, the chest x-ray may be delayed until the second trimester.

In 2012, because of the increased prevalence of pertussis in the U.S., the ACIP recommended that every pregnant woman be given Tdap during the third trimester to protect her from pertussis around the time of delivery and to provide passive immunity to the newborn. Maternal antibodies are short-lived, so re-vaccination is required during each pregnancy. Infants are at highest rate of death from pertussis.

Women who express the intention to terminate the pregnancy should be provided with support and appropriate resources and referrals. Until reliable documentation of termination has been obtained, the patient must continue to receive the same care as other pregnant women. Some women express a desire to terminate the pregnancy but do not follow through.

#### 4.1.9. Medical Counsel Regarding MAT during Pregnancy

Many pregnant women seeking MAT for OUD feel guilty and fearful. These feelings stem from a variety of beliefs and misconceptions, many promoted and endorsed by society or medical providers unfamiliar with substance use disorders and treatment. Patients may believe that they cannot genuinely be in recovery while on opioid medication. They may think that they should be able to achieve and maintain abstinence on their own, fearing that friends, family, and society will not accept them if they are on methadone or buprenorphine. They may fear that methadone or buprenorphine is bad for their health or bad for the baby, and that withdrawing from methadone or buprenorphine is worse than withdrawing from heroin or the prescription opioids they were using. The physician should be very sensitive to the fear these mothers have of having their baby taken away from them and the anxiety about how their participation in MAT will be perceived.

Pregnant women often present for admission to MAT after being advised that detoxification is contraindicated during pregnancy. Despite this, many pregnant women feel they are pursuing a mode of treatment that will ensure their own comfort, assuming that it is at the baby's expense.

The admitting physician should explain the risks of continued use of heroin or other illicit drugs during

pregnancy, including small-for-gestational-age infants, increased incidence of SIDS, prematurity, and low birth weight. If needles are shared, the risks expand to include infection with HIV, HTLV I/II, hepatitis and soft tissue infections. The lifestyle associated with drug use increases the risk of trauma, STDs, lack of prenatal care, and loss of custody of the baby. The consequences of opioid withdrawal during pregnancy should be discussed, including:

- The baby experiences the stress of cyclical withdrawal states, which compromises growth and may have long-term “epigenetic” consequences.
- The uterus may become hyperactive resulting in miscarriage or preterm labor and delivery.
- Cravings for opioid may make it difficult for the woman to avoid illicit use.
- Nausea may suppress the appetite resulting in malnourishment and maternal depletion.
- Vomiting may lead to dehydration and loss of part of the methadone or buprenorphine dose.

This information needs to be re-visited during on-going physician/patient meetings. Discussing the research that indicates that infants exposed to methadone in utero have normal physical and mental development is very important to convey to the mother, the partner and concerned family members. (Rattleback & Finnegan 1987; Kaltenback & Finnegan 1984; Kaltenback, Graziani & Finnegan 1979; Kaltenback & Finnegan 1989).

NAS is a critical issue for detailed discussion as it is the major contributor to maternal fear of MAT and problematic desires to withdraw or suffer through withdrawal to minimize exposure of the baby to the medication (see [NAS section](#)). Women should be counseled about the risk of NAS, the symptoms, the timing of onset, the treatment, the things she can do during and after pregnancy to decrease the risk/minimize the symptoms. Above all, mothers should be reassured that NAS is treatable and much safer than a growing baby undergoing in utero withdrawal.

Not all hospitals and pediatricians are equally experienced in the treatment of NAS. It is helpful if the OTP physician is familiar with local hospitals and with the level of comfort of the medical staff in managing babies with NAS.

## 4.2. MAT Induction during Pregnancy

The physician’s objective should be to stabilize the pregnant woman on a therapeutic dose of medication as quickly as is safely possible in order to minimize withdrawal and/or ongoing drug use. To ensure that the initial dose of medication is given as soon as possible, the patient should see the physician early in the admission process. Medication may be started after the physician has confirmed the diagnoses of opioid use disorder and pregnancy, evaluated for current physical dependence and observed for signs of withdrawal. In the event the patient presents in an intoxicated state, induction must be delayed.

Table 4.2

### Dosing Guidelines for Pregnant Women

1. An initial dose of 2 mg is given in the clinic under observation. Should any precipitated withdrawal occur, another 2 mg should be repeated immediately. If no withdrawal is precipitated, the patient should be observed for 1-2 hours, monitoring vitals and COWS every 30-60 minutes. Decisions about further dosing are made on the basis of the presence of withdrawal. If present 1-2 hours after the initial dose, another 2-4 mg dose should be given.
2. The patient is sent home once symptoms of withdrawal have been suppressed. If the patient appears sedated after a dose, vitals should be monitored to ensure stability of the pulse, blood pressure and respirations until the peak has passed (2 hours).
3. The patient should be sent home with a 2 mg dose for the PM, to be taken if symptoms of withdrawal return and a dose to be taken the following morning prior to coming to clinic for day 2 of induction. The AM dose taken at home on day 2 should be the total dose from day 1 (dose in clinic + dose taken at home). The patient should be advised to bring in any unused buprenorphine on day 2. Instructions should be provided verbally and in writing.
4. When the patient presents on day 2, the physician will be able to observe the patient after the home dose. If symptoms of withdrawal returned at home on day 1 and were not completely suppressed by the PM dose, or returned again before the morning dose, an additional dose of 2-4 mg should be given in clinic and the patient sent home with 2-4 mg to be taken in the PM should withdrawal return. The patient should be provided with a dose to be taken at home before coming to clinic on day 3 (the total dose from day 2).
5. For patients that appear unable to follow these instructions or to secure medication, the next morning’s dose may be omitted. The patient should be scheduled to return to clinic first thing in the morning for evaluation and the next day of induction.
6. Most patients will stabilize on a therapeutic dose within a few days. Patients using ½ gram of heroin per day, or equivalent, often stabilize on 16 mg per day. Patients with pain complicating addiction or using high amounts of heroin, may need up to 24 mg/day.

### 4.2.1. Pregnancy and Buprenorphine Induction

Buprenorphine, because it is a mixed mu receptor partial agonist/antagonist, carries special risks during induction that are not a problem with methadone, which is a full mu receptor agonist. If there are significant amounts of an opioid agonist on maternal/fetal mu receptors when buprenorphine is started, precipitated withdrawal will occur, which may result in acute onset of labor and acute fetal distress. Therefore, women **MUST** be in some level of withdrawal before buprenorphine can be started.

The research on buprenorphine induction during pregnancy was done in-patient and involved a complicated protocol of transitioning from heroin to morphine to buprenorphine ([the MOTHER study](#)). This induction protocol is not practical, and at this time, there are no research-supported protocols for safe induction of pregnant women who are physically dependent on opioids. Inductions are currently being done in the outpatient setting, but without any formal reporting in the literature.

Note that the transition from methadone to buprenorphine during pregnancy is absolutely contraindicated.

Methadone's length of action makes precipitated withdrawal very likely and is therefore too dangerous to be recommended. Transitioning from buprenorphine to methadone is not a problem; methadone will not displace buprenorphine from mu receptors, but rather, will gradually gain access to receptors as they are vacated by buprenorphine.

Prior to the first dose of buprenorphine, physical dependence on short-acting opioids should be established. The date, time and amount of the last opioid use should be documented. Objective signs of early withdrawal should be present, meaning a COWS of at least 10 (moderate or higher), not including subjective symptoms. The patient should be advised that precipitated withdrawal is more likely to occur if she has used a long-acting opioid or used any opioid within the last few hours. Special care should be taken to ask about use of opioids not detected by the on-site urine drug test used in clinic.

Although buprenorphine metabolism during pregnancy is not as impacted as methadone, and buprenorphine can be administered once a day, the principle of avoiding peaks and troughs of fetal exposure applies. A strong case can be made for divided dosing, usually twice per day, except for patients who have pain, when three to four times per day is more effective. It should be noted that when the dose is divided, the patient may stabilize on a lower total daily dose.

Patients who are being treated to prevent a relapse, meaning they have a history of opioid use, but are not currently dependent, are given a 2 mg dose on day 1 and observed for signs of sedation. A PM dose may be added if once per dosing does not control craving. The dose should be adjusted gradually, every couple of days, to avoid sedation.

### 4.2.2. Pregnancy and Methadone Induction

It is a misconception that methadone induction should be done in an inpatient setting. This is unnecessary, as methadone induction is very safe once opioid dependence has been established and may cause delays posing increased risk to the fetus. Once opioid dependence has been established, the patient may be safely given 15 mg of methadone provided there are no signs of intoxication. Then the rest of the usually long admission process can be completed without exposing the maternal/fetal dyad to withdrawal.

The patient should be re-evaluated 3-4 hours later to determine the response to the first dose. Another 15 mg is usually given at that time, unless there is uncertainty about the degree of dependence or signs of sedation from the first dose. A usual starting dose for a woman who reports using ½ gram of heroin or more daily is 30-40 mg. The same is true for heavy users of prescription opioids. Women who are using relatively low doses (1.5x maximum therapeutic dose) of weaker prescription opioids, such as hydrocodone, codeine, or tramadol are started on 10-20 mg methadone per day. Daily evaluation and dose assessment should occur until the patient reports 24-hour stability.

Under California regulation, no more than 30 mg may be legally administered at one time on the first day of dosing. Additional methadone may be given on the first day but must be administered after a physician-specified observation period. The physician must note the rationale for a dose above 40 mg on the first day. Doses >40 mg may be necessary for patients who have an established dependence on higher doses of methadone, such as pain patients. The patient should be advised that the total dose given in clinic on day 1 will not normally relieve all symptoms for a full 24 hours. Symptoms that begin as the methadone blood level falls (about 5 hours after dosing) will usually subside after the blood level of methadone has stabilized (about 5 days).

The first step in establishing a therapeutic dose is to completely suppress symptoms of withdrawal at the time of the methadone peak, meaning 5 hours after dosing. When symptoms of opioid withdrawal are present at the peak, it is safe to increase the dose daily. Doses are generally increased in 5-10mg increments. By the time the dose is 50 – 60 mg, 10mg increases are generally required. It may be necessary to have the patient remain in clinic or return to clinic 5 hours after dosing for a face-to-face evaluation to ensure that it is safe to increase the dose.

Once a patient is comfortable at the time of the peak, the duration of complete suppression will last longer every day for 3-5 days. Dose increases are made at 3-5-day intervals, to allow the patient to experience the full effect of the current dose before adding to it. Increasing the dose more frequently may cause sedation or overdose. Once symptoms of withdrawal are completely suppressed between doses, the dose should be raised if the woman reports cravings or ongoing illicit opioid use. **Peak and**

[trough methadone blood levels \(PTR\)](#) or [methadone/metabolite ratios \(MMR\)](#) may be helpful in determining a therapeutic dosing schedule.

If the patient experiences sedation after dosing, the dose must be decreased promptly to avoid overdose over the next few days. A person who metabolizes methadone at a normal rate will find that as the dose is increased, it suppresses withdrawal for longer and longer periods of time. When the right dose is reached, withdrawal remains suppressed for the entire 24-hour period between doses. A person who metabolizes methadone at a more rapid rate, which includes most pregnant women, may find that they begin to feel sleepy at the time of the methadone peak while continuing to experience withdrawal between doses. Merely increasing the dose in rapid metabolizing pregnant patients would unnecessarily increase the peak, while having a minimal effect on the trough<sup>[116, 117]</sup>. In this situation, a divided dose is required for stabilization.

Federal and California regulations do not allow a daily take-out dose of methadone for the PM until a patient meets the “8-point criteria” ([42 CFR 8.12 – Federal Opioid Treatment Standards and Title 9, 10370 California Code of Regulations](#)) for take-out doses<sup>[7]</sup>. Federal regulations also require that a patient be in treatment long enough to qualify for 6 take-home doses/week, which is 270 days. It is therefore necessary to submit a SAMHSA/CA exception request to allow a daily take-out dose for the PM prior to initiating split dosing. The rationale for the request is the fetal need for stability of opioid exposure. SAMHSA/CA will generally approve these exception requests, except in the case of a woman who is using non-opioid substances. Approval is generally contingent on the patient becoming abstinent from illicit opioids on the divided dose and remaining abstinence from all illicit drugs.

As soon as regulatory requirements are satisfied, a second dose should be added to be taken 10-12 hours after the AM dose. The PM dose is increased in 5-10 mg increments every 3-5 days. The AM and PM doses may or may not be the same. Some patients require a higher dose during the day, when they are more active. In the event that a woman experiences sedation after dosing and withdrawal between doses on a twice/day dosing schedule, the dose will need to be divided three or even four times/day. Computerized dosing systems do not allow for more than two doses/day. The patient should be advised to make a line or lines on the take-out bottle to allow them to take the dose in 2 or 3 parts as directed. This is precise enough to be effective and reduces the risk of spilling that could occur if the dose is poured into a separate container.

When a [divided dosing regimen](#) is used, the use of “high” doses (average 152mg/day) has not been associated with high serum levels, but with average serum levels in the mid-therapeutic range: 275 ng/mL<sup>[94]</sup>. It should be noted that when the dose is divided, the patient may stabilize on a lower total daily dose.

### **Risks of Once a Day Methadone Dosing Regimens for Rapid Metabolizers**

Peak/trough extremes are likely to be associated with daily episodes of maternal/fetal withdrawal in the late PM and

early AM. Use of single doses of methadone in pregnant women has been associated with adverse effects on fetal physiology. Depressed fetal movement and decreased fetal heart rate have been documented at the time of elevated methadone peak levels, and fetal hyperactivity and cardiac rhythm irregularities have been observed at the time of sub-therapeutic methadone trough levels<sup>[118, 119]</sup>. In one study, blinded radiologists were able to identify pregnant patients on single daily methadone doses because of the observation of reduced fetal movements in the hours following dosing and increased fetal movements in the evening<sup>[118]</sup>. These findings suggesting over sedation of the baby at peak blood levels and withdrawal-related hyperactivity as methadone blood levels fell in the evening. Split dose patients had ultrasound exams with fetal movements similar to controls.

It has been postulated that the fetus may become “sensitized” to repeated withdrawal<sup>[111]</sup>. Sensitization may be associated with the increased risk of NAS found in many single-dose studies. NAS may be partly a learned fetal response, one that may occur during erratic opioid misuse or under dosing conditions that disrupt normal fetal physiology.

There is compelling research to support giving all but the most impaired pregnant patients divided doses (BID – QID schedules) based on fetal and maternal needs. For all patients, the physician must weigh the clinical benefits and risks of take-home doses, especially for emotionally unstable patients or those in an unstable home environment. If at all possible, patients who are too unstable to be considered for a daily take-home for the PM, should be offered referral to a higher level of care, where daily doses are delivered and a PM dose can be secured.

### **The Importance of a Therapeutic Dose of Methadone**

Some obstetricians continue to advocate low doses of methadone or even methadone tapers to avoid the risks of NAS<sup>[120]</sup>. However, the literature on the relationship of dose to NAS is inconclusive (see also the [Etiology of NAS](#) below), and it has not been established that babies exposed to higher doses of methadone in utero are at greater risk of adverse outcomes. (McCarthy, Leamon, Parr, Anania 2005). It is well established that therapeutic doses of methadone are associated with decreased illicit drug use, increased participation in prenatal care and longer retention in treatment. It is clear that babies exposed to ongoing illicit drug use are at greater risk of adverse outcomes.

The current recommendation is to treat pregnant women according to the same dosing guidelines as non-pregnant patients, meaning to use a dose sufficient to eliminate withdrawal, drug use, and drug cravings, without arbitrary limits on the dose. Clinical experience has shown that after initial stabilization many women require dose increases as pregnancy progresses to maintain a therapeutic methadone dose and to suppress re-emergence of signs and symptoms of withdrawal. The pharmacokinetic changes play a significant role and there is an increasing volume of distribution during pregnancy (see [Pharmacokinetic Changes during Pregnancy](#)).

Serum methadone levels and metabolic ratios are important tools to help physicians to stabilize pregnant patients on methadone during pregnancy and to ensure that doses remain therapeutic throughout the pregnancy and the post-partum period.

### Peak and Trough Methadone Levels

Serial serum methadone levels are a well-established, readily available, and effective way to follow a pregnant patient's changing metabolic rate during and after pregnancy. Serum levels correlate very well with the clinical picture during pregnancy and provide reassuring, objective evidence for the OTP physician and patient. Seeing that the serum level has gone down in spite of dose increases helps a pregnant patient to feel comfortable requesting and accepting dose increases as necessary to prevent withdrawal between doses. Trough serum levels done every 4-6 weeks during pregnancy and for up to 8 weeks post-partum give an accurate assessment of changing maternal metabolism and fetal exposure.

Serum levels are the only way of scientifically assessing fetal exposure. Fetal cord blood has about half the concentration of methadone as maternal blood. It is helpful for the mother to understand that it is not her oral methadone dose that determines fetal exposure; it is her serum methadone level, which counters the common sense, but very inaccurate idea, that the more methadone a mother takes, the more her baby is exposed to.

Serum levels do not predict dosing needs. A relationship between methadone serum concentration and therapeutic effect is not precisely defined<sup>[121]</sup>. Some patients stabilize with low serum levels and some need levels at the upper end of the therapeutic range, related largely to individual pharmacogenetics. A trough concentration range of 200-600 ng/mL serves as a guide to effective treatment<sup>[122]</sup>. This range is clinically safe and effective for pregnant patients<sup>[94]</sup>.

Peak to trough serum ratios (PTR) are used to evaluate the rate of methadone metabolism. They are somewhat invasive and inconvenient, requiring two blood draws on the same day, one before dosing and another four hours after dosing. A ratio greater than 2 indicates more rapid clearance than the usual 24-hour norm<sup>[116, 117]</sup> and the necessity for a multiple dose regimen. Serial peak to trough ratios are useful for monitoring the dynamic changes in a mother's metabolic rate throughout pregnancy and post-partum.

Serum methadone levels may change dramatically in the postpartum period. Checking serum levels within the first week after delivery should be the standard of care, as they provide a clear measure of individual changes to guide safe dosing, especially when late third trimester levels are used for comparison. Monitoring postpartum levels is important for patient safety, as escalating serum levels can cause over-sedation and impair mothering. In one study, 4 of 13 post-partum patients (31%) had serum levels that exceeded the therapeutic range of 600 ng/mL, one going as high as 1020 ng/mL. The postpartum period may be the most dramatic period of pharmacokinetic change in adult human physiology.

For most patients in the immediate postpartum period, dose reductions should occur. This is especially true for

patients who required higher doses. Split dosing should be continued postpartum to maintain maternal opioid stability and avoid even more dangerous peak methadone levels. Further, it is important that the mothers not become dependent on high, clinically unnecessary, serum levels. There is evidence from a study of midazolam (a3A4 substrate) metabolism in pregnancy that the return to a pre-partum metabolic state may take longer than 10 weeks, making serial serum level monitoring advisable<sup>[123]</sup>.

### Methadone/Metabolite Ratio

A newer test, called the methadone/metabolite ratio (MMR), measures methadone, the EDDP metabolite, and the methadone to EDDP calculated ratio with a single blood draw. This is more practical and provides a more dynamic picture of metabolism than simple serum levels, with the important ability to categorize individuals based on their ratios. This test has not been as widely used and may not be available at/familiar to all labs. Individuals may be categorized, based on their ratios as poor metabolizers (PM), ratio >16, intermediate metabolizers (IM), ratio 12-15, extensive metabolizers (EM), ratio 5-11, and ultra-rapid metabolizers (URM), ratio 4 or less<sup>[124]</sup>. The MMR gives information regarding the net effect of the multiple enzymes involved in methadone metabolism. A lower ratio indicates more rapid metabolism, and accordingly less opioid activity at a given dose. MMRs have been studied in MMT populations, and a study of 32 non-pregnant methadone maintenance patients measured ratios at peak and trough and found that the mean ratios were virtually identical.

A study using MMRs in pregnancy estimated a mean 6.1 for all pregnant patients<sup>[96]</sup>. Even pregnant patients in the first trimester had ratios well below that in non-pregnant patients, with an average of 7.2. Ratios changed significantly over time. Average ratios decreased from 7.2 in the first trimester to 5.9 in the second trimester, to 5.1 in the third trimester. Equally important, ratios increased to 7.2 post-partum. The percent of pregnant women that had ratios of 4 or less, indicating ultra-rapid metabolism, increased from 8% (N=1/13) in the first trimester, to 30% (N =9/13) in the second, to 38% (N=9/24) in the third and decreased to 5% (N=1/22) postpartum. Forty-four percent (N=10/23) of individual patients had at least one pre-partum ratio of 4 or less. The number of ultra-rapid metabolizers by trimester was N=1 (9%) in the first trimester, N=7 (44%) in the second trimester, N=5 (31%) in the third trimester, and N=1 (9%) postpartum. Postpartum ratios increased rapidly, by 41%, compared with third trimester values, making the post-partum period, arguably, the most dramatic period of pharmacokinetic change in adult human physiology.

While this pilot study focused on pregnancy as an inducer of methadone metabolism, the MMR may have important use in other clinical situations. Foremost is the potential use of MMRs to monitor drug-drug interactions, such as may occur with co-administration of some antidepressants, anticonvulsants, and antifungals. The effect of these interactions of methadone concentration is poorly predicted by current studies. Further, there is not yet full consensus on the involvement of the various CYP450 enzymes known to metabolize methadone<sup>[125]</sup>, and it has been suggested that

guidelines warning of CYP3A4-mediated drug interactions may be incorrect <sup>[126]</sup>. The metabolic ratio, representing the net effect of the specific CYP enzymes involved in a particular patient, could provide a quantitative alert to the clinician of the effect of such medications on methadone metabolism, provided a baseline ratio is obtained before starting the new medication. One could even make a case for establishing a baseline ratio on all patients treated with methadone. The MMR is a unique identifier for an individual patient, based on his/her genetic polymorphisms for the enzymes that are involved with the kinetic conversion of methadone. Ratios identify ultra-rapid metabolizers who are at risk for poor treatment response, as well as poor metabolizers who are at risk for unusually high serum levels at routine doses with potential for sedation, overdose <sup>[127]</sup> and arrhythmias <sup>[98]</sup>.

### 4.3. Considerations for Pregnant Patients on MAT

#### 4.3.1. Prenatal Considerations

It is important for NTP physicians to be aware that there are specific regulatory requirements when treating pregnant patients on Medication Assisted Treatment. These regulations are listed below.

#### Regulatory Requirements for Pregnant Patients on MAT

- Clarification of pregnancy within 2 weeks of the possibility of pregnancy being raised
- Documentation of prenatal care within 2 weeks of confirmation of pregnancy
- Weekly urine drug testing
- Monthly follow up visits with the OTP MD
- OTP MD visit within 60 days of delivery to document whether a woman remains “Fit for MAT”
- Documentation that a copy of the hospital delivery summary including urine drug screening results for mother and baby have been requested
- Verification of pediatric care and immunizations after baby is born

Per California Code of Regulation, Title 9, Section 10285, the following specific information must be provided to all female patients of childbearing age:

1. Knowledge of the effects of medications used in replacement narcotic therapy on pregnant women and their unborn children is presently inadequate to guarantee that these medications may not produce significant or serious side effects\*\*
2. Abrupt withdrawal from medications used in replacement narcotic therapy may adversely affect the unborn child,
3. The use of other medications or illicit drugs in addition to medications used in replacement narcotic therapy may harm the patient or unborn child,

4. The patient should consult with a physician before nursing,
5. For a brief period following birth, newborns exposed to medications used in narcotic replacement therapy may show irritability or other ill effects from the patient’s use of these medications.
6. Provisions for patient acknowledgement of orientation shall be a part of the patient record.

*\*\*While regulations require that women be given this specific statement, NIDA Factsheet on MAT, Section 1: Factsheet 2 states, “Healthcare professions may want to reassure women that, to date, research has not shown that buprenorphine and methadone can cause an increase in birth defects (Committee on Healthcare for Underserved Women, ASAM, & American College of Obstetricians and Gynecologists, 2017; Holbrook & Rayburn, 2014) and has minimal long term neurodevelopmental impact (ASAM, 2015).”*

#### Prenatal Care

Regular prenatal care has been shown to improve outcomes for patients on MAT, and participation in regular prenatal care is one of the best-documented effects of MAT. Barriers to accessing care and keeping appointments need to be identified and addressed. The name and location of the prenatal care provider and the hospital of delivery should be documented in the record and written authorization obtained to allow coordination of care. Patients should be informed under what circumstances the prenatal care provider and/or hospital staff will be contacted including:

- To provide assistance to schedule/reschedule prenatal care provider appointments or access care for urgent conditions
- To obtain verification of participation in prenatal care
- To answer questions/concerns raised by the prenatal care provider about continuation on MAT or the dose of methadone/buprenorphine
- To inform of ultra-rapid methadone metabolism requiring an unusually high dose
- To advise of ongoing use of drugs or alcohol putting the pregnancy/baby at increased risk of adverse outcomes and necessitating a higher level of care
- To advise of multiple missed doses of methadone or buprenorphine or discontinuation of treatment
- To provide information regarding pain management (particularly around delivery) or breastfeeding
- To verify the current dose of methadone or buprenorphine during hospitalization
- To inform that if IV methadone dosing is required, half the oral dose is equivalent
- To ensure the prenatal care provider is aware of the absolute contraindication to the use of mixed agonist/antagonist analgesics, such as Nubain (nalbuphine), which will immediately precipitate severe withdrawal in the MAT dependent mother and baby, which will require high doses of pure opioid agonists to reverse.



## Attachment 4.1

## Letter to Hospital Obstetrical Staff Regarding Pregnant Patients in Treatment at Bi-Valley

To Hospital Obstetrical Medical Staff

Re: Bi-Valley Medical Clinic Pregnant Patient

This letter is an explanation of treatment with methadone during pregnancy at our clinic, explaining the unique aspects of methadone dosing during pregnancy and at the time of delivery.

During pregnancy, methadone metabolism is accelerated, such that what is normally a long acting, once-a-day medication becomes shorter acting, requiring divided methadone doses for the stability of the mother and to avoid withdrawal in the fetus. Some mothers become ultra-rapid metabolizers during pregnancy (documented by methadone serum levels done routinely during the pregnancy) and require unusually high doses for stability. Their doses do not translate into high fetal exposure because the methadone is rapidly metabolized into an inactive metabolite and excreted. Serial methadone serum levels allow us to monitor fetal exposure to be sure that exposure is within a strict therapeutic range.

In many pregnant patients, the half-life of methadone is shortened to 6-8 hours requiring TID or QID dosing to avoid withdrawal. Our research indicates that reducing risks of maternal/fetal withdrawal during pregnancy will reduce risks of neonatal withdrawal. That is the goal of

our approach. On the day of delivery, the patient may be instructed to take a greater portion of their dose (if possible) before delivery. This is done because the severity of neonatal abstinence has been correlated with how rapidly the neonatal methadone level falls.

After delivery, methadone metabolism returns to the "normal" (non-pregnant state) and the methadone serum level can increase, sometimes rapidly, so the mother is instructed to report any signs of over-sedation immediately. Even in the hospital, a mother may require dose reduction, and will have serum levels and dose reductions when she returns to the clinic.

Please call the clinic if there are any questions regarding our mutual care of these patients. Patients are given the doctor's cell phone number to facilitate ease of communication.

Sincerely,

Dr. John McCarthy

A detailed published description of the dosing science employed in our program can be found in: The Effect of Methadone Dose Regimen on Neonatal Abstinence Syndrome. McCarthy JJ, Leamon ML, Willis NH, Salo R. Journal of Addiction Medicine 2015. A copy can be requested from the clinic.

Table 4.3.1

### Subjective Opioid Withdrawal Scale (SOWS) Augmented for Pregnancy

#### Withdrawals Symptoms\*

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>■ Restlessness</li> <li>■ Bone/muscle aches</li> <li>■ Hot flushes</li> <li>■ Anxious</li> <li>■ Nausea</li> <li>■ Perspiring</li> <li>■ Lacrimation</li> <li>■ Vomiting</li> <li>■ Cold</li> </ul> | <ul style="list-style-type: none"> <li>■ Muscle twitching</li> <li>■ Tearing</li> <li>■ Goose bumps</li> <li>■ Stomach cramps</li> <li>■ Shaking</li> <li>■ Feel like using</li> <li>■ Uterine cramping</li> <li>■ Increased fetal movements</li> </ul> |
|--|---|

\* Severity Range: (0) "Not at all" to (4) "Severe"

See [Attachment 4.1](#) for a sample letter used by Bi-Valley Medical Clinic to provide information to Obstetrical staff regarding methadone in pregnancy.

### Monthly Follow-up Visits with the OTP Physician

While monthly physician visits are a regulatory requirement, this is a minimal requirement, and the dynamic nature of pregnancy often requires more frequent assessments, especially regarding adjusting the dose of medication as pregnancy progresses.

The first follow-up visit should be scheduled within a few days of the patient's admission because of the high likelihood that she will have questions and the dose of medication (especially methadone) will need to be raised. Weekly physician visits may be needed until the patient is stabilized on a therapeutic dose of methadone. The Subjective Opioid Withdrawal Scale (SOWS) Augmented for Pregnancy may be particularly helpful as it includes symptoms specific to pregnant patients<sup>[94]</sup>. Patients and clinic staff need to be aware that uterine cramping and fetal hyperactivity are symptoms of opioid withdrawal.

The patient should be encouraged to request dose adjustments between physician visits as needed and advised of the procedure to accomplish this. It may be helpful to designate one of the program's counselors and/or one of the dispensing nurses to track monthly physician visits, prenatal care visits and to ensure that barriers to care are identified and addressed. The patient should be encouraged to request dose adjustments between physician visits as needed and advised of the procedure to accomplish this. All program staff need to be alerted that when a pregnant or newly delivered mother raises a concern about her dose, this needs to be addressed promptly, on the day it is raised, not delayed until the next physician visit.

At the first follow-up visit, the physician should keep in mind that the patient may have been sufficiently anxious and uncomfortable during the admission interview that

she may remember little. The basic information about methadone use during pregnancy should be reviewed and the patient encouraged to ask any questions she may have. Questions about drug use or urine drug test results are important but must be asked in a neutral fashion, so that the patient does not feel she is being accused of being bad if she reports ongoing use. The physician should provide assurance that with a therapeutic (and, if necessary, blocking) dose of methadone/buprenorphine, coupled with good psycho-social counseling, abstinence is not only achievable, but is the norm.

Monthly follow up visits provide an opportunity to discuss the importance of regular prenatal care, to verify that the patient is attending prenatal care consistently, and to discuss any issues or concerns the prenatal care provider has about the pregnancy. Other topics discussed over the course of pregnancy may include: necessity of informing all treating MDs about MAT, necessity of verifying that all medications, including OTC medications, are safe during pregnancy, the effects of various substances (including alcohol, cigarettes, cannabis, prescription and illicit drugs) on the body, pregnancy and the baby, issues around delivery and post-partum including dose verification when hospitalized and upon release, pain management, breastfeeding, postpartum depression, NAS, contraceptive choices, risk of relapse after delivery, medication monitoring and postpartum adjustment. Be sure to give the patient the opportunity to ask questions.

### Comorbid Conditions

STI surveillance data from the California Department of Public Health shows a dramatic increase in cases of syphilis among women of childbearing age (7-fold in 2017 compared with 2012). Mother to child transmission can occur at any state of syphilis infection. In 2017, 278 babies in California were born with congenital syphilis, which can cause premature birth, low birth weight, birth defects, blindness, hearing loss and even death. The number of infants born with congenital syphilis has increased every year for the past 5 years. Prenatal screening and prompt

Table 4.3.2

## Child Protection — Mandatory Reporting

**It is important for pregnant women and mothers on MAT to be aware that physicians and other treatment program providers are mandatory CPS reporters. Some of the issues that could arise requiring a report include:**

- Clinic staff observing a child left unattended in a car
- Patient presenting to clinic with a child while under the influence of alcohol or drugs
- Patient driving with a child while under the influence of alcohol or drugs
- Patient exposing a child to hazardous situations, such as domestic violence, drug use or being present while drugs are being obtained
- Clinic staff observing a child who appears to be physically or medically neglected or abused
- Clinic staff becoming aware that a woman is breastfeeding while using alcohol or drugs
- Clinic staff becoming aware of a child accessing a patient's methadone or buprenorphine

treatment for pregnant women is essential to prevent devastating birth outcomes. Treatment must be completed 28 days before delivery. Women at risk may need repeated screening throughout the pregnancy and at delivery.

Women who are HIV positive can reduce the incidence of HIV transmission to the infant by taking anti-virals during pregnancy. The OTP physician and staff are in a position to support compliance with this prophylaxis and may even be able to dispense the medications at the dosing window. Women with risk factors for HIV should be offered screening during each trimester of pregnancy and at delivery.

When a pregnant woman is hepatitis C positive, the risk of virus transmission to the child is up to 5%. Pregnant women who screen positive for hepatitis C should be counseled about this risk and advised to make sure the child's pediatrician is aware, so that the child may be screened for hepatitis C at twelve to eighteen months of age, sooner if there are any indications of illness. Antibody in the child prior to one year of age may be maternal. The natural history of hepatitis C virus acquired in the perinatal period is not completely known, but disease appears to be less severe with slower and less frequent progression to cirrhosis.

Hepatitis B screening provides the opportunity to offer immunization to women not already immune and to protect the infants of women who are hepatitis B carriers.

### Advocacy

The physician should be available to intervene with medical staff around issues of pain management and/or breastfeeding. The physician should be prepared to provide information to social workers or CPS staff who are not familiar with MAT or have biases against this treatment. The physician may need to educate the protection system and/or the courts on the critical role of MAT in long term recovery, the complete compatibility of MAT with good mothering, and the assistance that participation in treatment provides to women in their parenting role. The physician should assure the patient of assistance with these issues.

Within the program, the physician should ensure that women are provided with exception take-home doses when they are medically necessary and pose greater benefit than risk. Women put on bed rest for obstetrical complications, such as pre-term labor or who are recovering from C/S or traumatic delivery may be better served by take-home doses. It will be necessary to obtain a waiver from SAMHSA/CA if the woman does not meet regulatory requirements for take-home doses. When ongoing use or an unsuitable home environment makes take-home doses too risky, car dosing may be considered.

### Inadequate Level of Care

Pregnant women who continue to use or are unable to dose daily due to impaired functioning should be offered a more intensive level of care, either Intensive Outpatient Treatment or Residential Treatment, while on MAT, to enable them to stabilize and achieve a sustained abstinence.

Patients should be cautioned that they and their baby will be drug tested at the time of delivery and counseled that participation in treatment is viewed favorably. Women who are not in treatment and/or test positive at delivery are at increased risk of losing custody of their children.

### Voluntary Withdrawal during Pregnancy

Despite overwhelming evidence of the multiple advantages of MAT during pregnancy, MAT is voluntary. A patient's choice about how and when to withdraw from methadone or buprenorphine must be honored. If a pregnant patient is adamant in her desire to withdraw from MAT, after education and discussion of risks of fetal stress, relapse, and potential developmental problems, the physician should obtain an informed consent for withdrawal and help the patient to plan a very slow taper with obstetrical monitoring. The taper should be reversible upon request, and the patient should be directed to seek obstetric evaluation promptly in the event of symptoms of premature labor. Every effort should be made to help mothers view tapering off MAT as secondary to maintaining long term abstinence and protecting the baby. A decision to discontinue tapering and to stabilize on a therapeutic dose should be reinforced as a commitment to recovery, not a failure.

### Involuntary Discharge

Involuntary discharge and discontinuation of MAT during pregnancy should be avoided if at all possible. Acts of violence/threats of violence by the patient towards other patients or program staff may necessitate immediate discharge. Transfer to another program should be facilitated if at all possible. Multiple missed doses of methadone or buprenorphine, such that it is never possible to achieve a stable medication blood level, may necessitate discontinuation of treatment. Every effort should be made to identify barriers and salvage treatment. Pregnant patients should not be withdrawn from MAT for issues such as sporadic attendance at program services (other than dosing), or failure to remain free of illicit drug use, provided use is not putting them at high risk of overdose. Methadone maintenance is associated with a significant reduction in drug use and high-risk behavior as well as an increased likelihood of receiving prenatal care, even when some illicit drug use continues. These benefits provide significant protection to the fetus. Pregnancy and delivery can be life-changing experiences, so ongoing attempts to engage these patients in treatment are often successful. Programs that provide parent education, childcare and transportation facilitate participation, especially when a patient has young children.

### 4.3.2. Postpartum Considerations

#### Breastfeeding

Breastfeeding should be encouraged. It promotes maternal-infant bonding, provides the ideal neonatal nutrition and has been shown to ameliorate NAS symptoms. Nursing is the cornerstone of the "rooming-in" model of NAS

management, which dramatically reduces NAS intensity, the need for NAS treatment and the length of hospital stay. All mothers should be educated about these benefits and encouraged to hold the baby skin-to-skin and to begin breastfeeding their babies immediately after birth and on demand. Nursing may provide some protection against SIDS, which is more prevalent in drug-exposed infants [128].

Contraindications to breastfeeding include abuse of illegal drugs and maternal HIV infection or risk factors. Any woman whose risk factors for HIV are recent (within the past year) should be advised of the risk of transmission of HIV to the baby through breastmilk. The Center for Disease Control has concluded that HCV infection is not a contraindication to nursing as there is no evidence to date of an increased incidence of HCV infection in nursing infants (CDC). A woman who is infected with HCV should be counseled to pump and discard if she experiences nipple trauma, until she has healed, to avoid the baby ingesting HCV infected blood. Smoking is a relative contraindication to breastfeeding [129].

MAT is not a contraindication to breastfeeding. The amount of methadone passed in breast milk has been found to be very low, an average of 0.05mg/day in a newborn ingesting about 500 mL/day [130], and certainly far less than in-utero exposure. At least 8 studies since 1974 have confirmed this [128]. The American Academy of Pediatrics has determined that maternal methadone maintenance, with no dose restrictions, is compatible with breastfeeding [131]. Buprenorphine appears to be equally safe for nursing, although less well studied.

Divided MAT doses should be continued while the mother is breastfeeding to assure a more constant level of neonatal ingestion. Due to reversal of accelerated metabolism after delivery, significant serum methadone level increases have been documented in the postpartum period [94, 96]. This increased serum level will result in increased methadone exposure for the neonate. Continuing to monitor serum methadone levels post-partum will alert the OTP physician to the magnitude of change in maternal metabolism, so that the maternal dose may be adjusted.

Breastfeeding while on buprenorphine is normally considered safe. In a single case of a woman allowing her baby to routinely suckle all night, disruption of breastfeeding at 6 months resulted in acute withdrawal symptoms (author personal communication). It was postulated that “pooling” of buprenorphine in the baby’s mouth allowed for absorption of unusual amounts of buprenorphine, which is absorbed from contact with the buccal mucosa, but not after swallowing. It is probably best to advise mothers on buprenorphine to avoid this type of nursing.

The nursing mother may need support and assistance to get breastfeeding successfully established. Involvement of a lactation specialist may be necessary as drug exposed babies may experience logistical problems with nursing. Neonatal over-sedation from high serum methadone levels or single dose regimens may make it difficult for the baby to achieve the necessary alert and aware stage; hypertonicity may make positioning awkward; nasal stuffiness may frustrate a baby’s efforts to remain latched [128].

## Neonatal Abstinence Syndrome (NAS): The Etiology

NAS has a complicated, multi-factorial etiology that includes risks primarily related to chronic maternal opioid use (licit or illicit), but exacerbated by co-occurring alcohol, benzodiazepine, or tobacco use. It also involves the baby’s genetics, meaning how quickly an individual neonate clears methadone or buprenorphine post-partum. Symptoms of neonatal abstinence usually begin within the first 24-36 hours after birth and may be so mild as to be indistinguishable from normal newborn behavior or may be moderate in severity. On very rare occasions, withdrawal might intensify after hospital discharge, and this must be evaluated in person by an experienced neonatologist or pediatrician.

Many older studies purported to find an association between higher methadone doses and the need for NAS treatment, with an equal number refuting this association. Justification for attributing any adverse outcome, like NAS, to high doses of methadone, relies on documentation of actual higher fetal exposure, i.e. unusually high serum levels. No study has shown such an association. In fact, the literature on dose, serum levels, and potential side-effects is compromised by nearly universal failure to document actual dosing conditions and serum levels.

A large meta-analysis found no relationship between methadone dose and NAS severity [132]. Two studies of “high dose” treatment, up to 200 mg/day, have shown no association between severity of neonatal withdrawal and methadone dose or maternal serum level [133, 134]. A study of 100 mother/infant pairs on doses above and below 80 mg daily compared the rates of illicit drug use before delivery, the NAS score, the need for treatment of NAS and the duration of treatment [134]. Findings indicated that the NAS score, the need for treatment of NAS, and duration of treatment were similar for the two groups. However, the women on doses below 80 mg had a trend toward a higher incidence of illicit drug use before delivery. McCarthy et al. (2005) studied 81 mother/infant pairs looking at the effect of high (>100 mg with a mean of 132 mg) vs. low (<100 mg with a mean of 62 mg) methadone during pregnancy, looking particularly for differences in the rate of medication treatment for NAS symptoms, the days of infant hospitalization and the number of women using illicit drugs at delivery [133]. They found that high doses of methadone were not associated with higher rates of NAS symptoms or more days of infant hospitalization.

The idea that higher doses would be correlated with increased fetal exposure, and adverse outcomes like NAS, ignores the known pharmacokinetic science of pregnancy. Higher doses would only be needed in the context of *increased* methadone clearance and the resulting *decrease* in fetal exposure. Higher doses may be needed to treat maternal/fetal withdrawal in an effort to compensate for increased clearance, without increasing fetal exposure.

Studies have shown that NAS can be exacerbated by separation of the baby from his/her mother and further exacerbated by an overstimulating NICU environment and care by multiple strangers [107, 108].

In a prospective study of long-term effects of different post-delivery mother-infant separation practices (in a normal population), the practice of skin-to-skin contact, early suckling, or both, during the first 2 hours after birth positively affected maternal sensitivity, infant self-regulation, dyadic mutuality and reciprocity at one year after birth, compared to neonates exposed to various separation practices<sup>[135]</sup>. The negative effect of a two-hour separation was not compensated for by the practice of rooming-in. Swaddling decreased the mother's responsiveness to the infant and decreased the mutuality and reciprocity in the dyad. The study suggests an early "sensitive period" during which close contact between mother and infant induced long-term positive effects on mother-infant interactions. The authors state that, "Newborn babies should not be separated from their mothers except for significant medical reasons but be placed skin-to-skin as soon as possible after birth"<sup>[135]</sup>.

A further study of maternal-neonate separation found an 186% increase in autonomic activity (a sign of anxious stress) and an 86% decrease in quiet sleep duration, compared with infants provided skin-to-skin contact<sup>[136]</sup>. While this study was in "normal" neonates, it clearly demonstrates that symptoms on the Finnegan scale can be worsened by maternal-neonate separation. The NAS scoring should be done in the room with the mother, to eliminate maternal separation as a cause of neonatal distress.

The neonate needs its mother to assist with warmth, nutrition, cardiac and respiratory regulation, oxygen saturation, sleep, pain relief, neurobehavioral development, mental/motor skills, and attachment. NAS vulnerability affects many of these basic functions, and to deprive the neonate of its mother under these vulnerable circumstances compounds the problem. NAS severity from this perspective may be largely iatrogenic, due to a misplaced emphasis on medicalization at the expense of physiological and psychological needs of the maternal/neonatal dyad. The frequency and severity of NAS are likely to be reduced markedly if doses of methadone/buprenorphine are optimized during pregnancy and neonates routinely placed in the room with their mothers.

## Management of NAS

The traditional approach has been to put neonates at risk of NAS in the NICU for observation, using a standardized scoring tool, like the Finnegan NAS scoring system, to evaluate infants every 8 hours and assign a score. Moderate symptoms, as reflected by 2 or 3 scores on the Finnegan scoring system of 8 or above, may require medication (usually morphine). Medication use in no way precludes rooming-in. The medication dose is titrated until NAS is controlled, then gradually tapered as tolerated. This approach has been challenged by research showing that nonpharmacologic intervention may be more effective.

A study at Yale New Haven Children's Hospital<sup>[106]</sup> showed that the babies who "roomed-in" and remained close to their mothers after birth, rather than being taken to the NICU for observation, were significantly less likely to need treatment with morphine (14% vs 98%) and had much

shorter hospital stays (5.9 days vs 22.4 days), which decreased the average cost (\$10,289 vs \$44,824). This study developed a different approach to assessing babies, focusing on babies' crying, feeding and sleeping habits. This method of assessment was less intrusive and less likely to aggravate symptoms of NAS. When symptoms of NAS increased, the first intervention provided was to increase the comfort measures by the infant's mother and father. If these measures were ineffective, morphine was used as needed to ensure that infants could feed well, sleep well, and be easily consoled.

Holmes et al. (2016) described implementation of a "Family-Centered Care" model<sup>[109]</sup> using rooming-in on a pediatric unit instead of the NICU, and an "infant-centered" scoring system based on scoring with the mother present with minimal infant disruption. They found NAS treatment rates were reduced from 46% to 27%, including reduced length of stay and reduced costs. They found no medications differences in NAS outcomes.

Grossman et al. (2017)<sup>[106]</sup> in an extension of the rooming-in concept, found a treatment rate of 16% of methadone exposed neonates, compared to rates at the same institution (Yale New Haven's Children's Hospital) of 98% of methadone exposed neonates in the period (2003-2009) before implementing a rooming-in model, and compared to the 57% rate of treatment for methadone and 47% for buprenorphine in the MOTHER study<sup>[104, 106]</sup>. Furthermore, the treatment rate for methadone exposed neonates was only 6% when babies who were transferred to an NICU for problems other than NAS excluded.

The "rooming-in" model of NAS management allows intensive maternal nurturing, avoids NICU separation, and has been associated with dramatic reductions in NAS symptoms that are of far greater magnitude than the effects of medication. Hospital policies that support maternal/infant bonding, physical closeness, and reduced neonatal stimulation will reduce NAS severity. Policies that limit maternal-infant contact—by post-delivery separation for assessment, interventions, and care in a Newborn Nursery, or by a low threshold for placing the baby in the NICU—worsen NAS severity.

In light of the above, medical counsel to prepare the expectant mother for her role in the management of NAS is crucial. Mothers need to understand the benefits of "rooming-in" and the role of intensive maternal nurturing of baby in the prevention/treatment of NAS for methadone/buprenorphine exposed neonates. They need to be familiar with the Finnegan NAS scoring system in general use, so they will be prepared for the range of symptoms that may emerge and understand the criteria for starting medication. This knowledge empowers the mother to be active in the process of interacting with hospital staff.

Education about the important role of the mother in assuring normal bonding to her baby must be stressed, especially because this bonding is also beneficial for NAS symptom mitigation. Mothers should be strongly advised to request immediate undisturbed time with their newborn after birth without unnecessary medical interventions, like taking the baby away to wash, weigh or to do NAS scoring.

## Postpartum Changes

After delivery, many women find they are exhausted, achy, and more emotional. Some experience frequent and severe episodes of diaphoresis. These symptoms remind many opioid dependent women of opioid withdrawal. A careful history, focusing on the nature of the symptoms, the time of onset of symptoms and whether they are relieved by the morning dose of methadone will help to clarify the source. Post-partum withdrawal, when a mother was on a therapeutic dose at the time of delivery, is extremely rare given post-partum pharmacokinetics.

Preparing a woman for postpartum changes before delivery can help prevent her from becoming anxious, assuming she is in withdrawal and relapsing, to manage the symptoms. For many women, being pregnant provides strong motivation to avoid use. Post-delivery, some women experience a return of cravings and drug dreams that may be aggravated by coping with a demanding infant. Discussing these issues prior to delivery gives mothers a chance to think through how they will handle them in a healthy way. Postpartum depression puts a woman at increased risk of relapse. Women should be counseled regarding the symptoms and provided early assessment and treatment if depressive symptoms occur.

The dramatic pharmacokinetic changes that occur post-partum have been discussed in other sections of this document (see sections on Pharmacokinetics and Dosing and on Breastfeeding). Women should be counseled prior to delivery that serial methadone troughs will be necessary starting within a week of delivery and that methadone dose reductions are necessary for most women in the very early post-partum period to address rapidly rising serum levels. The clinical picture can be confusing, as mothers may not experience sedation with rising methadone levels, and post-delivery fatigue is common for new mothers. Women should be advised to let clinic staff know promptly if they experience sedation after dosing.

### The Post-Delivery Visit

According to California Regulation, each woman who qualified for methadone maintenance treatment due to pregnancy must be seen within 60 days of delivery or termination of pregnancy to determine whether she remains an appropriate candidate for continued methadone maintenance treatment. Practically speaking, continued MAT is critical for all new mothers. Opioid withdrawal is a relapse risk and a physiologic stress and should be avoided in the postpartum period when the focus needs to be on adjusting to a newborn baby, to major post-partum physiologic changes, and often, to care of other children. Post-delivery, women will normally require more than one visit. Monitoring serial methadone levels, making dose reductions as needed, observing for post-partum depression, and other psychosocial stressors, usually requires visits every 1-3 weeks during the first 60 days.

During these visits with the NTP physician, a primary focus will be ensuring that the dose of methadone or buprenorphine continues to be appropriate, but the physician should explore the patient's progress in recovery

generally. It is important to revisit the patient's status with regard to substances that were stopped due to pregnancy, which may include cigarettes, marijuana, alcohol, prescription sedatives/stimulants or illicit drugs, and screen for cravings, drug dreams, lapse or relapse. New mothers should be strongly encouraged to participate consistently in group or individual counseling to support ongoing abstinence. Continued treatment is the best assurance that relapse will not compromise a mother's ability to provide appropriate care for her new baby. In the event of relapse, women should be assisted to access the appropriate level of care (residential with baby and doses of methadone delivered if available).

The physician should ensure that the patient is aware of contraceptive choices and that follow-up OB care occurs. Women should be reminded of and encouraged to follow up with medical issues that were delayed due to pregnancy such as INH prophylaxis for PPD converters, TwinRix vaccination, Hepatitis C evaluation/treatment, abnormal PAPs, dental procedures, etc.

The physician should inquire about how the baby is doing and ensure that the baby has a pediatric care provider and is being followed for normal newborn care and other medical concerns. A referral to public health nursing may be offered if there are particular concerns. On very rare occasions, NAS can be delayed and occur 3-4 weeks post-partum. The reasons are not clear but may relate to unusually slow infant clearing of methadone. The baby's pediatrician needs to monitor for delayed NAS and be prepared to treat the baby if it occurs. If the mother is Hepatitis C positive, the baby will need to be screened after 12-18 months. A copy of the baby's immunization record should be included in the mother's file to document that the baby is receiving routine well child care.

### Conceiving while on Methadone

Many opioid dependent women of childbearing age will conceive on methadone. While it is not an ideal situation for a pregnancy to be complicated by opioid dependence, outcomes for women maintained on methadone throughout pregnancy have been found to be better than for women with shorter periods of methadone exposure during pregnancy, referring to women entering treatment partway through pregnancy while actively addicted. In a study of 83 women who delivered babies in a specialized methadone pregnancy program, 26 (31%) were in treatment at the time of conception<sup>[133]</sup>. These 26 women had the best drug treatment and obstetrical outcomes, with lower levels of drug use, higher birth weights, and lower rates of NAS that required treatment with medication, (40%) compared with those admitted to the program acutely addicted. The importance of this observation is that in spite of a much greater total methadone exposure throughout the entire pregnancy, there were better outcomes and less risk for NAS. This information should be conveyed to women to relieve some of the concerns about conceiving on methadone.

While there have been decades of research "speculation" about adverse developmental consequences of methadone exposure, no rigorous study has supported this. Studies

on this issue have usually been based on retrospective assessments of babies with NAS without controlling for other confounding variables, such as drug use during pregnancy (Kaltenback and Finnegan, Jones et al MOTHER). Although there is an association between OUD and negative postpartum outcomes, these outcomes often stemmed from continued drug use problems or family dysfunction rather than methadone exposure<sup>[137]</sup>.

All women of childbearing age who enter MAT should be advised that conceiving on methadone or buprenorphine will result in the complication of fetal dependence. While such dependence may not occur until the fetus is 10-12 weeks, when mu receptors are fully functional, withdrawal in the first trimester presents a significant risk of miscarriage. In Dr. McCarthy's clinical experience, 4 miscarriages occurred among 6 buprenorphine patients

who abruptly discontinued buprenorphine (on their own or on advice from a non-addiction medicine physician) when they discovered they were pregnant. While not a controlled study, no miscarriages were noted in a small group of women who maintained buprenorphine after conception.

Contraceptive counseling should be provided to all women on methadone and buprenorphine. Women can be assisted to try to taper off MAT prior to a planned pregnancy to see if such a plan can successfully avoid the complication of methadone or buprenorphine dependence without jeopardizing the woman's recovery.

See Attachment 4.2 below for an informational document developed by Bi-Valley Medical Clinic and given to women of childbearing age at admission to provide appropriate information and informed consent.

#### Attachment 4.2

### Considerations Before Pregnancy – Letter Provided to Women of Childbearing Age at Admission to Bi-Valley Medical Clinic

You are being given this letter because you are on methadone and have the potential to become pregnant. We want our female patients to understand that conceiving on methadone means that your baby will be dependent on methadone and subject to opioid withdrawal.

Although there is a possibility that a woman could withdraw from a low dose of methadone during pregnancy, any withdrawal attempt must be very slow and carefully monitored to assure that the baby is not experiencing withdrawal distress in the womb. Also, there is risk of causing a miscarriage or premature labor if the withdrawal is too fast. Finally, there is a risk to the mother of relapsing to drug use during a withdrawal attempt. Most mothers who conceive on methadone remain on the medication for the duration of the pregnancy as the best option for a healthy baby.

At the time of delivery, the baby will be assessed in the hospital for signs and symptoms of withdrawal, which is called neonatal abstinence. Most babies will have some mild symptoms of withdrawal. But some will have symptoms that require treatment with medication. The mother's dose does not determine the withdrawal severity. Many mothers will need high doses because their body gets rid of methadone more rapidly. This is a normal physiologic change in pregnancy.

When methadone is given in divided doses adequate to prevent maternal withdrawal during pregnancy, most babies will have withdrawal that is mild enough that it will not need to be treated with medications. These babies go home with the mother, usually within the first 2-4 days. In a recent research at Bi-Valley, only 29% of babies required medications. If the baby has withdrawal symptoms that are severe enough to require medications, the baby will likely be kept in the hospital for between 3-6 weeks to be tapered slowly off opioids.

We recognize that some women may feel that methadone treatment provides the best way to remain drug-free, healthy and prepared to parent. There is no evidence that babies exposed to methadone have any long-term problems, beyond the short-term problem of neonatal withdrawal. There is no increased risk of withdrawal in the newborn from exposure to methadone for the entire pregnancy, compared to shorter periods of methadone exposure. Also, you can nurse your baby while on methadone, which we strongly encourage.

For these reasons we respect a woman's decision to conceive on methadone, and we certainly understand that unplanned pregnancies may happen on methadone. We will provide our unequivocal support to any woman who does conceive on the medication and will provide counseling to you about things you can do to minimize the risks of withdrawal in your baby.

In summary, conceiving on methadone carries a risk of withdrawal with the potential for up to 6 weeks of hospital treatment after delivery. For this reason, we cannot recommend conceiving on methadone, but we respect a woman's right to make her own decision about this. Please inform your counselor as soon as you think you are pregnant, so that our specialized care for you and your baby can begin as soon as possible. If you have any questions, please contact our medical staff for more information.

Sincerely,

John J. McCarthy, MD

# CHAPTER 5

# COMORBID

# POLYSUBSTANCE

# USE

**Authors:** Albanese, A.; Shoptaw, S.; Cermak, T.; Montero, Y.; Selby, P.

## 5.1. Introduction

Many patients with Opioid Use Disorder (OUD) are also using, or are addicted to, other substances (see Table 5.1.1) <sup>[138, 139]</sup>. Caring for these patients presents many additional challenges: they are at higher risk for a range of infections including HIV, HCV, MRSA, and infectious endocarditis <sup>[138]</sup>, which in turn predisposes them to various cardiovascular and cerebral vascular diseases like myocardial infarction and stroke <sup>[139]</sup>.

People with polysubstance use disorders suffer a high level of psychological and socio-economic stresses from loss of employment, housing and social support <sup>[138]</sup>. Their treatment responses are accordingly poorer as well. When used concurrently, substances can interact with medications used in the treatment of OUD, further complicating the treatment process, and can contribute to intentional and unintentional overdoses. Many clinicians, in part out of concern for these patients' safety, simply avoid prescribing medications to treat these patients' OUD. (Miller) Those who do prescribe medications, like methadone and buprenorphine, often do so with reluctance and stringent precautions such as regular drug screens, short prescriptions, and frequent clinic visits.

Clearly, the added complexity and difficulty of treating patients with OUD and polysubstance use requires careful treatment planning and caution. In many cases a more intense level of care, such as day treatment or residential treatment, may be needed. In practice, a standard patient with OUD tends to engage in polysubstance use when accounting for tobacco, alcohol, and cannabis are considered. Over 80 percent of people with opioid use disorder use tobacco, and a majority of them also drink (see Table 5.1.1) <sup>[140]</sup>.

The DSM-5 removed polysubstance use disorder from the diagnostic listing. Instead each mind-altering substance is rated individually using the 11 criteria to determine whether there is a use disorder and its severity on the continuum from mild to severe, as explained in Chapter 1 of this Guideline describing the changes from DSM IV to DSM-5.

## 5.2. Recommendations for Treatment for Other Substances

### 5.2.1. Methamphetamine and Cocaine

#### Pharmacology and Types

Methamphetamine (MA) is the secondary drug most commonly used by patients with OUD. Use of methamphetamine and cocaine (including crack cocaine) has increased nationally (Table 5.1.1). MA and cocaine are both psychomotor stimulants with similar effects in increasing dopamine availability in the reward pathway in the nucleus accumbens <sup>[142]</sup>. The combination of either of these stimulants with an opioid is known as a "speedball" <sup>[143]</sup>. The stimulant-opioid combination produces greater positive subjective effects than either drug alone. Among those using heroin, up to 92 percent report concomitant use of cocaine <sup>[143]</sup>.

#### Psychiatric Signs and Symptoms

Psychiatric indicators of stimulant intoxication include euphoria, anxiety, agitation, irritability, paranoia, psychosis and suicidal states <sup>[144]</sup>. Signs and symptoms of stimulant withdrawal include anxiety, depression, fatigue, and possibly



Table 5.1.1

## Type of Secondary Drug for Opioid Use with Methadone/ Buprenorphine Detoxification in CA, 2016 <sup>[143]</sup>

Secondary Drug	Frequency	%
<b>None</b>	18243	50.2
<b>Methamphetamine</b>	8716	24.0
<b>Cannabis</b>	2311	6.4
<b>Cocaine/Crack</b>	1693	4.7
<b>Other opiates/Synthetics</b>	1400	3.9
<b>Alcohol</b>	1281	3.5
<b>Oxycodone/Oxycontin</b>	944	2.6
<b>Tranquilizers (Benzodiazepines)</b>	610	1.7
<b>Heroin</b>	391	1.1
<b>Non-prescription Methadone</b>	261	0.7
<b>Other</b>	227	1.3

higher suicidal states. This withdrawal period may last three to five days and may contribute to clinic absences. Patients may feel they are “not addicted” because withdrawal is less obvious than with opioids, although craving is severe. Patients may present with sedation if they come to clinic while “crashing.”

### Epidemiology

Physiologically, cocaine use increases risks for strokes <sup>[145]</sup> especially among young adults and in crack smokers <sup>[146]</sup>. Young adults who use cocaine often experience chest pain, myocardial infarction, congestive heart failure, arrhythmias, and renal failure <sup>[147]</sup>. Methamphetamine also causes cardiovascular <sup>[148]</sup> and cerebrovascular disease, especially in younger adults <sup>[149]</sup>.

Psychologically, patients who use stimulants and opioids together often have concomitant psychological distress and increased risk of non-fatal overdoses <sup>[150]</sup>. Stimulant use has long been recognized for its links with infectious diseases following condomless sex with multiple and concurrent partners under the influence <sup>[151, 152]</sup>. The powerful synthetic opioid, fentanyl, is frequently used as an adulterant for street heroin,

methamphetamine and cocaine, contributing significantly to overdoses <sup>[153]</sup>. In 2016, over 7,200 people in the U.S. died from combining cocaine with opioids <sup>[154]</sup>.

### Treatment

Early identification of stimulant use in patients receiving treatment for opioid addiction is critical for ensuring patient safety and effective treatment. A thorough history and physical, as well as urine drug screen can help identify the specific stimulant(s) involved, which should be addressed in the initial treatment plan. Proper evaluation may include requiring some period of abstinence from stimulant use to test for the ability to stop using stimulants. This may require stimulant-specific program interventions, such as mandated treatment in groups focused specifically on stimulant use. Treatment of psychosis and paranoia should not be delayed because of ongoing use.

Treatments for stimulant use disorders are almost entirely behavioral, as there are no drugs approved for the treatment of cocaine or methamphetamine <sup>[155]</sup>. Methadone or buprenorphine can be an appropriate treatment option when used in conjunction with a multi-pronged

approach including behavioral intervention, support groups, and motivational enhancement for people with co-occurring stimulant use disorders and opioid use disorders <sup>[142]</sup>.

More research is necessary to determine buprenorphine's effectiveness over long periods of time, if there a dose- and/or administration-dependent relationship, and if there are significant side effects or issues with safety that providers should be aware of when managing patients with opioid and stimulant addiction <sup>[156]</sup>.

## 5.2.2. Alcohol

### Epidemiology

Alcohol use disorder (AUD) is a common problem among patients with OUD, and contributes significantly to the high mortality rate in this population. About 20% of patients receiving treatment (OUD) with methadone or buprenorphine/naloxone also have AUD <sup>[157]</sup>. Moreover, Superscript reference AUD is a risk factor for increased overdose and mortality in patients with OUD—accounting for about 40% of deaths in these patients. AUD is also associated with poor compliance with

Table 5.2.1

## Stimulants – Other Important Information

- The major difference between cocaine and methamphetamine is that cocaine acts extracellularly, but methamphetamine acts both extracellularly and intracellularly. Clinically, this means methamphetamine’s effects last much longer, are more severe, and potentially more neurotoxic and destructive.
- Patients suffering acute effects of methamphetamine may appear like patients with acute schizophrenic psychosis, but they are often at least vaguely aware that what is happening to them is connected to the drug they took. These patients often respond to the “talking down” strategy (quiet room, low light and noise level, calm, reassurance).
- Consider hospitalizing the patient when you see: danger to self or others; inability to safely travel from clinic.
- Psychosis from chronic methamphetamine use can persist and often be “encapsulated,” meaning that it isn’t obvious until the subject of their delusion is brought up in conversation.
- Methamphetamine psychosis can be induced in almost everyone; it is dependent mostly on total lifetime exposure.
- There is no real evidence that methamphetamine can cause schizophrenia, but persistent psychosis is more likely in people with a family history of psychiatric disorders.

pharmacotherapy, increased risk of relapse, increased risk of hepatotoxicity leading to cirrhosis, and exacerbation of psychiatric comorbidities among patients receiving opioid agonist treatment (OAT) [157, 158]. Alcohol withdrawal may pose serious health complications among patients with co-occurring OUD and AUD during and outside of treatment [159].

### Treatment

Given the prevalence of health and safety risks for patients with OUD, treatment for AUD needs to be an important component in their treatment plans. Patients with OUD and AUD should be screened for hepatotoxicity. Patients with OUD and AUD have heightened risk of opioid overdose, and may require administration of naloxone to block opioid receptors and restore normal respiration [160]. Patients with OUD and AUD who are at risk of developing severe, complicated alcohol withdrawal should be identified, as they may require inpatient care or benzodiazepine therapy for withdrawal management before proceeding with treatment of OUD [159].

### Alcohol Testing

An alcohol history should be part of the initial admission evaluation; standardized screening instruments such as the CAGE or AUDIT may be used. For patients who present in alcohol withdrawal, a CIWA should be used to document need for

Table 5.2.2

## Health Risks of Excessive Alcohol Use

System	Effects
<b>Brain</b>	<ul style="list-style-type: none"> <li>■ Interferes with brain’s communication pathways</li> <li>■ Altered mood and behavior</li> <li>■ Impaired thinking, movement, coordination</li> </ul>
<b>Heart</b>	<ul style="list-style-type: none"> <li>■ Cardiomyopathy</li> <li>■ Arrhythmias</li> <li>■ Stroke</li> <li>■ Hypertension</li> </ul>
<b>Liver</b>	<ul style="list-style-type: none"> <li>■ Steatosis</li> <li>■ Alcoholic hepatitis</li> <li>■ Fibrosis</li> <li>■ Cirrhosis</li> </ul>
<b>Pancreas</b>	<ul style="list-style-type: none"> <li>■ Pancreatitis</li> </ul>
<b>Immune system</b>	<ul style="list-style-type: none"> <li>■ Weakening of the immune system</li> <li>■ Increased susceptibility to infection (e.g., pneumonia, tuberculosis, etc.)</li> </ul>
<b>Cancer</b>	<ul style="list-style-type: none"> <li>■ Head and neck cancer</li> <li>■ Esophageal cancer</li> <li>■ Liver cancer</li> <li>■ Breast cancer</li> <li>■ Colorectal cancer</li> </ul>

acute withdrawal treatment using benzodiazepines. Alcohol breathalyzer testing can be used to identify patients who are unable to control their drinking. It may also help clarify a patient’s drinking pattern (daily versus weekend or holiday binges). Be aware that some patients are able to titrate

their alcohol consumption, stopping early enough in the day to avoid a positive breath test in clinic the next day; urine screens can be helpful in this situation, especially for detecting episodes of binge drinking, as urine remains positive longer than breath.

## Alcohol and Methadone Treatment

AUD impacts methadone in two specific ways: acute use, specially combined with methadone, leads to synergistic sedative effects. Chronic use stimulates the metabolic activity of the P450 enzymes leading to more rapid methadone metabolism, and thus a reduced methadone blood level. Achieving a stabilized methadone dose may be complicated by the concomitant use of alcohol. Early screening, intervention and treatment planning are essential to effect change in this potentially lethal behavior.

## Alcohol Testing and Methadone Treatment

The patient who presents for dosing with a positive Breathalyzer test poses a clinical dilemma. Safety is the critical issue. A dose of methadone on top of an unknown quantity of alcohol puts the patient at risk for sedation or overdose. Missing a dose of methadone increases the likelihood that the patient will use heroin in addition to alcohol. Serial Breathalyzer tests (i.e. two tests about 30 minutes apart) may be used to determine whether the patient's serum alcohol level is on the way up or down. The physician's role is to determine whether it is safe for the patient to receive his/her regular dose of methadone or some portion of it. There is no body of literature establishing the best course of action, and physician practices vary.

Some physicians decline to administer a dose of methadone to a patient who has any positive Breathalyzer score. This practice may deter patients from coming to clinic to dose when they have been drinking. Other physicians withhold the dose if the patient appears under the influence or has a Breathalyzer >.04. Intoxicated patients should be advised not to drive and assisted to arrange other transportation home. Some physicians will order a partial dose (half) for patients with a positive Breathalyzer that is <. 04 provided they do not appear under the influence. When the Breathalyzer is <. 02, it may be reasonable to continue the regular dose. See also [Methadone Section](#) for more specific dosing guidance.

These protocols depend partly on clinic philosophy. Because of the high prevalence of hepatitis C, some clinics have a lower threshold for holding the dose to discourage alcohol use in this group. The clinic's policy regarding alcohol use, BAC levels and dosing should be established and discussed with patients during the initial orientation process.

In the alcohol-tolerant patient, blood alcohol levels do not necessarily correlate with functional impairment. Even if the patient is alert with alcohol "on board," the effect of methadone in synergism with the alcohol may significantly reduce alertness after dosing.

When alcohol use is identified, the patient's treatment plan should reflect this and include approaches to address it. Frequent follow-ups may be offered in order to provide brief interventions (see CSAT Tip 34) and possibly pharmacotherapy. Withdrawal from alcohol can be medically dangerous. Patients whose Breathalyzer results are positive on more than one occasion should be

evaluated for the presence of physical dependence and assisted to obtain medical detoxification from alcohol when needed. Some programs offer outpatient detoxification from alcohol with phenobarbital or benzodiazepine. Patients whose past history includes severe alcohol withdrawal, such as seizures, blackouts or DTs, or patients who are medically fragile or pregnant, require hospitalization for detoxification from alcohol use. (*ASAM Principles of Addiction Medicine*)<sup>[161]</sup> In some communities the prevalent stigma associated with MMT, even in some addiction treatment programs, makes it difficult to place methadone maintained patients in inpatient alcohol treatment facilities.

When physical dependence is not, or no longer an issue, pharmacotherapy with disulfiram (Antabuse®) may be considered. The typical dose is 250 mg to 500 mg per day. The first dose should not be given until the patient has been alcohol free for at least 48 hours. Patients should be given [information](#) about inadvertent alcohol ingestion in mouthwash, sauces, vinegars, cough suppressants, cosmetics, etc.<sup>[162]</sup> and sign a consent that explains the potential adverse physical reaction to alcohol exposure while on disulfiram. The physician must make sure that the patient understands the purpose and effects of the medication before prescribing or dispensing it. Dispensing the medication at the clinic's dosing window increases the likelihood of compliance. The use of this deterrent medicine has been shown to be effective in several studies with methadone patients, but requires regular liver function testing<sup>[162]</sup>. It is explained more fully in Chapter 6 of the textbook, *Methadone Treatment for Opioid Dependence*<sup>[163]</sup> The chapter title is "Other substance use disorders in methadone treatment: prevalence, consequences, detection and management."

## Alcohol and Buprenorphine Treatment

Alcohol use has not been generally highlighted as a serious clinical concern in patients receiving buprenorphine for treatment of OUD; the literature suggests that buprenorphine may even reduce alcohol intake<sup>[164]</sup>. However, in the present context, alcohol use should be discouraged, and where signs of excessive use exist, appropriately addressed, because of the effects of alcohol on treatment adherence, which, in turn, may have deleterious effects on other aspects of treatment.

## Alcohol, Other Opioid Agonist Treatments (OAT) and Other Interventions

Other effective interventions for AUD include the patient receiving OAT plus clinician-delivered brief intervention, motivational interviewing, and cognitive-behavioral coping skills<sup>[165, 166]</sup>. While there are medications that have shown effectiveness for alcohol prevention in the general population, generally their effectiveness in the OAT population has not been studied or their use is contraindicated. For example, naltrexone should not be administered to patients receiving OAT as it can precipitate opioid withdrawal, acamprosate has not been studied in the OAT population and disulfiram has yielded unclear results<sup>[167]</sup>. Medications like gabapentin, baclofen, and topiramate are promising options for medication assisted therapy but more research is necessary to determine if they are feasible treatment options.

### 5.2.3. Nicotine

#### Nicotine Use is Ubiquitous

People who use opioids overwhelmingly use nicotine-containing products as well, especially cigarettes. Nicotine likely serves as a primer for other drugs, including opioids, prolonging the action of other substance and potentiating their effects<sup>[168]</sup>. Cigarettes are the most common nicotine product used in the United States, but cigars, cigarillos, hookah pipes, smokeless tobacco, and electronic-nicotine delivery systems (i.e. e-cigarettes) are also common<sup>[169]</sup>. The prevalence of tobacco use among OUD patients is higher than in other addictions and almost five times greater than in the general population<sup>[168]</sup>. In a study of OAT patients on methadone or buprenorphine, 97% used cigarettes, smoking on average 20 cigarettes per day<sup>[169]</sup>.

#### Nicotine and Methadone Treatment

Nicotine and methadone have a synergistic action. Patients on nicotine replacement therapy have been observed to have decreased opioid withdrawal symptoms and patients on methadone seem to have decreased nicotine withdrawal symptoms and increased euphoria<sup>[169]</sup>.

#### Nicotine Treatment

Although the high morbidity and mortality of smoking is generally understood, many patients do not recognize the specific impact that smoking is already having on their own health, nor are they aware of the inevitability of lung disease in everyone who smokes for 30-40 years.

Many patients express an interest in quitting and find the recovery skills they are learning to address opioid addiction to be useful in addressing nicotine addiction. Some patients will cut down, temporarily quit, or repeatedly try to quit, and may be discouraged if they have been unable to quit.

#### Nicotine Treatment Pharmacotherapy

Nicotine Replacement Therapy (NRT), bupropion and varenicline are three medications that have been approved in the United States as treatment for smoking cessation<sup>[170]</sup>. The Cochrane's (2013) review of pharmacological interventions revealed the following:

- NRT and bupropion are more effective than placebo. For every 10 people who quit with placebo, about 18 people quit smoking when using NRT or bupropion.
- Varenicline more than doubled the likelihood of quitting when compared with placebo.
- Varenicline is more effective than NRT (including the patch, lozenges, gum, tablets, sprays and inhalers).
- Combining two types of NRT is as effective as varenicline, and more effective than using a single type of NRT.

The efficacy of pharmacotherapy increases when patients attend a cessation support group. The OTP can encourage smoking cessation by having cessation support groups on site and by prohibiting smoking on clinic premises, so

that patients do not have to see and smell cigarettes when they come to the clinic. Addressing smoking behavior in treatment plans and at annual examinations and offering smoking cessation interventions on-site encourages patients to cut down and eventually quit smoking.

Co-existing depression is a factor that reduces success in smoking cessation. It is advisable to assess for depression before a patient launches an attempt to quit. Those already on antidepressants may require a dose adjustment once they quit. Interventions demonstrated to increase likelihood of nicotine cessation include:

1. Brief counseling provided by a clinician. (This intervention has been shown to improve the likelihood that a smoker will successfully quit and remain a nonsmoker for subsequent 12 months.)<sup>[171]</sup>
2. Smoking cessation group counseling and individual therapy based on cognitive behavioral therapy<sup>[172]</sup>.
3. Pharmacological interventions<sup>[170]</sup>.
4. Referral to toll-free telephone quit-line numbers such as 1-800-NO-BUTTS or 1-800-QUIT-NOW<sup>[173]</sup>.

In November of 2007, the FDA required a black box warning regarding the possibility of serious neuropsychiatric symptoms observed in post-marketing surveillance when using varenicline for smoking cessation that involved hostility, suicidal thoughts and agitation. In 2016, the FDA reviewed data on efficacy and adverse events (the EAGLES trial)<sup>[174]</sup> in an RCT evaluating varenicline, bupropion, nicotine replacement and placebo in a large sample of controls and of psychiatric patients who were seeking smoking cessation. Findings showed no higher rates of adverse events for varenicline and showed superior smoking cessation outcomes for varenicline across control and psychiatric groups. This led the FDA to recommend removal of the black box warning and to include a statement that varenicline produces superior smoking cessation outcomes compared to bupropion and nicotine replacement. Best practice would involve a discussion of the risks and benefits with patients willing to start another quit attempt using varenicline.

### 5.2.4. Benzodiazepines, Sleep Drugs, and Muscle Relaxants

Benzodiazepines (particularly clonazepam (Klonopin®) and alprazolam (Xanax®) are often and increasingly used with opioids as they seem to amplify and prolong the opioid effects<sup>[175]</sup>. This is particularly problematic because benzodiazepine produces synergistic sedative effects with opioids such as methadone. Patients may use benzodiazepine to suppress the agitation produced by stimulant abuse or to potentiate an opioid high. Some patients say that they abuse benzodiazepine because “it makes the methadone feel like heroin.”

Unfortunately, patients may use benzodiazepines with other sedating substances, such as muscle-relaxants (combination of an opioid, a benzodiazepine and carisoprodol) or antihistamines (combination of a benzodiazepine and an antihistamine) (see Table 1 in Polysubstance Abuse Section for statistics.)<sup>[176, 177]</sup>

## Assessment and Testing

Due to the frequency of abuse and patients' inconsistent reporting at admission, adding benzodiazepine to the admission drug screen is recommended and to subsequent screens in patients whose history is suggestive or who screen positive at admission. Note that testing for clonazepam (Klonopin®) and lorazepam (Ativan®) requires special assays; routine benzodiazepine screens will not detect them. In addition, routine drug screenings also do not identify carisoprodol. Patients who present for dosing appearing under the influence of a sedative must be carefully interviewed and assessed. It may be necessary to have the patient transported to a local emergency room for evaluation of altered mental status and observation. If the patient has already been dosed before the sedation is noted, the patient will need to be under observation until the methadone has peaked (3-4 hours). The patient should relinquish their car keys and arrange other transportation home.

## Adverse Effects

Concurrent use of benzodiazepines and opioids can lead to respiratory depression, CNS depression, overdose and overdose fatalities<sup>[175]</sup>. Respiratory depression is the chief mechanism leading to overdose mortality. It is estimated that 40 and 80 percent of methadone- or heroin-related deaths are associated with benzodiazepines.

## Pharmacology

Opioids act through  $\mu$ - and  $\delta$ -receptors while benzodiazepines act on the GABA receptors to inhibit the respiratory center in the medulla. [Jones] Thus, when used concurrently they have an additive effect on respiratory depression, placing the patient at higher risk for overdose.

## Benzodiazepines and Buprenorphine

Buprenorphine is safer than methadone when used alone due to its "ceiling effect" on respiratory depression. Unlike barbituates, benzodiazepines, when used alone, do not cause respiratory depression. **However, when buprenorphine and benzodiazepines are used concurrently, the protective "ceiling effect" on respiratory drive is eliminated**<sup>[178, 179]</sup>.

## Use in Treatment

Benzodiazepines, opioids and OAT are still being prescribed concurrently. Although there is a theoretical risk of over-sedation or overdose in patients undergoing concurrent opioid and alcohol withdrawal treatment, no research to date has demonstrated clear interactions or quantified the risk of administering these treatments simultaneously. [Nolan] Thus, all MAT patients with AUD should be offered treatment, monitored closely in a setting where methadone or buprenorphine doses can be promptly adjusted and monitored closely for any other adverse effects. [Nolan] An [FDA Drug Safety Communication](#) was issued in 2017 recommending not to withhold MAT for patients who are being treated with benzodiazepines or CNS depressants. The statement recognizes the potential harms of the combined medications, but cautions that these are likely outweighed by the certain harms of withholding MAT. The [Communication](#) also contains recommendations for clinicians to address with patients their use of benzodiazepines and CNS depressants in MAT.

Patients may obtain benzodiazepine illicitly or by prescription from a physician unaware the patient is on MAT. Benzodiazepines and other CNS depressants are often requested to combat anxiety and insomnia associated with withdrawal<sup>[180]</sup>. The MAT physician should meet with a patient who is taking a prescription benzodiazepine or CNS depressant to discuss the risk of overdose and misuse/addiction and to explore the possibility of alternative medical and behavioral treatments. The patient should be asked to sign a release allowing the MAT physician to communicate with the physician prescribing the benzodiazepine or CNS depressants. Because of the potential for overdose when a benzodiazepine is mixed with another/other sedatives, it is appropriate to discuss the risks and benefits of continuing use of the benzodiazepine or depressants with the patient and to make an agreement that use of the medication will be monitored. As well, the physician treating anxiety using benzodiazepines should be made aware that the patient is on opioid agonist therapy. Careful tracking of prescription records using the prescription drug monitoring program (CURES) and urine screening tests provide information that can alert both the MAT physician and the prescribing physician to prescription drug misuse.

Carisoprodol (Soma®), a non-benzodiazepine sedative-hypnotic drug, is a frequently found, concomitantly abused drug. Its use in the context of a maintenance program should be strongly discouraged. The prescribing physician needs to be aware that the patient is on MAT, so the patient should be asked to sign a release allowing communication and coordination with the prescribing physician, using procedures identical to those for benzodiazepines and other CNS depressants. Routine drug screenings do not identify carisoprodol; special testing is required to detect it.

When a patient is using benzodiazepines, alcohol or other sedatives and is seeking admission to MAT or is currently receiving MAT, it is the responsibility of the OTP physician to weigh the risks and benefits of initiating or continuing methadone or buprenorphine given the specifics of the patient's situation. In the event that the risk is felt to be too great (such as when a patient is repeatedly presenting to clinic appearing too sedated to dose or has had ER visits/ICU stays for overdose), an alternative plan for treatment should be offered to safely address the opioid and sedative use disorders.

Recommendations for treating patients with concurrent use of benzodiazepines, other CNS depressants and opioids include<sup>[181]</sup>:

1. Educate patients about the risks (including risk of death) inherent when benzodiazepines, depressants and opioid agonists are combined.
2. Diligently assess for benzodiazepine use, including asking about substances used, dose, and frequency of use.
3. Consider and discuss adjustments in induction procedures and requirements for monitoring patients.
4. For treatment of anxiety, consider use of non-benzodiazepine medications, which have a better safety profile, like SSRIs and SNRIs in combination with behavioral therapy. Benzodiazepines should not be the treatment of choice for anxiety.
5. If a patient has a history of long-term benzodiazepine use, he/she should be evaluated to determine the safest treatment plan. In some, taper/detox and monitoring at

a higher level of care may be indicated prior to initiating OAT. In others, gradually decreasing to the lowest effective dose is indicated.

6. Generally, medication-assisted treatment should not be discontinued for persistent benzodiazepine use, however, close monitoring and risk management strategies should be implemented.
7. Once OAT is initiated, if a patient presents to clinic appearing sedated, consider holding or decreasing the methadone or buprenorphine dose until further medical assessment can be performed.
8. Assessment for diversion or abuse should be carried out regularly for patients with controlled substance prescriptions. Toxicology screening may help to determine whether a patient is taking the prescribed medication and whether illegal drugs are being used. Confirmatory testing should be considered if there are concerns about misuse or substitution.
9. Routine review of the Prescription Monitoring Drug Program, CURES in California, should be carried to confirm one single provider, one single pharmacy and reduce the risk for misuse, abuse or diversion.

### 5.2.5. Cannabis and Cannabinoids

Over the past decades, cannabis use has become almost as prevalent as tobacco use in California. Cannabis contains over 80 cannabinoids. Its effects on the brain are characterized by the altered sense of time, mood, movement, thinking, and memory<sup>[182]</sup>. In the brain, the CB1 receptors are responsible for THC's psych-activity. The CB2 receptors are not psychoactive and are related to the immune system's anti-inflammatory effects. Delta-9-tetrahydrocannabinol (THC) is the psychoactive cannabinoid found in cannabis and likely responsible for the euphoria and increased sociability associated with cannabis use<sup>[183]</sup>. Cannabidiol (CBD), the other cannabinoid of therapeutic interest, is not psychoactive and does not act on the cannabinoid receptors<sup>[183]</sup>. It has effects opposing those of THC. The ratio between THC and CBD is thus important in any cannabis product. The concentration of THC is rising from selective cultivation<sup>[184]</sup>. There are new risks emerging from ongoing use of synthetic cannabinoids, which are compounds created in the laboratory and often sprayed on spices or other organic material that can be smoked or ingested<sup>[184]</sup>.

#### Cannabis and Opioids – A Limited, Mixed Bag

There are only a few things known about cannabis that are supported by scientific findings, even fewer that are relevant to SUD in general and to OUD in particular. Cannabis use among patients receiving opioid agonist therapy in California is highly prevalent. Though cannabis remains classified as a Schedule 1 drug, it is now legal in California. It is imperative to consider the possible effects cannabis use might have on public health. Certain research studies have shown a positive effect of cannabis legalization, particularly among patients receiving opioid agonist therapy<sup>[185]</sup>. Cannabis use has been associated with lower opioid overdose mortality rates, and less opioid use and increased quality of life among patients with chronic pain<sup>[186, 187]</sup>. On the other hand, cannabis use is associated with polysubstance use, impaired cognition, and psychotic episodes and disorders in specific

groups in the population<sup>[188, 189]</sup>. There are harmful impacts on the developing brain that are not seen in the adult brain. In addition, population based studies suggest that using cannabis at baseline is associated with increased rather than decreased use of prescription opioids in follow up<sup>[190]</sup>.

Among patients receiving opioid agonist therapy, research study findings seem to be contradictory. In general, OAT patients tended to use cannabis heavily and are at increased risk of premature dropout from treatment<sup>[185]</sup>. However, other studies have found contradictory evidence. Thus, differences in gender, demographics, and age should be considered. More research is necessary to determine the long-term effects of concurrent cannabis use and OAT.

#### Relevant Clinical Use

Cannabis has primarily been used in combination with opioids for pain relief<sup>[191]</sup> (Academy of Medicine report). Epidemiological evidence suggests use of cannabis may reduce opioid use in some patients, though findings have yet to be demonstrated in a randomized controlled trial.

#### Cannabis Use Disorder

Cannabis use can lead to a SUD, which is likely to increase with its availability and rising potency. Symptoms of cannabis use disorder can include disruptions in daily functioning, tolerance, cravings, and withdrawal symptoms, such as sleep disturbance, restlessness, nervousness, anger, or depression<sup>[192]</sup>. There is ongoing debate about whether or not cannabis is a “gateway drug,” however in practice, it is commonly used in conjunction with alcohol and other substances.

#### Cannabis Adverse Effect

Daily or nearly-daily use has been associated with several adverse health outcomes including anxiety, dysphoria, paranoia, cannabis addiction, poorer cognitive performance, higher association with psychotic symptoms, increased risk of myocardial infarctions, respiratory infections, and higher risk of mouth, tongue, esophagus, and bladder cancer<sup>[193]</sup>.

Still, there can be no argument that the adverse consequences of cannabis are far less than with opioids, which argues in favor of its being a potentially effective harm reduction strategy. Of particular interest are two facts:

1. There are few, if any, deaths by cannabis overdose. This is largely because there are no CB1 receptors in the lower respiratory centers.
2. States with medical cannabis laws have generally seen a fall in opioid overdose deaths.<sup>[194]</sup>

#### Advice to Patients

Physicians might have difficulty deciding how to address the use of cannabis by their patients on MAT. Ideally, share the facts about the lack of evidence and the risks associated with use and impact on recovery. Avoid judgment, but explore fears of stopping cannabis use. Regardless, focus on pragmatic outcomes such as improved functioning in various domains, better mental health, progressing in recovery (being/becoming someone who does not meet criteria for OUD or cannabis use disorder) and participating in the program. After all, if recovery is to be considered, getting high every day is still getting high every day.

# CHAPTER 6

# CONCURRENT MEDICAL CONDITIONS

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## 6.1. Introduction

People who use drugs may experience a wide spectrum of medical complications and typically experience worse health outcomes compared to people who do not use drugs. Some of these conditions are urgent or life threatening. Therefore clinicians in OTPs need to be able to recognize and address these conditions at initial contact and address them even when the sedating and analgesic properties of opioids have the potential to mask symptoms. Chronic conditions that result from drug use may last a lifetime and require the OTP clinician's ongoing care, compassion, and advocacy.

The main objectives of this chapter are to: (1) describe some of the common, urgent needle-related illnesses and other serious medical complications encountered when caring for persons who inject drugs; (2) outline a general approach to the prevention and treatment of viral hepatitis and HIV disease in persons who use drugs; and (3) recommend how to screen for and manage the reportable infections seen more frequently in persons who use drugs. One framework for thinking about the medical complications of drug use organizes conditions according to routes of drug administration; drug contamination or adulteration; drug-specific effects; behaviors or conditions associated with drug use; and co-occurring mental health disorders.

## 6.2. Medical Complications from Routes of Drug Administration

### 6.2.1. Needle-Induced Illness or Injuries

Needle related injuries can be categorized into infections (bacterial, fungal, viral), intravascular reactions (venous thrombosis, arterial insufficiency), cutaneous reactions (tracks, foreign body granulomas), and scarring. The first two require urgent medical attention, and clinicians working with persons who inject drugs need to be able to recognize their presentations and treatment.

#### Needle-related infections

Needle-related infections can be further characterized as local skin and soft tissue infections, systemic infections, or the transmission of infectious viral agents.

Skin and soft tissue infections may present as cellulitis, abscesses, lymphangitis, and septic thrombophlebitis<sup>[195]</sup>. The most common bacterial organisms are Group A streptococcus (GAS) and Staphylococcus aureus. Less common causes are enteric organisms, anaerobes, Clostridia, oral flora, fungi (Candida albicans), and polymicrobial infections. Risk factors for developing abscesses include: subcutaneous or intramuscular drug administration, repeated flushing and pulling back on the plunger while injecting, injecting heroin and cocaine mixtures, injecting frequently, untreated HIV disease; non-sterile injecting equipment, and poor skin hygiene<sup>[196]</sup>.

Differentiating between cellulitis and an abscess is primarily clinical, but can be aided by bedside ultrasonography in unclear cases. An abscess is a localized collection of pus within the dermis and deeper skin tissues. It is indurated, warm, red, and tender, and eventually fluctuant. Staph aureus is the most common pathogen. When not associated with cellulitis, incision and drainage is the main treatment. Antibiotics may be given for complicated abscesses, meaning if they are large or incompletely drained, significantly surrounded by cellulitis, signs or symptoms of systemic infection are present, or the patient is immunocompromised. Cellulitis is an acute spreading infection of the skin, involving the subcutaneous tissues. It presents as an expanding superficial redness with warmth, and tense skin. If untreated with antibiotics, cellulitis may lead to more serious systemic infections. Beta hemolytic streptococci are the most common pathogens and usually respond to beta lactam therapy. Staph aureus is a less common pathogen but may be methicillin resistant. The choice of empiric outpatient treatment of cellulitis should be guided by antibiotic resistance patterns in the community, which can be obtained from a local hospital's antibiogram (see <https://idmp.ucsf.edu/>). Prevention includes use of clean needles and cleaning of skin areas prior to injection.

Necrotizing fasciitis is a deep soft tissue infection characterized by fulminant destruction of the muscle fascia and subcutaneous fat, systemic toxicity, and high mortality (30-80%), even with optimal therapy<sup>[197]</sup>. These infections are polymicrobial (type I) or monomicrobial (type II), predominantly Group A strep and other beta hemolytic strep. The affected area is usually red, swollen, warm, shiny, and exquisitely tender. Subcutaneous gas can be detected as crepitus in type II infections. Rapid progression of skin color changes from red-purple to patches of dusky blue and gray, bullae and frank cutaneous gangrene can develop in a few short days. Necrotizing infections of the skin and fascia are surgical emergencies. The goal of operative management is aggressive debridement until healthy, viable, bleeding tissue is reached. The wound is closed only after all necrotic tissue is completely removed and, in some cases, the resulting defects require allografts and tissue reconstruction. In other cases, amputation may be required to control the infection.

Needle-related systemic infections are among the most serious complications of injecting drug use. Intravenous injection of microbes or particulate matter can result in vascular endothelial damage and infection, most commonly heart valves as with infective endocarditis, but also arteries (e.g., mycotic aneurysms) and veins (e.g., septic thrombophlebitis). In any person who injects drugs and presents with fever, the clinician must seek an endovascular source<sup>[196]</sup>. Other needle-related systemic bacterial infections that require hospitalization include epidural abscess or discitis, osteomyelitis, septic arthritis, and sepsis. These will not be discussed in detail here, but should always be on the differential for febrile patients who inject drugs.

Infective endocarditis (IE) is defined as bacteremia with endocardial involvement and has a high prevalence among febrile persons who inject drugs. It is most often right-sided, involving the tricuspid valve in 70% of cases,

and mortality is high (6%). Predisposing risk factors are colonization with community-acquired methicillin resistant Staph aureus, prior IE, cocaine injection, daily injecting, and untreated HIV disease<sup>[197]</sup>. The most common pathogens are Staphylococcus aureus, followed by streptococci and enterococci. Infective endocarditis may present with fever, dyspnea, pleuritic chest pain, and cough; a murmur may be absent. Complications can range from abscesses and fistulas to septic embolization, pericarditis, and ring abscesses causing heart failure, valve rupture, and death. Serious left-sided complications can occur in the presence of a patent foramen ovale, which allows septic emboli to reach organs like the brain and spleen. Suspicion for endocarditis requires hospital admission. The cornerstones of diagnosis are blood cultures to detect bacteremia, echocardiogram, and clinical observation. Early empiric therapy should cover staph, strep and enterococci. Intravenous vancomycin is the appropriate initial therapy for most patients. Transthoracic echocardiogram is 88-94% sensitive in persons who inject drugs. Confirmed cases require 4-6 weeks of intravenous antibiotics based on in vitro susceptibility, and early consultation with a cardiac surgeon is recommended for potential valve replacement.

### Needle-related viral infections

The most common needle-related viral infections are due to blood contamination by hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV. The "Rule of 3's" is a memory tool to estimate the relative risks of viral transmission from an occupational percutaneous needle stick exposure after a needle is used on an infected patient: HIV (0.3%), HCV (3%), HBV (30%). The probability of acquiring HIV when sharing needles to inject drugs is estimated to be 63 per 10,000 exposures or about 0.6% per act<sup>[198]</sup>. Additional information about the estimated per-act probability of acquiring HIV from an infected source, by exposure act, is provided by the CDC and can be found at: <https://www.cdc.gov/hiv/risk/estimates/riskbehaviors.html>.

Prevention starts with access to sterile injecting and all other drug use equipment including pipes, tourniquets, and water. Skin hygiene and appropriately discarding used equipment are also important. Clinicians at OTPs should screen for these viral infections. HBV infections are preventable with immunizations in those who are susceptible and should be made available wherever persons who use drugs access care. A preventive HCV vaccine is not yet available but under investigation in clinical trials with high-risk negatives. Post-exposure prophylaxis antiretroviral regimens can be given within 72 hours of exposure to blood or other potentially infectious body fluids from a known HIV-positive or high-risk source. Pre-exposure prophylaxis (PrEP) has been associated with an impressive 49% reduction in HIV incidence in a randomized trial of high-risk people who inject drugs in Bangkok<sup>[199]</sup>. Therefore, all persons who inject drugs, and their partners, should be screened and offered PrEP against HIV. National guidelines and free expert telephone consultation services (<http://nccc.ucsf.edu/>) can help clinicians to assess and treat persons with or at risk of viral exposures.

Hepatitis B virus (HBV) is transmitted through percutaneous and mucosal contact with infected blood or body fluids and



will infect a high proportion of persons who inject drugs if they are not immunized in childhood or adolescence. While the rate of new HBV infections declined from 1990–2014 as a result of universal childhood immunization, an increase in HBV incidence since 2014 has been attributed to increasing injection drug use<sup>[200]</sup>. Determining who needs immunization or treatment for chronic HBV infection requires understanding the different serologic courses of infection. The CDC offers free online hepatitis serology training at: <https://www.cdc.gov/hepatitis/resources/professionals/training/serology/training.htm>. All unvaccinated or non-immune patients who are in a drug treatment program should receive HBV immunizations, according to CDC guidelines at <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hepb.pdf>.

The presence of hepatitis B core and surface antibodies generally indicate recovery and immunity from re-infection. The presence of hepatitis B surface antibody alone suggests prior immunization. Some 5-10% of acute adult cases progress to chronic HBV infection, in which both surface antigen and core antibody remain persistently detectable, generally for life. By contrast, 90% of infants infected at childbirth progress to chronic infection. A helpful guide to interpret HBV test results is at: <https://www.cdc.gov/hepatitis/hbv/pdfs/SerologicChartv8.pdf>. While chronic infection is less common than with HCV infection, the prevalence of chronic HBV is still 10-20 times higher among persons who inject drugs than that of the general U.S. population. About 15% of those who become chronically infected as adults die prematurely from cirrhosis or liver cancer, and the majority remain asymptomatic until onset of cirrhosis or end-stage liver disease. The American Association for the Study of Liver Diseases (AASLD) Practice guidelines for the treatment of chronic hepatitis B are useful, updated frequently, and available at: <https://www.aasld.org/publications/practice-guidelines>.

**Hepatitis C virus (HCV)** infection is the most common blood-borne infection in the U.S. with a conservative estimate of 3.5 million chronically infected persons. The prevalence of HCV infection among persons who inject drugs ranges from 38.1% to 68.0%<sup>[201]</sup>, and antibodies to HCV in OTPs range from 67-96%<sup>[202]</sup>. Chronic HCV infection accounts for more than 50% of new cases of hepatocellular carcinoma, which is the fastest-growing cause of cancer-related death, and is one of the leading indications for liver transplantation in the U.S. Death certificate data show that HCV-related deaths have outpaced deaths due to HIV.

The natural history of HCV infection has wide variability. Factors that decrease the risk of progression include female gender and younger age at infection. Factors that increase disease progression include alcohol consumption and co-infection with other viruses, such as HIV and hepatitis B virus (HBV). Once cirrhosis is established, the risk of hepatocellular carcinoma is 1 to 4 percent per year. The care of the OTP patient with cirrhosis requires attention to effects on multiple organ systems. Patients may be greatly debilitated by symptoms that include anorexia, fatigue, muscle wasting, ascites and edema, and bleeding diatheses. In patients at risk of active gastrointestinal bleeding, opioid withdrawal with onset of nausea and

vomiting becomes potentially life threatening. Sudden or abrupt decreases in methadone dose should be avoided. Men with cirrhosis also may experience erectile dysfunction, gynecomastia, and testicular atrophy. High ammonia levels result in encephalopathy, which may cause the patient to demonstrate confusion, memory loss, and erratic behavior. In advanced disease, the liver is unable to metabolize methadone efficiently. The usual methadone dose may need to be gradually reduced to avoid oversedation. Methadone blood levels and clinical observation assist in re-establishing the correct dose.

OTPs have a unique opportunity to screen and assess persons for HCV infection, to educate them about HCV prevention and treatment, and to administer onsite curative treatment. Since only 1 in 5 patients infected with HCV presents with acute symptoms, most infections are diagnosed when chronic, by screening patients who are at risk. Past or present injection drug use is the most important risk factor for HCV acquisition. Screening is recommended for persons who have a history of injecting drugs, persons with specific medical conditions, past recipients of transfusions or organ transplants and persons with a recognized exposure. Screening should also be considered for persons with high-risk sexual behaviors including multiple partners, HCV-positive partners, and men who have sex with men, persons who have received an unregulated tattoo and persons with a history of intranasal drug use. Additionally, people born between 1945 -1965 should be screened at least once regardless of other risk factors<sup>[203]</sup>. See here for a summary of testing recommendations: <https://www.hcvguidelines.org/evaluate/testing-and-linkage>.

In May 2013, the CDC recommended a new testing sequence for diagnosing HCV infections<sup>[204]</sup>. The algorithm shown in Figure 6.2.1. consists of initial testing for HCV antibody, followed by HCV ribonucleic acid (RNA) testing of all positive antibody tests. The HCV antibody test may be performed with a blood specimen that is sent to a laboratory or with a rapid, on-site finger stick. Currently, the HCV RNA test must be drawn as a blood specimen and sent to a laboratory for testing.

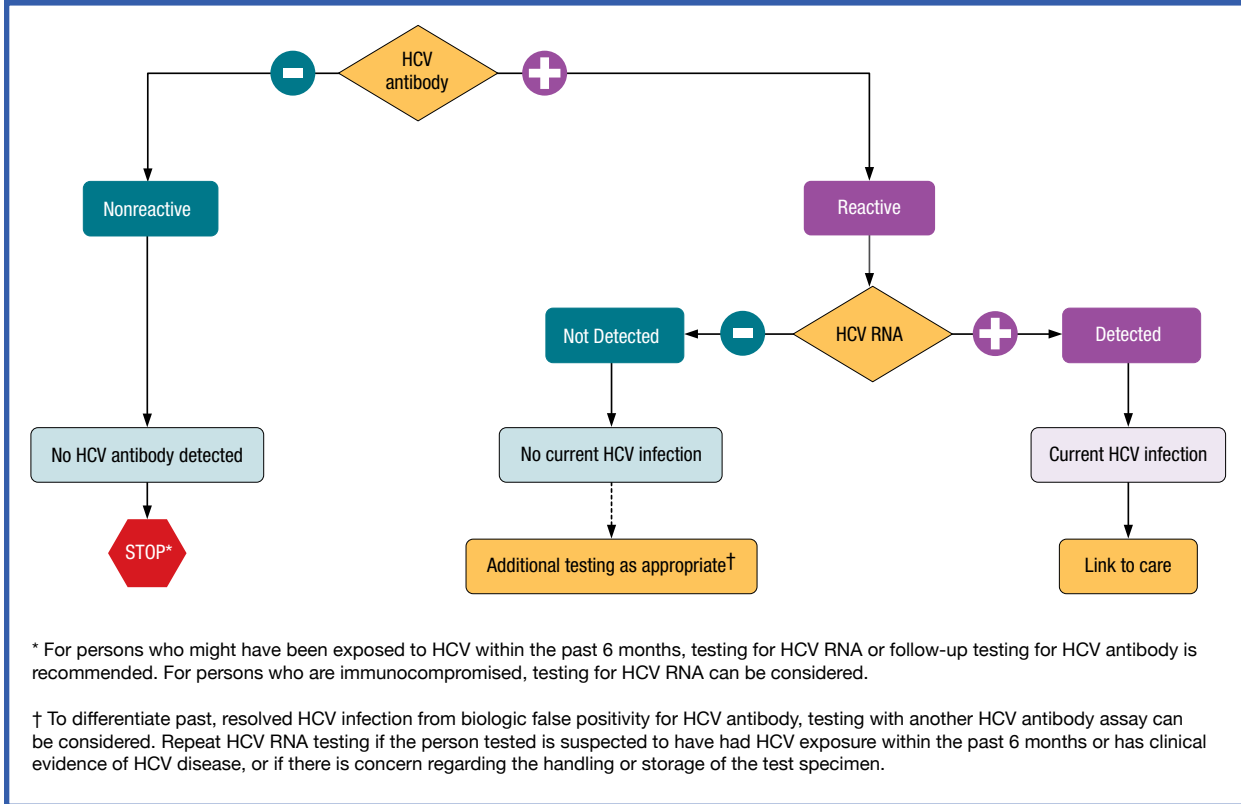
The HCV antibody test detects the presence of antibodies to the virus, indicating exposure to HCV. The HCV RNA test detects the presence (qualitative) or amount (quantitative) of virus to diagnose current infection. Between 20-25% of patients with antibodies to hepatitis C have spontaneously resolved infections (antibody reactive, HCV RNA not detected). In patients with current HCV infection (antibody reactive, HCV RNA detected), a minority of those will develop cirrhosis. For patients whose infections have been successfully treated, subsequent testing will reveal a reactive antibody but undetected HCV RNA. Table 6.2.1 describes the interpretation of HCV test results and further actions.

A model for HCV screening in an OTP has been developed by the Opiate Treatment Outpatient Program at San Francisco General Hospital and may be used as resource for other OTPs (see Table 6.2.2).

The treatment of patients living with chronic HCV is guided by the ability to reduce individual morbidity and

Figure 6.2.1

## Recommended Testing Sequence for Identifying Current HCV Infection



Source: [https://www.cdc.gov/hepatitis/hcv/pdfs/hcv\\_flow.pdf](https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_flow.pdf)

mortality and the risk of transmission to others. Current recommendations include liver protective advice (i.e. HAV/ HBV immunizations, avoidance of hepatotoxic agents like alcohol and large dosages of acetaminophen). Patients should be given medical counsel about the risk of alcohol use. Aggressive intervention, including medications for alcohol use disorder, is recommended for patients who continue to drink alcohol. Referral to a higher level of care may be considered. HCV-infected patients also should receive patient-centered counseling about safer injecting and sexual practices, engagement in medical care for evaluation, and curative treatment with a relatively short course of highly effective and well-tolerated directly acting antiviral (DAA) medications.

The advent of DAA medications in 2011 revolutionized the treatment of chronic HCV infection, such that more than 90% of HCV mono-infected and HIV-HCV co-infected persons can now be cured regardless of HCV genotype with 8-12 weeks of oral therapies, most of which are taken as once daily doses. The AASLD now recommends treatment for all patients with chronic infection who have a life expectancy greater than 6 months. Co-infected patients ideally are initiated on treatment for HCV following establishment of HIV viral suppression and treated using the same medications as HIV uninfected patients. OTP clinicians providing treatment for co-infected patients will need specific and ongoing training to review possible drug-drug interactions

before starting HCV medication. Frequently updated AASLD guidelines for the treatment of mono-infected and co-infected patients and drug-drug interactions can be found at: <https://www.hcvguidelines.org/>.

Historically, patients who injected drugs were denied HCV treatment. However, given new evidence about the effectiveness of treatment in PWID and the importance of treatment as prevention, **persons who actively inject drugs are among the highest priority populations for treatment in California** <sup>[206]</sup>. Therefore, all persons with current HCV infection should be linked to care, which increasingly can be delivered within the OTP. Indeed, HCV treatment has been delivered successfully to individuals in a number of OTP clinics across the country that integrate the identification, evaluation, and treatment of HCV under one roof <sup>[207]</sup>. Addiction treatment programs can play a significant role in HCV elimination, and their involvement is strongly encouraged in the American Society of Addiction Medicine policy statement on HCV infection <sup>[208]</sup>. **Model programs** typically offer directly observed treatment (DOT) to facilitate HCV medication adherence, support patients who are undergoing treatment, and educate patients about how to avoid reinfection once cured.

No clinically significant drug interactions are expected between methadone and most DAAs. Small increases in the methadone dose are sometimes required during

Table 6.2.1

## Interpretation of Test Results for HCV Infection and Further Actions

TEST OUTCOME	INTERPRETATION	FURTHER ACTIONS
<b>HCV antibody nonreactive</b>	No HCV antibody detected	Sample can be reported as nonreactive for HCV antibody. No further action required.  If recent exposure in person tested is suspected, test for HCV RNA.*
<b>HCV antibody reactive</b>	Presumptive HCV infection	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
<b>HCV antibody reactive, HCV RNA detected</b>	Current HCV infection	Provide person tested with appropriate counseling and link person tested to care and treatment.†
<b>HCV antibody reactive, HCV RNA not detected</b>	No current HCV infection	No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations,§ follow up with HCV RNA testing and appropriate counseling.

\* If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.

† It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.

§ If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Source: [https://www.cdc.gov/hepatitis/hcv/pdfs/hcv\\_graph.pdf](https://www.cdc.gov/hepatitis/hcv/pdfs/hcv_graph.pdf)

treatment with the less commonly used DAAs, boceprevir and telaprevir. In addition, no clinically significant drug interactions are expected between buprenorphine and most commonly covered DAAs in 2018 (e.g., elbasvir/grazoprevir, glecaprevir/pibrentasvir). Concentrations of buprenorphine may increase when administered with other common DAA regimens containing ledipasvir, velpatasvir, and voxilaprevir; however, this is a potentially weak interaction unlikely to be of clinical significance; additional action or monitoring is unlikely to be required. Review of specific drug-drug interactions, particularly for HIV-HCV co-infected patients, can be conducted in consultation with a pharmacist or by use of various online tools: <https://www.hep-druginteractions.org/checker>.

HCV cure is defined as sustained virologic remission with an undetectable HCV RNA test at 12 weeks after treatment (SVR-12). Persons who achieve SVR-12 should be monitored for re-infection at least annually and more frequently when reporting risk behavior. Cured persons with cirrhosis should continue to be monitored every 6 months by ultrasound for the development of hepatocellular

carcinoma (HCC). Patients that develop decompensated cirrhosis or non-metastatic HCC may require liver transplantation. Notably, liver transplant outcomes are improved with DAA-treated patients, and there are OTP patients who have received liver transplants. Some transplant services do not accept patients on methadone treatment. In this situation, the role of the OTP clinician is essential as an advocate on behalf of the patient.

Free clinician-to-clinician consultation on HCV mono-infection and coinfection management is available from the UCSF Clinician Consultation Center at: <http://nccc.ucsf.edu/clinician-consultation/hepatitis-c-management/>

### HCV Provider Education Resources:

- Addiction Technology Transfer Center, HCV Current Initiative  
[http://atcnetwork.org/projects/HCV\\_Home.aspx](http://atcnetwork.org/projects/HCV_Home.aspx)
- Association for the Advanced Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV Treatment Guidelines  
<http://www.hcvguidelines.org/>

Table 6.2.2

## A Model for HCV Testing in an Opioid Treatment Program

With only 24% of substance use treatment programs across the United States offering HCV testing in 2012 <sup>[205]</sup>, OTPs offer the ideal setting to screen for HCV in this highest risk population. Co-localization of treatment for OUD with screening for infectious diseases that are more prevalent among persons who inject or use drugs has been effective in identifying and treating both HIV and HCV. An OTP has the following advantages for integrating services:

- The OTP is often the patients' setting of choice for care.
- TB and syphilis screening are mandated at intake and annually, and can be linked to HCV screening.
- Frequent if not daily attendance is required initially, allowing for close follow up for results and referrals.
- Counseling services are on site.
- Maintenance treatment with methadone or buprenorphine has been shown to reduce HCV incidence among young people who inject drugs by 60% and has the potential to reduce HCV reinfection and support HCV treatment.

The goals of a model testing program are to provide universal, opt-out testing for HCV, identify persons with chronic HCV and refer for treatment, provide risk reduction education and counseling, and do this with minimal additional workload. A laboratory algorithm and process steps are depicted in the three diagrams below. Key elements to consider:

- If phlebotomy for mandated labs (TB and syphilis) is not performed onsite, coordination with the OTP's service lab may be needed for HCV lab testing.
- Provide education and training for the medical staff who will order and review labs, and for the counseling staff on HCV risk, risk reduction, results disclosure and linkage to HCV care and treatment.
- Identify a project champion to promote and monitor the HCV screening, testing, and linkage program.
- Expect 15-20% HCV antibody positivity and 60-75% HCV RNA positivity in an OTP setting, along with the associated high volume of HCV treatment linkage.
- OTPs licensed to offer clinical care, such as hospital-based programs, may consider offering on-site HCV treatment, including directly observed therapy.
- Establish relationships with HCV treatment providers as part of program implementation (or alert medical provider partners to the program to prepare them for HCV-related referrals/linkages).

- U.S. Centers for Disease Control and Prevention (CDC), Division of Viral Hepatitis  
[www.cdc.gov/hepatitis](http://www.cdc.gov/hepatitis)
- California Department of Public Health Office of Viral Hepatitis Prevention  
[www.cdph.ca.gov/programs/pages/ovhp.aspx](http://www.cdph.ca.gov/programs/pages/ovhp.aspx)
- Hepatitis B and Hepatitis C Screening Toolkit for Primary Care Providers  
<https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/HepatitisBandCScreeningToolkitforPrimaryCare.pdf>
- Clinical Care Options  
<http://www.clinicaloptions.com/hepatitis.aspx>
- Hepatitis C Online (University of Washington)  
<https://www.hepatitisc.uw.edu/>
- Medi-Cal Hepatitis C Treatment Policy  
<http://www.dhcs.ca.gov/Pages/HepatitisC.aspx>
- National Clinical Consultation Center – Hepatitis C Warmline
- Access the Warmline toll-free at: 1-844-437-4636

(Monday-Friday, 9 a.m. - 8 p.m. ET).

<http://nccc.ucsf.edu/clinician-consultation/hepatitis-c-management/>

- University of California San Francisco, HCV Project ECHO  
<http://echo.ucsfhealth.org/>

Human immunodeficiency virus (HIV) infection is transmitted through percutaneous and mucosal contact with infected blood or body fluids, most commonly through risky sexual behaviors and sharing needles, syringes, and other injecting equipment. An estimated 1.1 million people in the U.S. were living with HIV at the end of 2015, and as many as 15% were unaware of their infection <sup>[209]</sup>. Men who have sex with men are most severely affected, and blacks or African Americans face the most severe burden of disease. While the number of AIDS diagnoses in persons who inject drugs (PWID) peaked in the U.S. in 1993, injecting drug use still accounts for about one-third of all HIV infections. Annual HIV diagnoses among black and Hispanic/Latino PWID decreased by about 50% between 2008–2014, but diagnoses among white PWID dropped by only 28% between 2008–12 and not at all between 2012–14 <sup>[210]</sup>. An outbreak of HIV in the small, rural town of Austin, Indiana in 2014 underscored the changing landscape of injecting drug use and HIV risk in nonurban areas where

access to syringe service programs and addiction treatment are scarce.

Figure 6.2.4 is the New CDC Recommendations for HIV Testing in laboratories and describes the natural history of HIV infection, which until the development of effective combination antiretroviral therapy (ART) in 1996 led almost uniformly to death. While ART cannot cure HIV, it reduces the amount of virus in the body, protects the immune system, prevents disease progression to AIDS, and reduces HIV transmission. Diagnosis of HIV infection is delayed more often among persons who inject drugs, persons of color, and older adults than in other populations—many of whom develop AIDS-defining illnesses within 1 year of diagnosis. Some patients entering substance use treatment have never been tested for HIV or hepatitis because they are very fearful that they may already have one or both of these infections and have decided that if they do, they would rather not know. The stigma of HIV and addiction are significant barriers to the detection and effective treatment of both diseases.

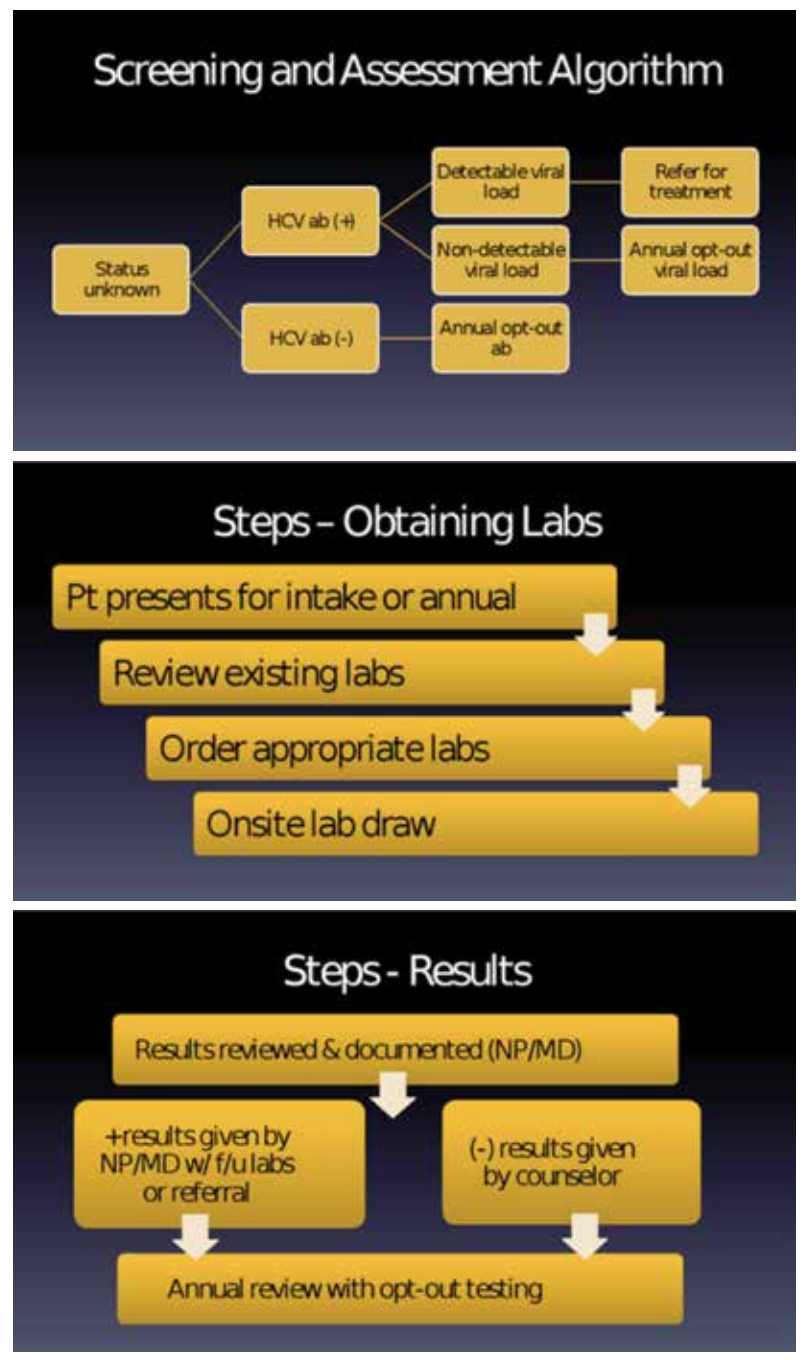
To reduce diagnostic and treatment delays, the CDC recommends opt-out HIV testing at least once as a routine part of medical care for everyone aged 13-64 and testing at least once a year for people at high risk for HIV [211]. This guidance applies to OTPs in the private and public sectors. HIV testing should be encouraged and offered annually on-site if possible.

There are three main types of HIV tests: (1) antibody tests, (2) combination antibody/antigen tests, and (3) nucleic acid tests (NAT) [212]. Antibody tests check blood or oral fluids for HIV antibodies only. The window period for antibody tests is somewhere between 3-12 weeks from the time of infection. A combination 4th generation assay that detects HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen from serum or plasma specimens reduces the window period to between 2-6 weeks. This antibody/antigen assay is being used more commonly and is recommended for all HIV testing done in labs. When combined with a NAT, the recommended HIV testing strategy (Figure 6.2.4.) permits earlier detection of infection by as much as 3-4 weeks.

The U.S. DHHS recommends

Figure 6.2.2

## HCV Screening and Assessment Algorithm



immediate initiation of ART for all persons with HIV regardless of CD4 cell count to achieve the primary goal of reducing the morbidity and mortality associated with HIV infection. An important secondary goal of treatment is to prevent HIV transmission [213]. With an increasing

array of co-formulated regimens with fewer toxicities, many patients can take a single pill once daily to achieve viral suppression. HIV disease in PWID can be treated successfully and with great public health impact. British Columbia enhanced its outreach through “test and treat” programs,

Figure 6.2.3

## New Treatments for Hep C

**Living with Hep C?**  
**New treatments**  
**have changed the game.**

**Got Hep C? Help is through these doors.**

**There is new hope for people with Hep C**  
**Come visit us. Talk about the new treatments. Get tested.**

Opiate Treatment Outpatient Program  
Zuckerberg San Francisco  
General Hospital and Trauma Center  
595 Potrero Ave  
Building 90, 3rd floor  
San Francisco 94110  
(415) 206-3364 / otop@endhepcsf.org  
For more info, visit [www.endhepcsf.com](http://www.endhepcsf.com)

**END HEP C SF**

ZUCKERBERG  
SAN FRANCISCO GENERAL  
Hospital and Trauma Center

Source: <http://www.endhepcsf.org/portfolio-items/opiate-treatment-outpatient-program/>

and demonstrated an association between expanded ART coverage, decreased community HIV viral load, and a 50% reduction in new HIV diagnoses among PWID. For persons with opioid use disorders and HIV, life-saving ART has been administered with methadone at OTPs efficiently and effectively as directly observed therapy (DOT) by dispensing nurses.

Patients and providers are often concerned about potential drug interactions between opioid agonist pharmacotherapies and HIV medicines. The two most clinically significant interactions occur with ART medications that are no longer among the recommended initial

regimens for most people living with HIV: (1) the induction of methadone metabolism by efavirenz (EFV); and (2) the inhibition of buprenorphine metabolism by ritonavir-boosted atazanavir (ATV)/r.

Updated drug interaction information is available at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview>

Protease inhibitor class: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/284/pi-drug-interactions>

Non-nucleoside reverse transcriptase inhibitor class: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/285/nnrti-drug-interactions>

<https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/286/nnrti-drug-interactions>

Nucleoside reverse transcriptase inhibitor class: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/287/insti-drug-interactions>

Integrase inhibitor class: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/287/insti-drug-interactions>

HIV care is rapidly evolving and requires open communication and partnership between patients and providers. For in-depth recommendations on high-quality HIV care to guide individual medical decision-making, the U.S. DHHS frequently updates national guidelines at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0>. Free peer-to-peer expert advice on the management of all aspects of HIV also is available to clinicians from the UCSF Clinician Consultation Center at <http://nccc.ucsf.edu/clinician-consultation/hiv-aids-management/>.

### 6.3. Medical Complications Caused by Drug Contaminants or Adulterants

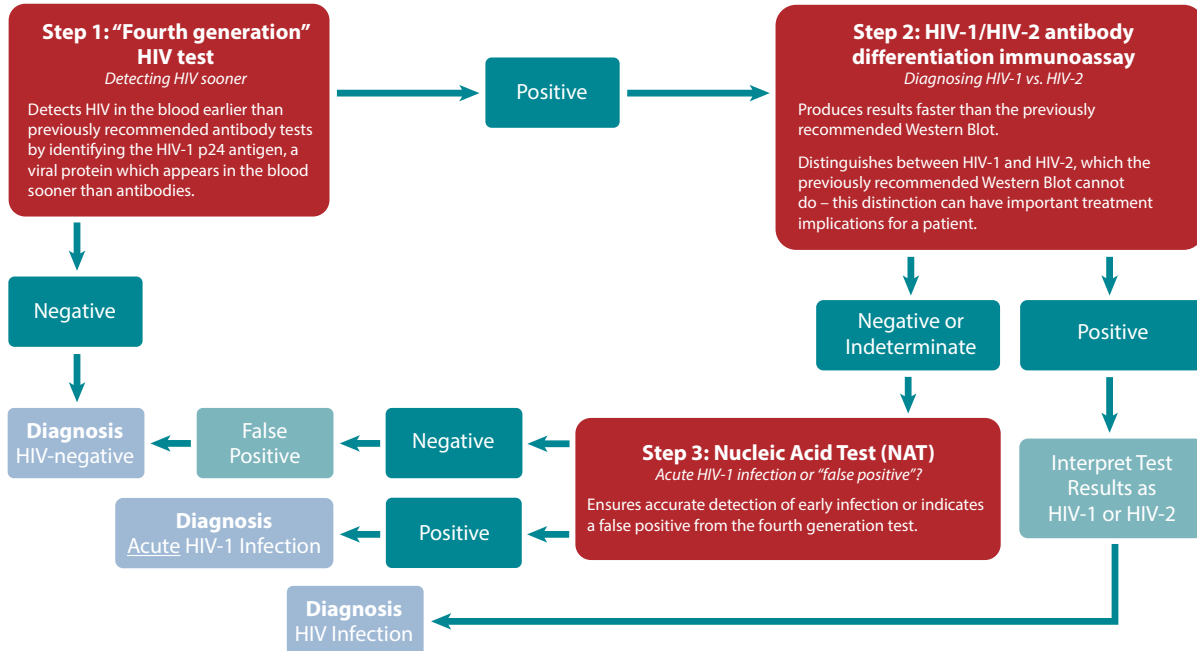
Contamination or adulteration of drugs can lead to severe illness or death in persons who use drugs. Examples of infectious agents that are known to have contaminated the heroin supply include *clostridia* species and *anthrax* [214]. In California and other western states, the contamination of black tar heroin with spores of the anaerobic bacteria *Clostridium* has been associated with outbreaks of wound botulism, tetanus, and necrotizing infections [215]. *C. botulinum* produces a potent exotoxin that binds to the presynaptic membrane and irreversibly disrupts acetylcholine release at peripheral cholinergic synapses. An acute descending paralysis involving autonomic and cranial nerves presents as dysarthria, diplopia, dyspnea, and progressive dysphagia that may require intubation. Ptosis, skin abscesses, sluggish pupils, and 6th cranial nerve palsies also can be seen on the

Figure 6.2.4

## New CDC Recommendations for HIV Testing in Laboratories

CDC's new recommendations for HIV testing in laboratories capitalize on the latest available technologies to help diagnose HIV infections earlier – as much as 3-4 weeks sooner than the previous testing approach. Early diagnosis is critical since many new infections are transmitted by people in the earliest (“acute”) stage of infection.

By putting the latest testing technology to work in laboratories across the United States, we can help address a critical gap in the nation's HIV prevention efforts.



This graphic is designed to illustrate key concepts of the new testing approach in laboratories. For more detail, please see the full guidelines here: <http://www.cdc.gov/hiv/pdf/HIVtestingAlgorithmRecommendation-Final.pdf>.

Source: <https://www.cdc.gov/nchstp/newsroom/docs/2014/hiv-testing-labs-flowchart.pdf>

physical exam <sup>[216]</sup>. *Clostridium botulinum* may be detected in serum and cultured from abscess specimens. While an antitoxin is available, toxin production in situ may still require aggressive wound debridement.

Adulterants are substances deliberately added to bulk, dilute, complement, or enhance a drug's effects <sup>[217]</sup>. These substances range from sugars and acetaminophen as bulking agents to more active substances, such as lidocaine in cocaine and fentanyl in heroin. Levamisole is an anthelmintic and immunomodulatory agent that may have noradrenergic effects and has been an adulterant in cocaine since at least 2003. In 2010, it was detected in about three-quarters of all the cocaine seized by the Drug Enforcement Agency and nearly all (88%) of the cocaine-metabolite positive urine specimens tested at San Francisco General Hospital <sup>[218]</sup>. Thus far, levamisole is clearly involved in three debilitating autoimmune-mediated syndromes: agranulocytosis, thrombotic cutaneous retiform purpura, and pauci-immune crescentic glomerulonephritis. They can occur together or separately and are associated with an ANCA-positive vasculopathy. Treatment consists of discontinuing the offending agent, and symptoms may recur after re-exposure. In 2018 in Illinois, adulteration of synthetic cannabinoids with brodifacum (an anticoagulant rat poison) led to multiple fatalities from hemorrhage.

Adulteration of the heroin supply with fentanyl analogues has led to an opioid overdose epidemic in the U.S. OTP staff may want to become familiar with fentanyl test strip technology, so that they can distribute test strips to patients as part of overdose prevention training. Useful results from a test strip pilot study can be found at: <http://harmreduction.org/issues/fentanyl/>. Fentanyl contamination has now spread beyond heroin to cocaine, methamphetamine, and street purchased opioid and benzodiazepine pills. Users of any street drugs should be counseled on this risks and provided with naloxone for overdose reversal.

### 6.4. Medical Complications Due to Drug-Specific Effects

There are numerous medical complications due to the specific effects of drugs. Opioids not only cause central respiratory depression but also affect endocrine and gastrointestinal systems. Stimulants have profound detrimental cardiac, neuropsychological, and renal effects. Alcohol is an established carcinogen that also causes gastrointestinal and neurologic disease. Tobacco use causes heart disease, stroke, chronic lung disease and is the leading cause of cancer and cancer deaths.

In the U.S., poisoning is the leading cause of death from injuries. The overwhelming majority are due to pharmaceutical and illicit opioids [219]. In 2016, there were more than 63,600 drug overdose deaths in the U.S., five times higher than in 1999. In 2015, annual drug overdose deaths surpassed the number of AIDS deaths at the height of the HIV epidemic in 1995. Increases in drug overdose deaths are involving not only heroin and synthetic opioids but also cocaine and psychostimulants.

The classic toxidrome of opioid overdose is apnea, stupor, and miosis, and the sine qua non is respiratory depressions. In opioid analgesic overdoses, clinicians should beware of multiple organ system involvement, altered pharmacokinetics that prolong intoxication, and the duration of action of different opioid formulations [221]. Overdoses are commonly the consequence of a higher dose or more potent formulation, the concurrent use of sedative hypnotics (e.g., alcohol, benzodiazepines), reduced opioid tolerance, or adulteration of the drug supply. At the community level, extraordinary efforts have been undertaken to train laypersons in the use of naloxone to reverse opioid overdoses. In addition to harm reduction and needle and syringe programs, hospitals, medical clinics (including OTPs) and physicians' offices have become effective venues for naloxone training and distribution to reach a wider population at risk for opioid overdose. The Drug Overdose Prevention and Education (DOPE) Project offers basic and comprehensive service provider trainings on overdose prevention: <http://harmreduction.org/issues/overdose-prevention/dope-sf/>.

## 6.5. Hypogonadism

**Research and clinical evidence suggest that all opioids, including methadone, impact gonadal function in both male and female patients. Opioids interfere with gonadal hormone regulation in two ways: they inhibit hypothalamic gonadotropin-releasing hormone (GnRH), resulting in reduced secretion of LH and FSH, and they exert direct effects on testicular and ovarian function. The net result is a decrease in testosterone and estrogen and an increase in prolactin levels.**

Different opioids have hypogonadal and androgen-inhibiting effects to varying degrees. It appears that methadone has a greater impact on gonadal hormones than buprenorphine [222], and that higher doses of methadone have a greater effect than lower doses. Hypogonadism should be considered in all patients receiving daily opioid treatment in amounts equal to or greater than 100 mg morphine equivalents (~25 mg methadone) [223]. Because of the hypogonadal effects of opioids, both men and women on methadone treatment may experience weight gain, fatigue, depression, sexual dysfunction, hot flashes and increased sweating. Problems with decreased libido and sexual dysfunction may interfere with therapeutic adherence to methadone treatment. Clinical experience suggests that sexual difficulties may prompt some patients on methadone to use stimulants to enhance sexual interest and performance.

Clinical presentation, diagnostic testing and treatment recommendations are gender specific.

Figure 6.4.1

### Age-adjusted Drug Overdose Death Rates, by Opioid Category: United States, 1999–2016 [220]

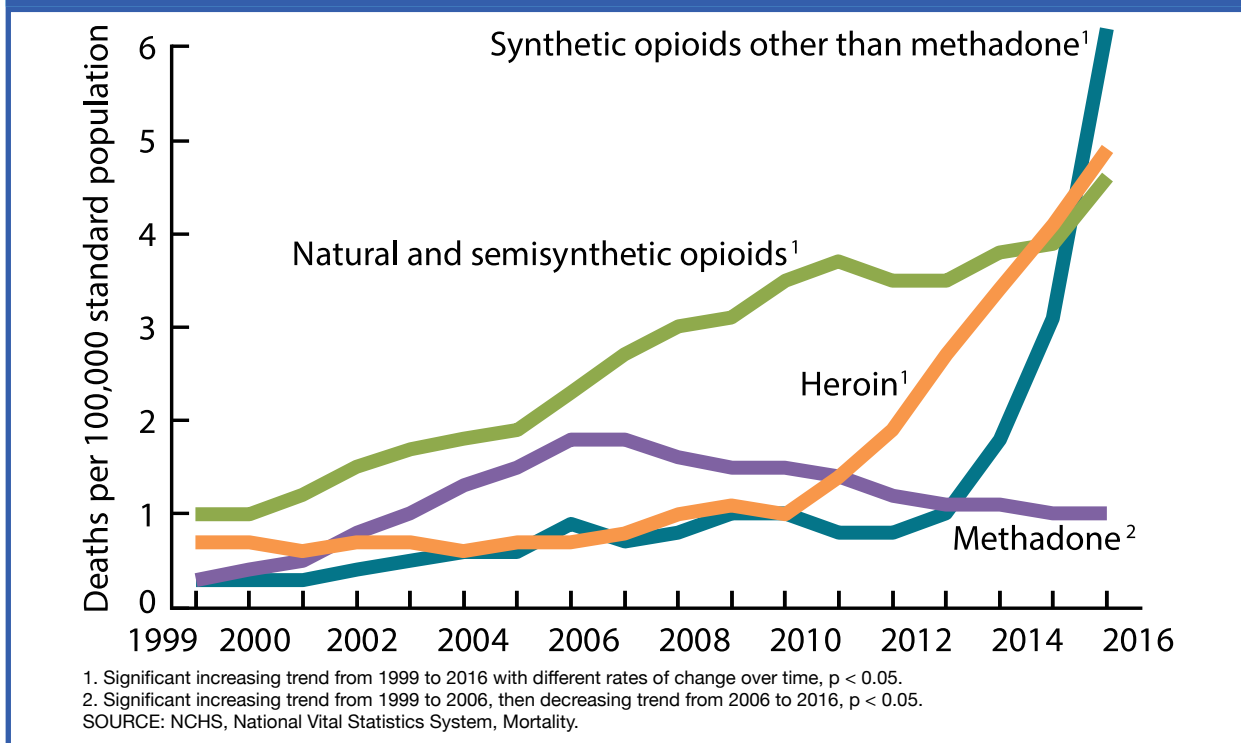




Table 6.5.1

### Screen Questions for Hypogonadism

- Have you experienced a decrease in sex drive?
- Have you noticed a decreased enjoyment in life or have you become depressed?
- Have you gained weight?
- Have you noticed increased sweating?
- Are you experiencing hot flashes?
- Have you noticed a lack of energy, strength, or endurance?
- Are you having difficulty with erections (men)?
- Have your menstrual periods become abnormal (pre-menopausal women)?

#### 6.5.1. Male patients

Many men on MMT complain of decreased libido and erectile dysfunction. While hypogonadism is a likely explanation, other risk factors for erectile dysfunction are common in this population and include use of tobacco and/or alcohol and chronic medical conditions, such as diabetes or hypertension.

There is a high prevalence of reduced bone mineral density in men on methadone, which may be related to chronic low testosterone levels. Other risk factors for reduced bone mineral density are common in this population and include use of tobacco, alcohol or anabolic steroids or HIV disease. Mild anemia may be seen as testosterone maintains red blood cell production.

OTP practitioners should strongly consider screening patients by history and physical examination, laboratory testing and imaging (DEXA bone scan). For symptomatic male patients, a medical work-up is recommended. The workup may include laboratory testing for luteinizing hormone (LH), follicular stimulating hormone (FSH), total testosterone (TT), free testosterone (FT), estradiol (E2), dihydrotestosterone (DHT) and prolactin. Blood samples should be drawn early in the morning as testosterone levels vary during the day. Referral to an endocrinologist may be indicated for diagnostic and treatment recommendations including testosterone replacement.

Testosterone replacement in men with hypogonadism results in significant improvements in libido, sexual function, depression and hematocrit. Replacement can occur with topical or injected treatment. Due to the fact that testosterone can be diverted, OTP providers may need to work with consulting teams, helping them to develop safe and medically sound plans and advocating on behalf of patients with consulting teams in order to develop safe and medically sound plans. Testosterone replacement is also associated with mild decreases in pain scores. Unfortunately, illicit opioid usage does not change with testosterone replacement<sup>[224]</sup>. Patients should be evaluated for elevated hematocrit, prostate cancer, and obstructive sleep apnea, among other conditions, both prior to and during treatment. For males with decreased bone density, treatment with bisphosphonates or testosterone (in those who also have hypogonadism) may be indicated.

#### 6.5.2. Female patients

In addition to opioid-induced impairment of GnRH production and impaired ovarian steroidogenesis, opioids also interfere with adrenal androgen production, which may produce a clinically significant deficiency in women. There is decreased adrenal production of dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS,) and androstenedione, which are themselves androgenic and are precursors of testosterone.

Many women on methadone treatment experience decreased libido and menstrual irregularities (amenorrhea and oligomenorrhea). Women with irregular menses may mistakenly believe they cannot become pregnant; others suspect they are pregnant when they are not. In view of the frequency of irregular menses in this population and the complications of pregnancy in the setting of substance use, discussions regarding patient preferences for family planning and the necessity of prompt identification of pregnancy are important. There is a trend toward menstrual cycle normalization when patients stay in methadone maintenance treatment long-term<sup>[225]</sup>. There is no definitive evidence for reduced bone mineral density in women.

For symptomatic female patients, a medical work-up is recommended. The patient's reproductive history and menstrual cycle history, both prior to and after the administration of methadone, are important. Luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels in pre-menopausal women change with the menstrual cycle, so are of limited value in diagnosing androgen deficiencies. Pre-menopausal women with absent menses should be screened for pituitary abnormalities by checking prolactin levels, after ruling out pregnancy and thyroid dysfunction. Testosterone deficiencies in women are an area of controversy; there is little agreement about testosterone reference levels. DHEAS levels may be the best indicator of androgen production when a woman's clinical findings suggest androgen deficiency. Referral to an endocrinologist or gynecologist may be indicated to identify or rule out other medical conditions that can cause amenorrhea or oligomenorrhea and/or for treatment recommendations.

## 6.6. Public Health-related Reportable Infections

Infections with significant public health impact are seen in higher frequency in persons who use drugs. Therefore, in addition to syphilis and tuberculosis, screening should be done for HIV, HBV, and HCV testing, and when indicated, other sexually transmitted infections. Immunizations should be provided to OTP patients that are susceptible to HAV and HBV. Annual testing of OTP patients for syphilis and tuberculosis is mandatory by Federal and State regulations.

### Syphilis

**Syphilis** is a systemic sexually transmitted disease caused by the spirochete bacterium, *Treponema pallidum*. Syphilis infection is a medical complication of behavior associated with drug use. Outbreaks in men who have sex with men have been attributed in part to methamphetamine or alcohol as disinhibiting agents that lead to high risk sexual activity. **Rates** of syphilis have been increasing since 2001. Without treatment, patients remain chronically infected and progress through active clinical stages interrupted by periods of latent infection. Chronic disease can cause significant morbidity, affect multiple organ systems, and even result in death, including fetal demise in untreated pregnant women.

The CDC has published resources, which OTP providers may find useful when discussing STIs with their patients. **Tips and tools for providers** include:

- **Guide** to taking a thorough sexual history and list of essential sexual health questions to ask of patients
- Tips for productive conversations with patients
- Guidelines for testing and treatment

There are two types of serologic tests for syphilis;

treponemal and non-treponemal. Both are required for diagnosis. Non-treponemal tests (i.e. VDRL, RPR) are labor intensive to perform, may take days to be resulted, can have low sensitivity and false positive results. Results are reported as a qualitative result and a quantitative titer, which usually corresponds with disease activity. A four-fold change in titer is clinically significant. Newer assays that detect treponema-specific antibodies can be performed more easily and have high sensitivity but cannot be used to assess disease activity or treatment response. Treponemal tests include T. pallidum particle agglutination (TP-PA), fluorescent treponemal antibody absorption (FTA-ABS), and other enzyme or chemiluminescent immunoassays. Many laboratories now offer a reverse syphilis testing algorithm where a treponema-specific test is used for screening, followed by a non-treponemal test to assess disease activity and treatment status. Local health departments can often provide information on whether the patient has been reported as having had syphilis in the past, including reported serologic test results and treatment history.

Patients with primary, secondary or early latent syphilis, or syphilis of unknown duration with a nontreponemal titer greater than 1:32 should be referred to the local health department's STD program for interview, partner elicitation, and partner follow-up. It is a public health priority to follow up patients with early syphilis. All states require that persons diagnosed with syphilis infections be reported to public health authorities. Reporting can be provider-based or laboratory-based.

Syphilis infections can be divided into a series of **clinical stages** that are used to help guide treatment and follow-up. Long-acting benzathine penicillin G is the preferred drug for treating all stages. An intramuscular injection of 2.4 million units will cure a person with primary, secondary or early latent syphilis. An appropriate treatment response is a fourfold decline in non-treponemal titer 6-12 months after treatment. Three doses of the benzathine penicillin G at weekly intervals is recommended for the treatment of

Table 6.5.2

### Opioid-Induced Deficiencies

Hypogonadism	Adrenal Androgen Deficiency	Symptoms
<ul style="list-style-type: none"> <li>■ Decreased GNRH</li> <li>■ Decreased LH</li> <li>■ Decreased Testosterone</li> </ul>	<ul style="list-style-type: none"> <li>■ Decreased DHEA</li> <li>■ Decreased DHEAS</li> <li>■ Decreased Androstenedione</li> </ul>	<ul style="list-style-type: none"> <li>■ Anemia</li> <li>■ Decreased Libido</li> <li>■ Decreased Muscle Mass</li> <li>■ Depression</li> <li>■ Erectile Dysfunction</li> <li>■ Fatigue</li> <li>■ Hot Flashes</li> <li>■ Menstrual Irregularities</li> <li>■ Osteoporosis</li> <li>■ Sweating</li> <li>■ Weight Gain</li> </ul>

late latent syphilis or latent syphilis of unknown duration. The CDC's 2015 STD Treatment Guidelines provide detailed information about the diagnosis and treatment of syphilis, including special considerations for pregnant women, neurosyphilis, and HIV coinfection: <https://www.cdc.gov/std/tg2015/syphilis.htm>. In addition, a self-study module is available as a free online learning experience that helps clinicians learn how to manage syphilis. It is frequently updated and integrates the CDC's most recent STD Treatment Guidelines: <https://www.std.uw.edu/custom-self-study/syphilis>.

## Tuberculosis

Tuberculosis is a disease caused by the bacterium *Mycobacterium tuberculosis* (MTb). Mycobacteria are transmitted through the air, inhaled, and usually attack the lungs, but they also can attack any part of the body, such as the kidney, gut, spine, and brain. Untreated TB disease can be fatal, and was once the leading cause of death in the U.S. Persons who inject drugs are at high risk for contracting TB and more likely to progress from latent TB infection (LTBI) to active TB disease. This higher risk of active pulmonary TB disease results from crowded living conditions, delays in diagnosis, lower treatment adherence, drug sharing practices, and a higher prevalence of HIV disease. OTP staff should be instructed to be alert to coughing patients. The patient may be provided with a mask to cover his or her mouth. Coughing patients should be interviewed promptly regarding the common symptoms of TB (current cough, fever, weight loss or night sweats). Patients who are symptomatic require prompt screening by CXR. All OTP staff and patients should be screened with symptom review and testing annually unless they have a history of prior infection. Patients and staff with a prior TB infection are screened by symptom review and chest x-ray.

There are two testing methods for the detection of MTb infection: tuberculin skin tests (TST) and interferon-gamma release assays. A 2-step TST algorithm reduces the likelihood that a boosted reaction to a subsequent skin test will be misinterpreted as a recent infection.

A skin test reaction, the diameter of induration, is measured 48-72 hours after PPD placement and is recorded in millimeters. The skin test result depends on the size of the induration and on the person's risk of TB infection and progression to TB disease, if infected. For persons who inject drugs, a positive skin test is 10 or more mm of induration. For persons with HIV disease, a positive test is 5 mm or more of induration. Positive skin tests among PWID range from 14-28% in the U.S. OTP staff require special training to demonstrate proficiency in the administration and interpretation of the TST, and they should be familiar with the criteria for classifying positive TST reactions: <https://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.htm>

The second testing method for MTb infection is the interferon gamma release assay (IGRA), which measures the immune response to TB proteins in whole blood. Compared to the skin test, the IGRA may be preferable

in the OTP setting for a number of reasons: (1) a second visit is not required to read the patient's test result, (2) the test does not boost responses in subsequent tests, and (3) it will not give a false-positive result for patients with a history of BCG vaccination. However, the test does require a blood draw, which may concern patients with poor venous access, but it can be drawn at the same time as the mandatory syphilis test.

Persons with a positive TB screening result should receive a chest radiograph. Sputum cultures should be collected from those with an abnormal chest radiograph or symptoms. These steps will help differentiate whether a patient should be treated for LTBI or TB disease (see Table 6.6.1). Failure to make this determination risks inadequate treatment and development of drug resistance.

**Latent tuberculosis infection (LTBI)** is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB. LTBI treatment is essential to controlling and eliminating TB disease in the U.S.

Patients with a normal chest film should receive treatment for LTBI. In HIV positive patients, this should be a 9-month course of isoniazid (INH) prophylaxis (see Table 6.6.2), which substantially reduces the risk that infection will progress to active disease. The addition of pyridoxine (vitamin B6) reduces the incidence of INH-associated peripheral neuropathy. In non-HIV positive patients, options include 6 months of isoniazid, 12 weekly doses of rifampentine and isoniazid over a 3-month period, or 4 months of rifampin—however rifampin can substantially affect methadone metabolism and should be avoided if possible. OTPs that can deliver these regimens as DOT provide an ideal opportunity for maximizing medication adherence.

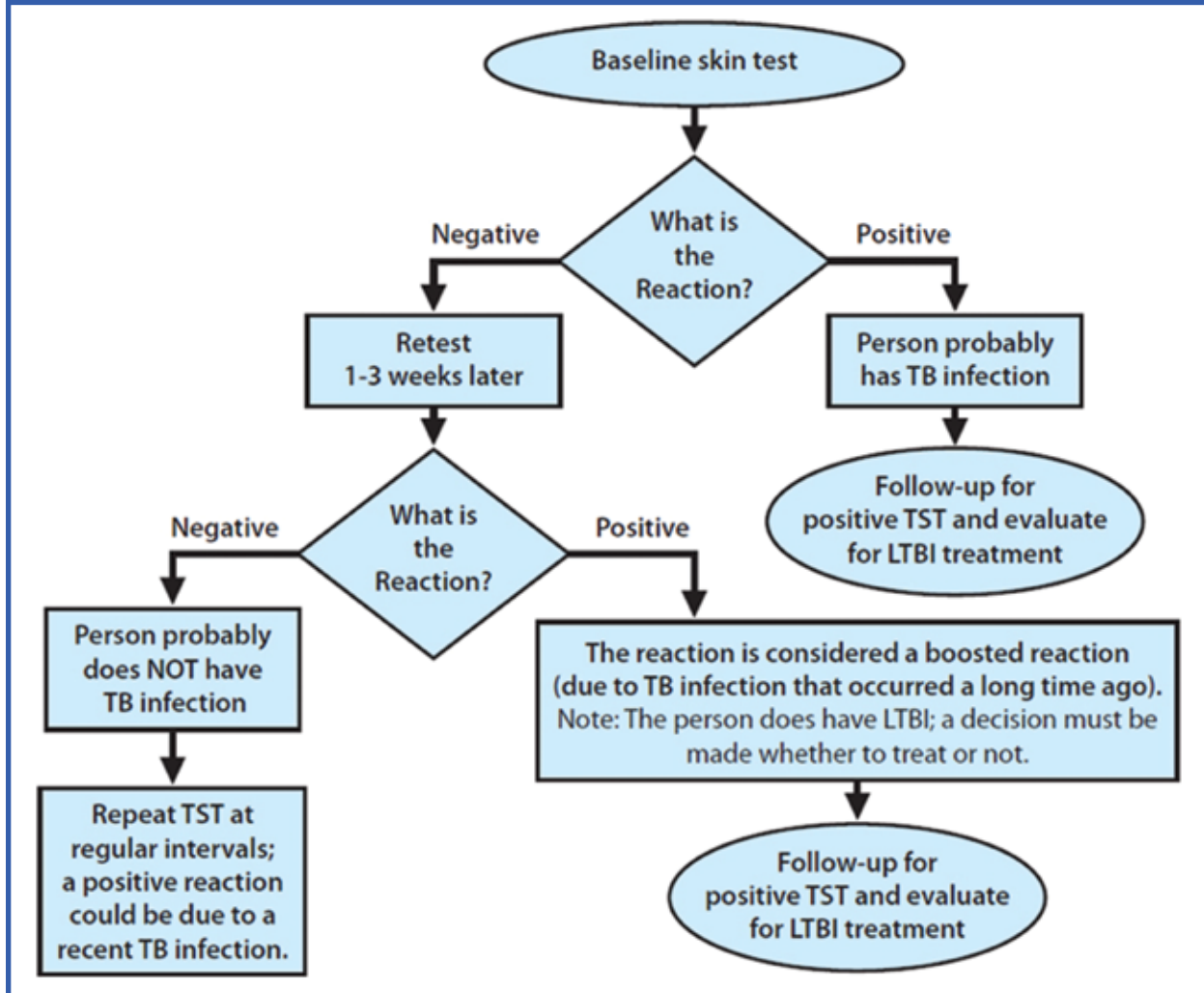
OTP providers should work closely with their local health departments to manage patients with active TB disease, which requires taking all of several medications for 6-9 months. Regimens for treating culture-positive TB disease typically include the medication rifampin, which is a potent inducer of methadone metabolism. Concomitant administration of rifampin can cause marked reductions in serum methadone levels and lead to the onset of opioid withdrawal symptoms. Therefore, rifampin should be replaced with rifabutin whenever possible for patients receiving methadone treatment. There is no drug interaction between the rifamycins and buprenorphine.

- TB resources for health care providers from the California Tuberculosis Control Branch (TBCB) can be found at: <https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TB-Resources-for-Healthcare-Providers.aspx>.
- The CDC provides extensive professional resources and tools, including information on testing, treatment, and education and training for health care workers: <https://www.cdc.gov/tb/topic/treatment/tbdisease.htm>.
- The WHO released updated and consolidated guidelines for the management of LTBI in 2018: <http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/>

## Hepatitis A virus (HAV)

Figure 6.6.1

## Two-step TST Testing — 2



Source: <https://www.cdc.gov/tb/publications/tbi/diagnosis.htm>

Hepatitis A virus (HAV) is a liver infection that occurs by fecal-oral transmission or by the consumption of contaminated food or water. Adults typically present with low appetite, fatigue, nausea, abdominal pain, pale stools, dark urine, and jaundice. While most infections are self-limited, fulminant hepatic failure with a high case fatality rate has been reported with HAV superinfection in persons with chronic HCV [226]. In the U.S., up to 48% of cases reported during **HAV outbreaks** are among persons who use injected and non-injected methamphetamine. In November 2016, an outbreak of HAV infections began in San Diego County and spread to Santa Cruz, Los Angeles, and Monterey counties. More than 700

**cases were reported in CA** with 461 persons requiring hospitalization and 21 deaths. Most cases were among persons experiencing homelessness and/or using illicit drugs in settings with limited sanitation.

HAV infection is preventable by inactivated vaccines, which have been included in the routine early childhood vaccination schedule since 2005. Following the end of the HAV outbreak in 2018, the California Department of Public Health continues to recommend providing hepatitis A vaccination for high-risk groups, including people experiencing homelessness, persons who inject drugs and use non-injectable drugs, and men who

have sex with men. Post-exposure prophylaxis can be given within two weeks of exposure by administering either hepatitis A vaccine or immune globulin. In counties without an active HAV outbreak, the administration of viral hepatitis immunizations at OTPs play an important role in preventing an outbreak locally. OTPs should develop procedures to routinely identify and immediately vaccinate non-HAV-immune patients that lack a record of serologic immunity or completed immunization. Serologic screening for HAV immunity is not recommended prior to vaccination. Information and resources about the identification and prevention of hepatitis A virus infections can be found at the **CDC website**.

Table 6.6.1

### Differentiating Between Latent TB Infection and TB Disease

LTBI	TB Disease
<ul style="list-style-type: none"> <li>■ No symptoms or physical findings suggestive of TB disease.</li> <li>■ TST or IGRA result usually positive.</li> <li>■ Chest radiograph is typically normal.</li> <li>■ If done, respiratory specimens are smear and culture negative.</li> <li>■ Cannot spread TB bacteria to others.</li> <li>■ Should consider treatment for LTBI to prevent TB disease.</li> </ul>	<ul style="list-style-type: none"> <li>■ Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite.</li> <li>■ TST or IGRA result usually positive.</li> <li>■ Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease.</li> <li>■ Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease.</li> <li>■ May spread TB bacteria to others.</li> <li>■ Needs treatment for TB disease.</li> </ul>

Source: <https://www.cdc.gov/tb/publications/ltbi/diagnosis.htm>

Table 6.6.2

### Latent TB Infection Treatment Regimens

Drugs	Duration	Interval	Comments
Isoniazid	9 months	Daily	Preferred treatment for: <ul style="list-style-type: none"> <li>■ Persons living with HIV</li> <li>■ Children aged 2-11</li> <li>■ Pregnant Women (with pyridoxine/vitamin B6 supplements)</li> </ul>
		Twice weekly*	Preferred treatment for: <ul style="list-style-type: none"> <li>■ Pregnant Women (with pyridoxine/vitamin B6 supplements)</li> </ul>
Isoniazid	6 months	Daily	
		Twice weekly*	
Isoniazid and Rifapentine	3 months	Once weekly*	Treatment for Persons 12 years or older <u>Not recommended for persons who are:</u> <ul style="list-style-type: none"> <li>■ Younger than 2 years old,</li> <li>■ Living with HIV/AIDS taking antiretroviral treatment,</li> <li>■ Presumed infected with INH or RIF-resistant M. tuberculosis, and</li> <li>■ Women who are pregnant or expect to become pregnant within the 12-week regimen.</li> </ul>
Rifampin	4 months	Daily	

\*Use Directly Observed Therapy (DOT)

# CHAPTER 7

# COMORBID

# PSYCHIATRIC

# ILLNESS

**Authors:** Connery, H.; Kim, S.A.

## 7.1. Introduction

Co-occurring mental health disorders among opioid treatment program (OTP) patients are more the rule than the exception. People with serious mental illness are three times more likely to suffer from alcohol or drug abuse. Similarly, people with substance use disorders (SUD) are three times more likely to have mental illness than those without SUD <sup>[227]</sup>. Among the homeless, rates of alcohol and drug abuse are six to seven times higher than those in the general population <sup>[228]</sup>. Eighty-two per cent of prisoners with mental health disorders have SUD <sup>[229]</sup>. Half of the total cigarette sales are to those with mental illness, and in California alone, 40,000 people died each year from tobacco-related diseases, at a 16 billion dollar cost between health care and lost productivity <sup>[230, 231]</sup>.

Although co-occurring disorders are common, they are often missed or neglected and many patients do not receive adequate treatment <sup>[232]</sup>. There is a general lack of SUD screening in the evaluation of psychiatric patients, and likewise, there is little psychiatric screening for presence of co-occurring psychiatric disorders among patients seeking treatment for SUD. OTP physicians can play an important role in closing this public healthcare gap by screening, diagnosing and initiating appropriate mental health treatment, and making referrals for provision of comprehensive, collaborative care.

## 7.2. Evaluation

Screening for co-occurring disorders is best incorporated into the admission evaluation process and continued

throughout treatment. Many validated screening and assessment tools are available in the public domain through the [Substance and Mental Health Services Administration](#). Table 7.2.1 lists examples of brief screening tools that use self-reported data and do not require special training to administer. For consistency, the clinic should establish a policy to determine the timing and methodology of screening.

Screening tools are just what they are called: screening tools. Each has strengths and weaknesses. Clinicians should familiarize themselves with the tools they choose to use and realize that a positive screen alerts the clinician to the need for more in depth evaluation. A screening tool is not a substitute for a thorough, face-to-face interview with an experienced clinician upon which a diagnosis is based. The current accepted psychiatric diagnoses are governed by the DSM-5 of the APA <sup>[2]</sup>.

Mental health disorders may pre-exist, coincide with, or occur independently of drug effects. They may also follow as a consequence of substance use. They may complicate the evaluation of, treatment planning for, and treatment response to both disorders. Until recently, many clinicians were taught that a mental health disorder diagnosis should not be made in the presence of drug use because drugs alter the clinical manifestations of mental health disorders. This may be true when patients are intoxicated or in early withdrawal, so the best time to evaluate for co-occurring mental health disorders is after acute drug effects have worn off, which is usually within a few days to a few weeks. Unfortunately, persistent psychosis, lasting months to years, can occur with chronic severe stimulant use, especially methamphetamine,

Table 7.2.1

### Example of Screening Tools

<b>Depression</b>	Patient Health Questionnaire (PHQ-9)
<b>Bipolar Disorder</b>	Mood Disorder Questionnaire (MDQ)
<b>Anxiety Disorder</b>	Generalized Anxiety Disorder 7-item (GAD-7) scale
<b>Trauma</b>	PTSD Checklist for DSM-5 (PCL-5) Life Event Checklist Domestic Violence Screening Tool: Hurt, Insulted, Threatened with Harm and Screamed (HITS)
<b>Suicide</b>	Columbia-Suicide Severity Rating Scale (C-SSRS)

and neurocognitive impairment may not resolve after toxic inhalant use. It is generally accepted among addiction physicians that a co-occurring mental health disorder is present if symptoms such as disabling depression or anxiety persist despite a sustained abstinence from substance use of around 6 months.

Accurate diagnosis may be difficult in the early stages of substance use treatment because symptoms of intoxication and withdrawal often overlap with common mental health symptoms like anxiety, depression, poor concentration, and psychosis. It is optimal to allow resolution of acute intoxication and/or withdrawal prior to initiating non-emergent, maintenance psychopharmacological treatment [233]. In cases requiring more urgent treatment, such as suicidality or persistent psychosis, consideration should be given to the patients' personal and family history of MH diagnosis and treatment, including suicidal ideation or attempts, and the temporal relationship of current symptoms to substance use. These factors may help to guide the preliminary MH diagnosis and treatment of acute mental health disorders. Patients presenting with risk of violent behavior (i.e., toward others or self) generally require the structure and safety of an inpatient setting in order to stabilize mental health and substance-related symptoms.

Other clinical information that can aid in diagnosing mental health disorders in this context include family history of SUD and mental health disorders, and the patients' temporal developmental history of the emergence of mental health symptoms. Collateral history from family, friends, and prior treatment providers, as well as toxicological monitoring, and serial clinical observations over time can all be helpful in determining whether the clinical presentation is due to substance use, an independent psychiatric disorder or a combination of the two.

## 7.3. Treatment

Fragmentation has been, and continues to be, a barrier to optimizing the management of co-occurring SUD and psychiatric disorders. This barrier is recognized, is an ongoing topic of discussion and has yet to be resolved. In general, treatment for co-occurring substance use and psychiatric disorders is provided in one of three models: sequential, parallel, or integrated.

The sequential model is perhaps the most traditional. In this model, the SUD that brought the patient into treatment, for example OUD would be treated while co-occurring disorders, like alcohol and tobacco would be left unaddressed or treatment would be postponed until later. A classic example of this is the residential treatment programs that allowed patients to bring cigarettes and smoking paraphernalia into the facility without restriction and/or incorporated smoking breaks into the program schedule. There was a widespread misconception that addressing the co-occurring disorders would detract from progress in recovery from the primary disorder. In the sequential model of treatment, patient with an OUD (for example) would be treated with methadone at the methadone clinic and later sent to a mental health clinic for the treatment of his or her PTSD or anxiety.

The parallel model is an improvement over the sequential approach. In this model, co-occurring disorders are treated at the same time but in different treatment settings and by different providers.

The integrated model is the ideal one. Truly integrated care means that patients with co-occurring disorders are offered services for both disorders in one location by a cross-trained staff. Integrated care lowers barriers to receiving treatment for both conditions.

Unfortunately, the term integrated services does not consistently refer to the optimized treatment described above. It may be used in a broad and imprecise way to include services that provide individual, group, couples and family therapy.

In reality, integrated models of care are uncommon in SUD treatment. Traditional OTPs, methadone clinics, are rarely equipped to handle the mental health needs of their patients on site. Historically OTP staff have a background in substance use treatment with limited mental health treatment experience. When these limitations exist in an OTP, patients with mental health symptoms would benefit from referral to a psychiatrist in the community or a mental health clinic. Coordination of care between the OTP physician and the mental health care provider is essential. The OTP is in a position to observe the patient more frequently, so can alert the psychiatrist/mental health provider if significant clinical change occurs.

### 7.3.1. Treatment of Acute Manifestations

The initial management of patients presenting with acute psychiatric symptoms is primarily determined by their clinical manifestations. The underlying psychiatric diagnosis, if one exists, is deferred for later consideration.

When treating patients with acute psychiatric manifestations, the paramount considerations are patient safety and resolution or stabilization of symptoms. Management strategies include: hospitalization, use of medication, behavioral therapies, and calm reassurance in a quiet, non-threatening environment in an effort to “talk down” the patient. The latter approach is often effective for patients with acute drug-induced psychosis. Patients with more persistent symptoms may require short term treatment with medications, generally a short acting antipsychotic or an anxiolytic. The risk of harm to self or others should be assessed by a qualified mental health clinician with training and experience in assessments for suicidality, and levels of risk for harm to self and others. A plan for care is essential. The need for hospitalization should be carefully considered. State law for managing the assessment results must be followed, including Duty to Warn.

In addition to acute stabilization of symptoms and assurance of patient safety, a major goal of this phase of treatment is establishing trust and to forming a treatment alliance that will facilitate the progression of treatment from the acute to the the maintenance phase.

### 7.3.2. Maintenance and Relapse Prevention

During the maintenance phase, the main goals are to avoid:

1. over-treating a drug-induced psychiatric disorder that may resolve with cessation of use, and
2. prematurely discontinuing treatment of an underlying psychiatric disorder that is prone to relapse once treatment is discontinued.

While there are no hard and fast rules about treatment during the maintenance phase, a reasonable approach is to proceed cautiously, being aware of the possibility of over treatment, observing for signs and symptoms of medication toxicity and watching for recurrence of symptoms after treatment is discontinued.

The choice of pharmacotherapy should be strategic, choosing one medication to address multiple issues whenever possible. For example, a medication like bupropion should be considered when smoking, stimulant use, and depression are clinical concerns.

Many times co-occurring substance use disorders and mental health disorders in a given patient are treated separately, with one prescriber managing the SUD and another MH disorder. Each prescriber adheres to the current recommended practices and applicable guidelines for the disorder he or she is treating. In this situation,

Table 7.3.1

#### Examples of Important Drug-drug Interactions Between Psychotropic Medications and Methadone [234, 235]

Medication	Interaction with methadone
<b>SSRIs</b>	<ul style="list-style-type: none"> <li>■ QT prolongation</li> <li>■ Fluvoxamine may increase methadone levels</li> <li>■ Methadone may enhance serotonergic effects (risk serotonin syndrome)</li> </ul>
<b>SNRIs</b>	<ul style="list-style-type: none"> <li>■ Duloxetine and methadone levels may increase</li> <li>■ Methadone may enhance serotonergic effects (risk serotonin syndrome)</li> </ul>
<b>TCA's</b>	<ul style="list-style-type: none"> <li>■ QT prolongation</li> <li>■ Methadone may increase desipramine levels</li> <li>■ Methadone may enhance serotonergic effects (risk serotonin syndrome)</li> </ul>
<b>St. John's wort</b>	<ul style="list-style-type: none"> <li>■ St. John's wort may decrease methadone levels</li> </ul>
<b>Antipsychotics</b>	<ul style="list-style-type: none"> <li>■ Sedation, cognitive dysfunction, QT prolongation</li> </ul>
<b>Benzodiazepines and zolpidem-like sedatives</b>	<ul style="list-style-type: none"> <li>■ Respiratory depression, sedation, cognitive dysfunction</li> </ul>
<b>Phenytoin, carbamazepine, phenobarbital</b>	<ul style="list-style-type: none"> <li>■ Decreases methadone levels and can cause opioid withdrawal</li> </ul>



the prescribers must be aware of common drug-drug interactions between such medications used to treat these disorders. This is particularly true when a patient is being prescribed methadone. Serious interactions may produce sedation, QTc prolongation and/or anticholinergic reactions. Many mental health medications have the potential to be a metabolic inhibitors or potentiators of methadone, which may produce fluctuation in serum methadone levels. When levels fall, patients are at a risk of adverse effects related to overmedication, or methadone toxicity (see Table 7.3.1).

When MH medications are prescribed for patients with co-occurring SUD, the abuse liability of the medication must be considered, whether or not the medication is a controlled substance. To the extent possible, medications with the least potential for misuse or adverse interaction should be prescribed. For example, non-benzodiazepines alternatives would be preferred for the management of anxiety in patients on opioid agonist treatment for OUD because the risk of respiratory depression increases when benzodiazepines are taken in combination with methadone or buprenorphine (CSAT 2005). In addition, patients with OUD are at increased risk of becoming addicted to benzodiazepines. When medications with abuse potential are prescribed, risk mitigation procedures are essential and include use of the lowest effective dose on a fixed dosing schedule (avoid “as needed”) dispensing medications at the OTP window to allow observed dosing, and close monitoring through toxicology testing, call backs, pill counts and review of CURES reports (CA’s PDMP).

## 7.4. Behavioral Therapies

In the treatment of patients with co-occurring MH and SUD, behavioral therapies may serve as an important adjunct to pharmacotherapies or may be sufficient on their own. In some cases, a trial of behavioral therapy should be considered first, and pharmacotherapy added if it proves insufficient. Behavioral therapies include individual, family and group modalities.

Examples of behavioral therapies developed for co-occurring disorders include:

- Integrated Group Therapy (for bipolar disorder and substance use; Weiss and Connery 2011)
- Seeking Safety (for PTSD and substance use disorder; Najavits 2002)
- The Women’s Recovery Group (for women with co-occurring substance use disorders and mental health/trauma disorders; Greenfield 2016).

Examples of behavioral therapies addressing substance use disorders include:

- Group Drug Counseling (Daley and Douaihy 2011)
- Cognitive Behavior Therapy for Relapse Prevention (Carroll 1998)
- Motivational Enhancement Therapy (Miller 1995).

Case management to address basic needs, such as housing, finances, access to social services, is an essential

aspect of an integrated and comprehensive treatment plan. Family education and support are critical to optimizing recovery outcomes.

People with SUD have higher rates of mortality than the general population, especially from suicide and violence (Dwyer-Lindgren et al. 2018). Because of this it is important to carefully assess suicidality and violence risk during longitudinal care of patients with opioid use disorders for risk of suicidality and violence during longitudinal care, especially in the presence of co-occurring disorders (Bohnert et al. 2017). Knowledge of risk factors (e.g., depression, personality disorder, psychosis, and prior self-harm or suicide attempts) and serial careful assessment throughout the course of treatment can help to identify patients at increased risk and facilitate timely and appropriate interventions.

Changes in a patient’s condition, such as worsening anxiety, and mood symptoms, insomnia, negative thoughts (despair, hopelessness), substance use, interpersonal conflicts, financial stressors, or other negative life events, warrant safety re-assessment. Changes in psychosis (hallucination, delusions, and disordered or disorganized thinking) are commonly associated with elevated risk of harm to self and/or others. In all cases, treatment planning includes interventions to address identified risk. Interventions may include increased frequency of monitoring, adjustment of medication(s), and provision of more intensive psychosocial adjuncts to assist a patient to acquire and use more effective coping skills. High-risk circumstances, involving imminent risk of harm to self or others, warrant immediate referral for hospitalization.

## 7.5. Most Common Psychiatric Disorders

### 7.5.1. Clinical Considerations for the Treatment of Common Co-occurring Disorders

#### Schizophrenia

Over a third of patients with schizophrenia meet the diagnostic criteria for a SUD. The most commonly used substances in this population include nicotine, cocaine, alcohol, and cannabis. In this context, some of the second-generation antipsychotics are advantageous, such as clozapine, risperidone, olanzapine, and aripiprazole. OTP physicians who come from specialties outside of psychiatry may choose to refer these patients to a psychiatrist, continuing to prescribe for the OUD and coordinating care as needed.

#### Bipolar disorder

Bipolar disorder, especially the rapid-cycling type, commonly co-occurs with SUD. Use of certain anticonvulsants may be advantageous over lithium, but the plan of treatment should be developed after and guided by the results of a thorough psychiatric assessment.

## Depression and Depressive Disorders

Depression is perhaps the most common psychiatric symptom reported by patients seeking treatment for SUD. Many of these patients are experiencing major life crises. Some are being compelled to enter treatment because of legal, social or financial issues. Not all patients presenting with symptoms of depression have a depressive disorder. Intoxication with and withdrawal from multiple substances may produce symptoms of depression. However, most depressive symptoms exhibited by patients admitted for treatment of alcohol, cocaine, methamphetamine and opioid use disorders cleared within a matter of a few days to a few weeks. Depressive symptoms that persist beyond a few weeks warrant serious consideration of a co-occurring depressive disorder requiring treatment, especially when there is a history of, depression, suicidal ideation or suicide attempts during a period of sustained abstinence. The co-occurrence of opioid use disorder and depressive disorder heightens suicide risks (Darke et al. 2015).

Intervention for presumed depressive disorder, especially in patients with significant functional impairment should be considered. Effective treatment includes the use of antidepressants (first-line agents include selective serotonin reuptake inhibitors or mixed serotonin-norepinephrine reuptake inhibitors, bupropion, mirtazapine) and behavioral treatments.

## Anxiety

Anxiety is common in patients with substance use disorders. It is important to distinguish between anxiety that is normal and helps to facilitate positive behavior change, and anxiety that is interfering with treatment or causing significant functional impairment. In the latter cases, behavioral therapies, especially cognitive behavioral therapies and exposure-desensitization therapies, provide the safest and most effective treatment for anxiety disorders and are preferred. These may be delivered alone or combined with serotonergic antianxiety medications.

The use of benzodiazepines for the treatment of anxiety in patients with co-occurring substance use disorders deserves some comments. Benzodiazepines are effective antianxiety medications, particularly in the short term, but this class of medication poses different risks for patients with SUD, especially opioid and alcohol use disorders, than it does for patients without use disorders.

Patients in treatment for SUDs are often anxious because of stressful life events and crises, past, present and anticipated. They find that benzodiazepines bring prompt relief for the duration of their pharmacologic effect, but that anxiety returns when they wear off. Having experienced this rapid relief, many become unwilling to try non-benzodiazepine alternatives that take weeks to months and several dose adjustments to reach full therapeutic effect. When these patients remain on benzodiazepine indefinitely, the dose tends to escalate as the patient develops tolerance. With chronic use, they may lose their efficacy, but despite describing significant amounts of anxiety, patients may believe that benzodiazepines are the only thing that works for them. Discontinuation causes

an unpleasant and potentially dangerous withdrawal. Attempts to taper must be gradual and work best if non-benzodiazepine anxiolytics are started to help manage anxiety associated with withdrawal and/or re-emergence of the original anxiety disorder. Because of the difficulties described, caution should be exercised when and if benzodiazepines are started; an exit plan is also recommended.

Patients who use heroin, or are prescribed methadone or other opioids, often find that taking a benzodiazepine at the same time produces a unique and highly enjoyable high, particularly when their tolerance to opioids no longer allows them to experience a high with the opioid alone.

## Trauma and PTSD

Patients with substance use disorder commonly experienced childhood and adult traumas, which may lead to posttraumatic stress disorder (PTSD). PTSD and substance use are often inter-reinforcing conditions: PTSD can lead to self-medication to manage symptoms, and substance use increases risk of exposure to trauma (e.g., intimate partner violence and sex trafficking, exposure to criminal violence and substance-related injury) as well as the risk of developing PTSD after experiencing a traumatic event (Chilcoat and Breslau 1998). Treating the affected population may be particularly challenging, as patients with a history of trauma may have more severe psychiatric and medical comorbidities, be mistrustful, and struggle with treatment engagement. Therefore it is important to assess for PTSD, recognize ways that trauma may be affecting the patient, and

Table 7.4.1

### The Role of the Opioid Clinician with Regard to Co-occurring Mental Health Disorders

- Evaluate for co-occurring mental health and trauma disorders at intake and establish a system of ongoing, longitudinal re-assessment
- Provide integrated treatment and/or appropriate referrals to community providers along with highly collaborative co-management
- Promote simultaneous treatment for both disorders to counter patients' tendency to favor addressing one disorder over the other
- Recognize risk factors for harm to self or others, assess carefully, and refer to acute treatment if needed
- Be aware of drug-drug interactions between medications used to treat MH disorders and OUD, especially methadone; choose medications to minimize the risk for adverse interactions
- Integrate family, significant others, and legal systems in patient care and emphasize the importance of this with patients receiving care

provide trauma-informed interventions. Additionally, both disorders should be treated concurrently, as a reduction in substance use may unmask PTSD symptoms. Evidence-based integrated therapies for co-occurring trauma disorders and substance use disorder include Seeking Safety (Najavits 2002) and Concurrent Treatment of PTSD and Substance Use Disorders Using Prolonged Exposure (COPE; Back et al. 2014). Case management is an essential aspect of ongoing safety assessment and family management in those with trauma disorders.

### Personality Disorders

Antisocial personality disorder (ASD) is common among people with OUDs, and associated with poorer treatment outcomes. At the same time, many patients with OUD may be misdiagnosed with ASD due to behaviors associated with the addiction. For instance, as with other illicit drug use disorders, patients who are actively using opioids may engage in antisocial behaviors to obtain heroin or illicit opioids. Daily use of opioids is expensive. People who are desperate to obtain opioids to avoid the painful opioid withdrawal syndrome may lie, steal, or sell drugs to obtain money to purchase opioids. These behaviors remit for persons without ASD when they are abstinent from illicit drugs and tend to return with relapse to drug use. This pattern is different from what the DSM-5 criteria required to diagnose ASD.

Thoughtful assessment is advised when evaluating patients who present with challenging behaviors that may relate solely to OUD or may reflect a co-occurring personality disorder. Patients with true personality disorder, especially borderline personality disorder, require specific treatments to reduce risk for self-harm and suicide. Many OUD patients with co-occurring personality disorder are also victims of intimate partner violence and sex trafficking, adding another compelling need for thoughtful and accurate assessment and provision of trauma-informed care and violence prevention. Positive treatment outcomes require individualized care for each person's history and social determinants of health.

Where ASD is diagnosed, in addition to referring the patient to appropriate treatment, a well-structured treatment plan includes clear behavioral boundaries and contingencies for OTP policy violations. Collaboration with legal systems is a protective component of comprehensive care and patients post-incarceration are at very high risk for opioid poisoning with relapse; thus OTPs serve an important transitional function for this population.

Treating patients with co-occurring disorders is challenging, but also equally rewarding. While some patients, especially those with personality disorders, may present a greater challenge, proper diagnosis, effective planning, and a cooperative approach to treatment can yield positive results.

# CHAPTER 8

# LABORATORY DATA

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## 8.1. Introduction

Historically, drug testing in America has been construed as an adversarial game of cat and mouse between the testers and those persons required to provide these sometimes-incriminating samples. This does not need to be the case, and in fact should not be in OTPs. The clinician's aim for testing is to help diagnose and treat patients; this is entirely different than of, say, law enforcement, workplaces, or airlines. Patient-Centered Urine Drug Testing (UDT) should be the basis for all clinical encounters involving patient care.

Unsanctioned drug use in a largely negative testing population is relatively easy to detect. However, when monitoring for compliance with prescribed medications (i.e. where the absence of the analyte causes concern), the challenges for urine drug testing are greater. Unfortunately, a lab report of "not detected" with a cutoff of 299 ng/dL vs. a "detected" reported with the same cutoff of 300 ng/dL is, from a scientific perspective, identical. Compliance testing using UDT results should be explored with caution.

Addiction specialists rely on urine drug tests to verify that drugs of abuse or street drugs are absent, and the therapeutic drugs such as buprenorphine or methadone and their metabolite are present. Federal and State of California regulations require certain levels of monitoring drug screens to help ensure that patients are complying with the directives of the treatment program. All drugs fall in one of two categories: medications (prescribed or unprescribed) and illicit substances. The former has a specified dose, and the latter an unknown amount of a pure drug or a mixture of components containing the drug. If a patient is taking a prescription that is part of the drug-testing panel while in

a treatment program, this is usually a strong indicator of the source of the positive result. However, since urine drug screens are often reported as positive or negative, it is not clear whether a positive test is the result of ingestion of a low therapeutic dose, a high illicit dose, or some combination of these. Owing to the concentrating effects of the kidneys, no meaningful relationship can be drawn between amounts of drug taken and the amount of drug extracted from a donor sample. This means that a monitored individual can abuse a prescribed medication with relative impunity. Patients seeking treatment for OUDs involving street methadone, street buprenorphine or opioids prescribed for pain present UDT challenges. Most drug testing is conducted using a twostep process. The first step is a quick and inexpensive screening test. This test identifies whether any drugs in a variety of classes are present or absent. It is not very specific. Most of the opioids are lumped together in one class, excluding some like methadone and gentanyl. Most of the benzodiazepines are grouped together in another class, again excluding some, like clonazepam and lorazepam. The second step is the confirmatory process, which is used to identify the specific drug(s) present in the class that had a positive screen. A positive screen for opioids may confirm positive for hydrocodone or for codeine, morphine or 6MAM, the metabolite of heroin. There is a quantity associated with each specific drug that is identified.

Attempts by the patient to mask drugs in the urine by adding chemicals or diluting the urine by liquid loading or addition of water further complicate the interpretation. The number and types of drugs in the screen along with the amount of the specific marker creatinine and the temperature of the urine sample will aid in ensuring that a reliable specimen is being tested. Adding methadone

directly to the urine sample in an effort to appear compliant has a specific result that requires interpretation. Understanding the detailed information in the laboratory report is a necessary requirement for treatment specialists to insure the integrity of the program and the safety of the patient. A good working relationship with the laboratory will help in these interpretations.

All clinic treatment personnel interpreting toxicology results must understand the benefits and the limitations of toxicological testing procedures. In order for the laboratory results to be an effective diagnostic tool, the details of the testing parameters that define a positive or negative value such as sensitivity (cut-off values) and specificity (cross-reactivity) should be well understood. This is an important issue in choosing a laboratory and knowing how to act on screened values and when to request a confirmation. For example, a positive screen for cocaine or fentanyl will indicate to a high degree of reliability that the drug is present. However, a positive screen for opiates must be confirmed to identify the specific drug in the opiate class that is present due to a lack of specificity in the screening assay. Furthermore, the interpreting healthcare personnel must have a working knowledge of the various factors that affect the adsorption, metabolism, and elimination of the drugs in question.

## 8.2. Regulations

### 8.2.1. Federal Regulations

Federal regulations require eight drug tests per calendar year and specify which drug categories are included in a general drug screen to include methadone and its metabolite. The federal regulations state that the drug screen typically includes opioids, benzodiazepines, barbiturates, cocaine, marijuana, methadone, methadone metabolite, buprenorphine, amphetamine, and alcohol (as the metabolite ethyl glucuronide). However, there is no mandated testing panel. Confirmation of the drugs in each screening class is left to the discretion of clinic personnel. In abnormal UDT results, all contested screen results should be confirmed by more advanced combination techniques. Uncontested results typically do not need further testing.

### 8.2.2. California State Regulations

Under current California regulations, random toxicology screens are required once a month for most OTP patients and are required once a week for pregnant patients. In California, drug testing performed to comply with state regulation must be sent to a state-approved laboratory. Under Title 17, the required drug-screening panel must include amphetamines, cocaine, opioids, barbiturates, methadone and methadone metabolite. Confirmation of all screening presumptive positives must be done before reporting, and the methadone and methadone metabolite must be confirmed if either one or both screen negative. The amphetamines screening positives must be confirmed for both methamphetamine and amphetamine, and opioids must be reported for morphine and codeine. Secobarbital,

pentobarbital and phenobarbital must be confirmed for the barbiturates class. This can create problems and misinterpretation for the drugs that are not specifically listed in the State of California's confirmation requirement.

The certified laboratory is usually not in the same geographical area as the clinic, so the specimen must be transported to the laboratory for testing. An off-site laboratory can delay the availability of the laboratory results and may not facilitate immediate clinical intervention with the patient. To compensate for this, some OTPs utilize additional on-site testing which allows prompt evaluation of acute clinical situations, even if they do so with some reduction in reliability and accuracy. This "non-Title 9" testing is used for in-house decisions and for medical-exception take-home decisions, but not for the state specified 'regular' take-home criteria. When using this "non-Title 9 (on-site, dip stick) testing" it is always preferable to check with the clinic referral lab with regards to the cross-reactivities and the cut-offs of the on-site test method. This will minimize the generation of conflicting results between the two different testing methods.

Urine is the best and preferred sample type for California drug testing under Title 9. There is a time-honored history in the published data with this type of testing. Urine as a matrix, will give a concentrated sample that represent the metabolism and excretion of drugs from the current collection to the previous void over a reasonable period of time (window of detection). Urine can offer only a semi-quantitative result because of the variations in water intake. Saliva and blood tests are also available. The serum values for drugs represent the effective amount of drug in the body. This quantitative value will represent the patient values for a given dose and it may be useful as a peak and trough comparison for split dosing or compliance issues involved with changing the patient's dose. Although these values may be of interest academically, their utility in clinical care has yet to be proven.

Many state-approved laboratories have a standard panel of drugs for which they routinely screen. This list is based on the tests required by OTP regulation, and panels often do not include tests for alcohol, marijuana, some benzodiazepines (notably clonazepam (Klonopin®) and lorazepam (Ativan®), and other sedatives such as muscle relaxants. Fentanyl, a synthetic opioid, is never detected by an opiate immunoassay screen, whereas oxycodone, a semisynthetic opioid, is not reliably detected in the opiate screening assay and must be ordered as a specific oxycodone screen if use is suspected. Additional tests should be ordered as needed on a case-by-case basis to assist in the medical management of the individual patient.

Periodic breathalyzer testing for alcohol may be needed for patients with a history of alcohol abuse or dependence; alternatively an ethyl glucuronide laboratory test will give results that correspond to past usage for three to five days (although interpretation of absolute levels remains under debate). Strategic breathalyzer screening for alcohol (after holidays or on weekends) may be particularly helpful to ensure that the patient is safe to dose on a given day. At times, daily breathalyzer testing may be needed to clarify the frequency and extent of a patient's alcohol use and

Table 8.2.1

## Urine Drug Testing Requirements: Federal vs. State

Drug Class/ Analytes	Federal Regulations			California Regulations		
	No Requirements			Certified Laboratory		
	8 drug tests per year			1 drug test per month		
	Screen	Confirm	POCT*	Screen	Confirm	POCT*
<b>Opioids**</b>	R	O	O	R	R	O
Morphine				R	R	O
Codeine				R	R	O
Hydrocodone						
Hydromorphone						
Fentanyl						
Oxycodone						
<b>Benzodiazepines</b>	R	O	O	O	O	O
Oxazepam						
Nordiazepam						
Temazepam						
α-hydroxy-Alprazolam						
Clonazepam						
Lorazepam						
Desalkylflurazepam						
α-hydroxy-Triazolam						
Nitrazepam						
<b>Barbiturates</b>	R			R	R	O
Phenobarbital				R	R	O
Pentobarbital				R	R	O
Secobarbital				R	R	O
Butalbital						
<b>Cocaine</b>	R			R	R	O
Benzoyllecgonine				R	R	O
Cannabinoids	R					
Delta-9-THC						
<b>Methadone</b>	R			R	R	O
Methadone				R	R	O
EDDP (Methadone Metabolite)				R	R	O
<b>Buprenorphine***</b>	R					
Buprenorphine						
Norbuprenorphine						
<b>Amphetamines</b>	R			R	R	O
Amphetamine				R	R	O
Methamphetamine				R	R	O
<b>Alcohol</b>	R					
Ethanol (Alcohol)	R					
Ethylglucuronide (EtG)	R					

\*POCT= Point of Care Testing

\*\*6-MAM = 6-monoacetyl morphine is the relatively short lived but definitive marker for recent heroin use

\*\*\* a negative buprenorphine report may not accurately reflect use of this drug

R = required test; O = optional test; Blank = discretion of medical staff

to identify patients who may not be able to stop drinking without medical assistance. At the present time, there is no evidence that safety is improved by withholding a methadone dose from an MMT patient who is otherwise clinically stable but has provided an incidental positive Breath Alcohol Reading. However, they certainly should be identified as higher risk and referred on for further evaluation and treatment.

## 8.3. Laboratory Practices

### 8.3.1. Urine Specimen Collection: Improving Sample Reliability

Urine specimen collection should be done in a therapeutic setting that respects patient privacy. This process should both minimize falsification and show respect and trust for the patient. Usually reliance on direct observation is not required, nor is it appropriate for most patients. Where direct sample collection is felt to be necessary, the witness observing the collection must be gender appropriate.

### 8.3.2. Substitution, Adulteration and Sample Tampering

Some patients may attempt to avoid testing positive for drugs of abuse by tampering with the urine sample. Many methods have been used, including adding various substances to the urine, diluting the specimen, substituting someone else's urine or submitting a sample of their own urine collected earlier. Some patients will consume copious quantities of water (volume loading) to decrease the concentration of drug in their urine. To discourage tampering, programs are required to test on a random schedule; patients are not informed in advance of the date/time of the next test. In addition, programs may require patients to remain in the clinic once they have been asked to test until testing is complete. Most laboratories offer a test for creatinine in the urine screening procedure, typically offered as a test in the point of care testing devices (POCT). This allows the programs to monitor the creatinine levels in the urine to screen for dilution. If the urine creatinine level is below 20, the specimen is considered to be dilute urine, and the sensitivity of the test is diminished. If the creatinine is below 5, the specimen is considered to be substituted, meaning it is not consistent with human urine. In the event that a patient is consistently providing dilute urines, he/she should be counseled and encouraged to regulate fluid intake to ensure that the creatinine will be above 20. In general, samples collected in the early morning are going to be more concentrated and so, more accurate in terms of drug detection.

The clinic staff conducting the collection procedure can also make observations regarding the urine color, clarity, viscosity and noting any foreign substances in the urine sample. If a provided sample is suspected of being tampered with or substituted, a second sample should immediately be requested. Both samples, appropriately labeled, should be sent in for testing.

There are also temperature recording devices that can determine the urine temperature very accurately. However, sample volume and any time delay of temperature testing can play key roles in assessment of sample integrity (see MRO Standards – [www.udtmonograph6.com](http://www.udtmonograph6.com)). Some Point of Collection (POC) testing strips are available that can give an indication of pH, creatinine, specific gravity, as well as common adulterants such as oxidizers, nitrites and bleach. Laboratory validity testing is often more sophisticated. These test strips are very inexpensive and can be used on suspected urines. If patients are diabetic, they may spill sugar in their urine sample. The sugar may ferment in the sample collection container, converting the sugar to alcohol. This alcohol may result in a positive test. The laboratory can supply sodium fluoride tablets (10 mg NaF) which when added to the collected sample will inhibit the fermentation process (glycolysis). Again, it is important to emphasize that the presence of ethyl glucuronide (EtG) is a totally independent marker of ethanol exposure.

### 8.3.3. Testing Methodologies

There are different drug testing technologies available. Most programs use EMIT (Enzyme Multiplied Immunoassay Test) as the screening technique. Since these screening assays are not specific, a confirmatory test, usually GC-MS or HPLC-MS/MS is done when there is a positive result – that is, when drugs of abuse are present, or methadone and/or methadone metabolite is absent. Although costly, gas chromatography/mass spectrometry (GC-MS) and the newer method high pressure liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) is the standard confirmatory test because of its high specificity and enhanced sensitivity. Newer technologies, such as fluorescence polarization immunoassay (FPIA), give semi-quantitative results, which allow detection of high dose use as well as monitoring of prescribed drugs, such as benzodiazepines, to assist in assessing compliance with therapeutic regimens.

When a urine drug screen is negative for methadone or metabolite, further investigation is necessary to determine whether there is a reasonable and legitimate explanation or whether this result indicates urine tampering or methadone diversion. Confirmatory testing with GC-MS or HPLC-MS/MS will clarify whether methadone and metabolite are present, but below the threshold for reporting on the screening test. Rapid metabolizers or patients on very low doses (< 10 mg) may legitimately present with a negative screen. Patients who have missed one or more doses prior to testing may be negative for methadone after a day or two and negative for both methadone and metabolite after a more prolonged absence. In fact, pH effects of urine can alter drug reabsorption and so reduce or enhance methadone parent excretion. Methadone metabolite (EDDP) however, is not subject to pH effects. Patients who are positive for methadone but negative for metabolite need careful evaluation; this result is consistent with a tampered specimen, i.e. urine from someone not on methadone to which methadone has been added to avoid detection.

Table 8.3.1

## Specimen Validity Testing

Test	Reason	Normal Range	Abnormal Range		Reason
			Low	High	
<b>Creatinine</b>	Dilution	<u>Normal</u> 20 – 200 mg/dL 6-19 mg/dL is dilute urine 5 and below = not consistent with normal human urine	0 to 10 Negative	n/a	<ul style="list-style-type: none"> <li>■ a waste product of creatine (urine)</li> <li>■ an amino acid contained in muscle tissue &amp; found in urine</li> <li>■ Creatinine and Specific Gravity are two ways to check for dilution and flushing</li> <li>■ low Creatinine and Specific Gravity levels may indicate diluted urine</li> </ul>
<b>Specific Gravity</b>	Dilution	<u>Normal</u> 1.003 - 1.030  <u>Average</u> 1.016 – 1.022	1.000	> 1.030	<ul style="list-style-type: none"> <li>■ tests for sample dilution</li> </ul>
<b>Nitrite</b>	Nitrites	<u>Normal</u> No trace	n/a	> 15 mg/dL	<ul style="list-style-type: none"> <li>■ tests for commercial adulterants such as "Klear" or "Whizzies"</li> </ul>
<b>Glutaraldehyde</b>	Aldehyde	<u>Normal</u> No trace  <u>Positive</u> Adulterant	n/a	Positive	<ul style="list-style-type: none"> <li>■ tests for the presence of an aldehyde</li> </ul>
<b>pH</b>	Acidic or Basic	<u>Normal</u> 4.5 - 8.0	4 or below	9 or above	<ul style="list-style-type: none"> <li>■ tests for the presence of acidic or alkaline adulterants in urine</li> </ul>
<b>Pyridinium Chlorochromate (Oxidants/PCC)</b>	Oxidants	<u>Normal</u> No trace*  <u>Positive</u> Adulterant	n/a	Positive	<ul style="list-style-type: none"> <li>■ tests for the presence of oxidizing agents such as bleach and hydrogen peroxide</li> <li>■ Pyridinium Chlorochromate (sold under the brand name "UrineLuck") is a commonly used adulterant</li> </ul>
<b>Bleach</b>	Bleach	<u>Normal</u> Negative	n/a	Positive	<ul style="list-style-type: none"> <li>■ tests for the presence of bleach in urine</li> </ul>

\*some traces may be found due to bacteria; nothing above 7.5 is normal



Table 8.3.2

## Urine Toxicology Detection Period

DRUG	CATEGORY	CUTOFF***	DETECTION PERIOD*	PLASMA HALF LIFE
<b>Amphetamines</b>	stimulant	1000		
Amphetamine			2-4 days	7-34 hours
Methamphetamine			2-4 days	6-15 hours
<b>Barbiturates</b>	sedative-hypnotic	200		
Amobarbital			2-4 days	15-40 hours
Butalbital			2-4 days	35 hours
Pentobarbital			2-4 days	20-30 hours
Phenobarbital			up to 30 days	2-6 days
Secobarbital			2-4 days	22-29 hours
<b>Buprenorphine</b>	Narcotic analgesic	10	2-4 days	2-4 hours
<b>Carisoprodol</b> (Soma)	Muscle relaxant	500	24 hours	8 hours
<b>Cocaine</b>	stimulant	300		
Benzoylcegonine			12-72 hours	0.5-1.5 hours
<b>Cannabinoids</b> (THC/Marijuana)	euphoriant	50		
Casual use			2-7 days	20-57 hours
Chronic use			up to 30 days	20-57 hours
<b>Ethanol</b> (Alcohol)	sedative-hypnotic	0.025	very short**	2-14 hours
Ethyl glucuronide (EtG)	metabolite	500	up to 72 hours	2-14 hours
<b>Fentanyl</b>	narcotic analgesic	2	3-4 days	3-12 hours
<b>Methadone</b>	narcotic analgesic	300	2-4 days	15-55 hours
<b>Methaqualone</b> (Quaalude®)	sedative-hypnotic	300	2-4 days	20-60 hours
<b>MDA/MDMA Ecstasy</b>	Psychotropic	500	2-4 days	4-12 hours
<b>Opiates</b>	narcotic analgesic	300		
Codeine			2-4 days	1.9-3.9 hours
Hydrocodone			2-4 days	4 hours
Hydromorphone (Dilaudid®)			2-4 days	1.5-3.8 hours
Morphine			2-4 days	1.3-6.7 hours
Oxycodone (Oxycontin®)			2-4 days	4-6 hours
6-Acetylmorphine (6MAM)			6-25 minutes	6-12 hours
<b>Phencyclidine</b> (PCP)	hallucinogen	25		
Casual use			2-7 days	7-46 hours
Chronic use			up to 30 days	7-46 hours
<b>Propoxyphene</b> (Darvon®)	narcotic analgesic	300		
Casual use			2-7 days	8-24 hours
Chronic use			up to 30 days	8-24 hours

\* Detection period varies; rates of metabolism and excretion are different for each drug and user. Detection periods should be viewed as estimates. Cases can always be found to contradict these approximations.

\*\* Detection period depends on amount consumed. Alcohol is excreted at the rate of approximately 1 ounce / hour.

\*\*\* Cutoff values are taken from Opioid Treatment Facilities.

### 8.3.4. Windows of Detection

Table 8.3.2 outlines common windows of detection for commonly tested and reported analytes. One important caveat to this is the fact that some analytes are actually optical isomers of one another. Chiral (handedness) testing is required to distinguish between over-the-counter decongestants vs. contested results.

### 8.3.5. Testing Strategies

Laboratory results should be used therapeutically as clinical data to support treatment objectives, not to activate penalties or punishment. Testing should serve the clinical purpose of identifying ongoing or sporadic drug use and potential safety issues. Urine drug testing can also help honest people to keep honest. Decisions made in early recovery can often be improved by the patient knowing that they may be required to provide a UDT sample.

Drug test results should be used as a treatment tool; a positive test provides an opportunity to discuss the patient's progress in recovery, to explore barriers to abstinence, and

identify strategies and resources to support future abstinence. Negative UDT results, combined with other markers of clinical stability, can serve to reinforce health changes made in a patient's recovery process and are often used to support decisions around increased take-home doses.

California regulations require that a patient's clinic attendance be increased if he or she tests positive for illicit drugs. This means the reduction and/or loss of take-home privileges unless the physician deems that the positive test is not the result of illicit drug use. The rationale for the physician's determination must be documented in the record. Some clinics will increase the frequency of urine drug testing after a positive result especially if the patient has been on a once/month UDT testing schedule, in order to clarify whether the patient has experienced a lapse or a full-blown relapse. Restriction beyond this in the form of dose reductions or discharge from treatment is usually inappropriate. In certain circumstances, it is appropriate to test beyond federal or state requirements. In these cases, the principle of "medical necessity" must be kept in mind to ensure that testing benefits the patient, rather than the clinician ordering the test.

As a general rule, there are many potentially "appropriate" actions to take in the context of an abnormal UDT result:

Table 8.3.3

## Interpretation of Confirmed Opiate Results

San Diego Reference Laboratory

### INTERPRETATION OF CONFIRMED OPIATE RESULTS

If the results are as follows:							Then the following condition exists:	
Morphine	Codeine	Hydro-codone	Hydro-morphone	6MAM	Oxy-codone	Oxy-morphone		
Positive	-	-	-	Positive	-	-	<b>Heroin use</b>	
Positive (M-C)	Positive	-	-	Positive	-	-	Heroin use plus Codeine use or Codeine impurity in the Heroin	M>C = Morphine Greater than Codeine
Positive (M-C)	Positive	-	-	-	-	-	Heroin or Morphine use plus Codeine use or Codeine impurity in the Heroin or Morphine	M>C = Morphine Greater than Codeine
Positive	Positive (C-M)	-	-	-	-	-	Codeine use (Morphine positive due to the metabolism of the Codeine in the body)	C>M = Codeine Greater than Morphine
Positive	-	-	-	-	-	-	<b>Heroin or Morphine use</b>	
-	Positive	-	-	-	-	-	<b>Codeine use</b>	
-	-	Positive	-	-	-	-	<b>Hydrocodone use</b>	(ex. Vicodin, Lortab, Norco or Panacet)
-	-	-	Positive	-	-	-	<b>Hydromorphone use</b>	(ex. Dilaudid)
-	-	Positive	Positive	-	-	-	<b>Hydrocodone use</b> Hydromorphone positive due to the metabolism of the Hydrocodone in the body OR Hydromorphone use as well	
-	-	-	-	-	Positive	-	<b>Oxycodone use</b>	
-	-	-	-	-	Positive	Positive	<b>Oxycodone use</b> (Oxymorphone is the metabolite of Oxycodone)	
-	-	-	-	-	-	Positive	<b>Oxymorphone use ONLY or Oxycodone Use</b> (ex. Opana) (Oxymorphone is the metabolite of Oxycodone and has a longer ½ life than parent drug)	

there is, however one absolutely wrong thing to do and that is to do nothing! An ignored lab result, especially one that is abnormal in some way, will almost always be viewed as a clinical deficiency.

In the context of randomized drug testing, some clinics are of the impression that randomizing sample collection around clinic or group visit days is true randomization. eg. “We only test on Tuesdays, but we don’t test EVERY Tuesday that the patient comes in.” This is a very common strategy but does not really approach the level of true sample collection randomization. Referral to the UDT Monograph is recommended for those who wish to pursue this further.

In some cases, such as end stage renal disease, a patient is unable to provide urine for drug testing. In other cases, urine may not be easily obtained for the random testing required by state and federal regulation. In these situations, it is necessary to submit an exception request to the state and to CSAT to allow another form of testing. Blood testing may be used for patients with renal failure, coordinating with the dialysis unit to send specimens for testing. Some clinics use saliva tests for patients who cannot urinate on demand, such as paraplegic or dialysis patients. These tests are useful to help monitor a patient’s progress in treatment and/or to help to clarify a patient’s status if they appear to be intoxicated. However, saliva tests are not approved for regular use under CCR Title 9. A state and CSAT exception would be required before the program could use these tests in place of urine testing for a particular patient.

In fact, the face of therapeutic drug testing in Opioid Treatment Programs is changing. More patients are seeking treatment with prescription drug use problems than street

heroin. Despite this, the need for specific strategies around treatment of this diverse population is evident. In the realm of therapeutic drug testing, it is critical to maintain a close working relationship with the reference laboratory that performs the urine testing for the clinic, so that any ambiguous results can have the benefit of expert consultation. A personal relationship with knowledgeable laboratory experts can be an invaluable resource.

### 8.3.6. Conclusions

In treatment of drug and alcohol patients, the role of drug testing can variously be patient-centered or adversarial. It often comes down to clinic/provider policies. Urine drug test results rarely lead to a definitive diagnosis in themselves, but when combined with relevant clinical context, can assist in opening a meaningful dialogue between patient and provider. Remember, when an otherwise clinically stable patient provides an unexpected result, the patient is owed a very detailed examination of these results before a definitive adverse inference can be applied. Sometimes this can be clarified with a simple call to the lab: in other cases, a knowledgeable expert clinicians’ advice should be sought. UDT results are only one piece of the puzzle that supports or challenges clinical stability.

The topic of urine drug testing is complex; it is impossible to go into sufficient depth to answer all clinical questions the reader may have. For those interested in examining patient-centered urine drug testing in greater detail, we recommend [www.udtmonograph6.com/](http://www.udtmonograph6.com/).

# APPENDIX I.

## USE OF CALIFORNIA'S CURES DATABASE BY OTPs

By Jara, G.; Ling, M.

California's Prescription Drug Monitoring Program (PDMP) is called CURES (Controlled Substance Utilization Review and Evaluation System). Since October 2018, California law has required that any health care practitioner who prescribes, orders, administers, or furnishes a controlled substance shall first consult CURES. Thus, the physicians in California OTPs should be registered and have access to CURES. OTP safety policy and procedures should include checking CURES prior to admitting a patient as well as periodically while the patient is enrolled in treatment. California law requires once every four months.

If the patient has ongoing relationships with prescribers from whom he or she may still acquire prescriptions for controlled substances or other psychotropics, the OTP should obtain releases of information from the patient so that the OTP can receive information from each prescriber in order to coordinate needed medical care and to avoid the use of medications that may interact with the OTP's pharmacotherapy for opioid use disorder.

It would be of particular concern if a patient refuses to sign a release of information to allow care coordination with prescribers because it may be an indication that the patient is using or furnishing to others the medications from the OTP or from the other prescriber. If there is polysubstance use, the OTP should address the patient's polysubstance use with appropriate levels and approaches to treatment. At the same time, the OTP should implement policies and procedures to prevent a patient from furnishing OPT medications to others or diversion of the OTP medications.

### Communicating with Other Prescribers

With the patient's release of information, OTP personnel can contact the patient's other prescribers to inform them that the patient is receiving medication assisted treatment and specify what medication the patient is receiving from the OTP. The other prescribers should be made aware that the medications from the OTP will not appear in the PDMP because of confidentiality regulations regarding substance use treatment records.

### Who Can Register? Who Can Access?

For complete information, visit the California Department of Justice's website page devoted to information about CURES 2.0: <https://oag.ca.gov/cures>.

Prescribers and dispensers can register to access CURES here: <https://cures.doj.ca.gov/registration/confirmEmailPnDRegistration.xhtml>

The 2015 Federal Guidelines refer frequently to how an OTP should use its state Prescription Drug Monitoring Program (PDMP). The section quoted here may be helpful:

### From: SAMHSA

#### HHS Publication No. (SMA) PEP15-FEDGUIDEOTP First Printed 2015

<https://store.samhsa.gov/product/Federal-Guidelines-for-Opioid-Treatment-Programs/PEP15-FEDGUIDEOTP>

#### Federal Guidelines for Opioid Treatment Programs

*While state programs may vary from one another, all OTP physicians and other healthcare providers, as permitted, should register to use their respective state's PDMP and query it for each newly admitted patient prior to initiating dosing. The PDMP should be checked periodically (for example, quarterly) through the course of each individual's treatment and, in particular, before ordering take-home doses as well as at other important clinical decision points. Querying the PDMP will result in a range of possible results. In some cases, no use of scheduled prescription medications will be identified. In others, the history of prescription use reported by the patient will be confirmed. If the patient has ongoing relationships with prescribers from whom they may still acquire prescriptions for controlled substances or other psychotropics, strategies to prevent or limit this activity should be established. Ideally, releases of information should be obtained from each prescriber in order to coordinate needed medical care while avoiding the use of medications that may interact with the pharmacotherapy for a substance use disorder. Lastly, the PDMP may reveal ongoing receipt*

of prescriptions not reported to the program for substances known to be misused by the patient. An assertive strategy of care coordination combined with additional treatment strategies, such as medically supervised withdrawal from the misused prescription medications and intensive behavioral interventions, may need to be implemented. In some situations, the presence of active diversion may lead to discharge for reasons of patient safety or the safety of the community. Of particular concern is when a patient refuses to sign a release of information to allow care coordination with other prescribers. The program should develop detailed policies and procedures to govern the use of and response to PDMP information for diversion control. Every effort, including full psychiatric assessment, higher levels of substance use disorder treatment, detoxification services, and intensive counseling, should be made to address the addictive behaviors underlying the individual's polysubstance use. The responsibility to implement and monitor each aspect of the diversion control program (DCP) should be clearly assigned to specific clinical, administrative, or medical staff members as appropriate. These staff members should have the opportunity to meet regularly to update one another on issues and communicate concerns. This may be accomplished during regular meetings of a specific diversion control committee. In smaller programs, the DCP may be a regular business item during meetings of all staff. Specific procedures for monitoring possible diversion in each of these areas and how to address it should be spelled out.

Treatment Improvement Protocol (TIP) 63 makes frequent references to use of the prescription drug monitoring program by OTPs. The sections quoted here may be particularly helpful.

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## From: SAMHSA

### Treatment Improvement Protocol (TIP) 63

#### Medications for Opioid Use Disorder

##### Page 2-16:

- **Although** OTPs are not permitted to report methadone treatment to PDMPs, pharmacies that dispense buprenorphine and other controlled substances do report to PDMPs.

##### Page 3-23:

- **Check** the state PDMP for opioid or benzo-diazepine prescriptions from other providers (see [www.nascsa.org/stateprofiles.htm](http://www.nascsa.org/stateprofiles.htm) for links to state PDMPs). Note that methadone for OUD treatment will not appear in the PDMP because of confidentiality regulations regarding substance use treatment records. Obtain the patient's consent to release information and speak with treating providers to coordinate care for patient safety.

##### Page 3-96:

- **Check** the prescription drug monitoring program for new patients and check regularly thereafter. Prescription drug monitoring program reports can be a useful resource when there is little history available or when there is a concern based on observation. Check for prescriptions that interact with buprenorphine and for other buprenorphine prescribers.

# APPENDIX II. HUB AND SPOKE MODEL IN CALIFORNIA

By Jara, G., Rawson, R.

In 2017, California implemented a system of care patterned after Vermont's "hub and spoke" model as one way to improve, expand, and increase access to MAT services throughout the state. The model is defined by California's Department of Health Care Services (DHCS) as a way to increase the total number of physicians, physician assistants and nurse practitioners prescribing buprenorphine, thereby increasing the availability of MAT for patients with opioid use disorders.

A "hub" is a licensed opioid treatment program (OTP) with the authority to dispense buprenorphine as well as methadone. "Spokes" are medical practices affiliated with the hub OTP for the purpose of assuming the ongoing care of patients referred to that practice for ongoing treatment with buprenorphine after the patient has been stabilized on buprenorphine treatment by the hub OTP. See Figure 1.

Implementation is regulated by DHCS. All Hubs and Spokes must obtain or be currently enrolled in California's Drug Medi-Cal or Fee-for-Service Medi-Cal, must apply to DHCS to be accepted into the hub and spoke system, and must remain in good standing throughout the period during which they serve as a hub or a spoke. Full information is available from the [DHCS website](#).

## Early Results of Vermont's Hub-and-Spokes Care Model

The early results of the Vermont Hub-and-Spokes Care model have just become available and will be published in early 2019 in the *Journal of Substance Abuse Treatment*. What follows are two illustrations of its key findings:

### Reference for figures:

"Assessment of medication for opioid use disorder as delivered within the Vermont hub and spoke system" *Journal of Substance Abuse Treatment* 97 (2019) xxx-xxx; Richard Rawson a,b,\*, Sarah J. Cousins b, Michael McCann, Regina Pearce a, Anne Van Donsel c

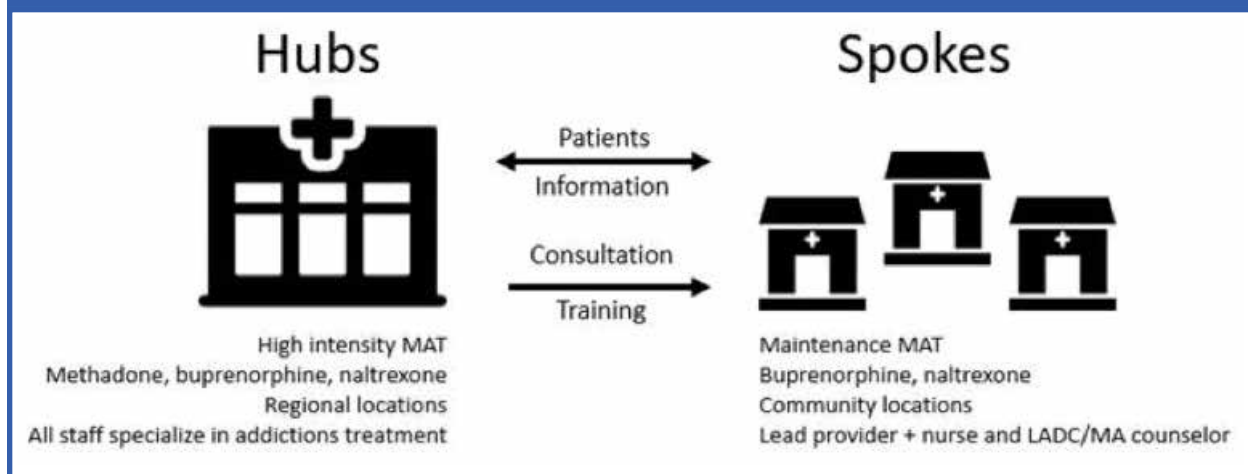
a. Vermont Center for Behavior and Health, Lerner School of Medicine, University of Vermont, 1 South Prospect Street, Burlington, VT, United States of America

b. Integrated Substance Abuse Programs, Geffen School of Medicine, University of California at Los Angeles, 11075 Santa Monica Blvd., Ste. 200, Los Angeles, CA 90025, United States of America

c. Alcohol and Drug Abuse Programs, Department of Health, State of Vermont, 108 Cherry Street, Burlington, VT 05401, United States of America

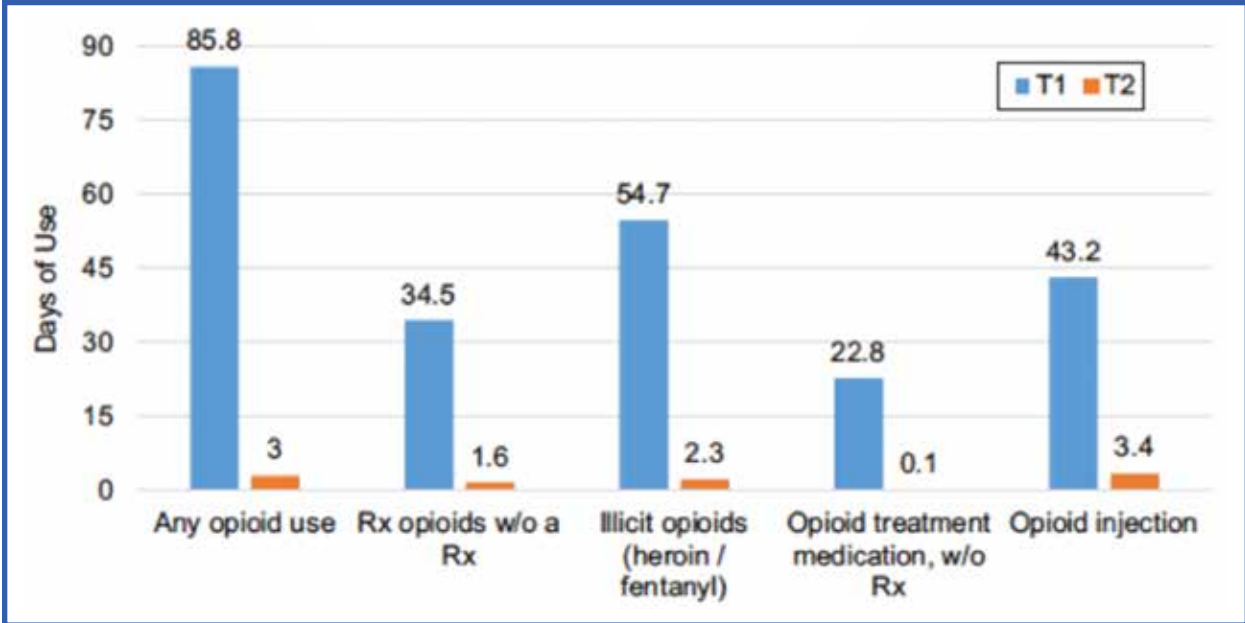
Appendix Figure 1

## Hub and Spoke System for Addictions Treatment



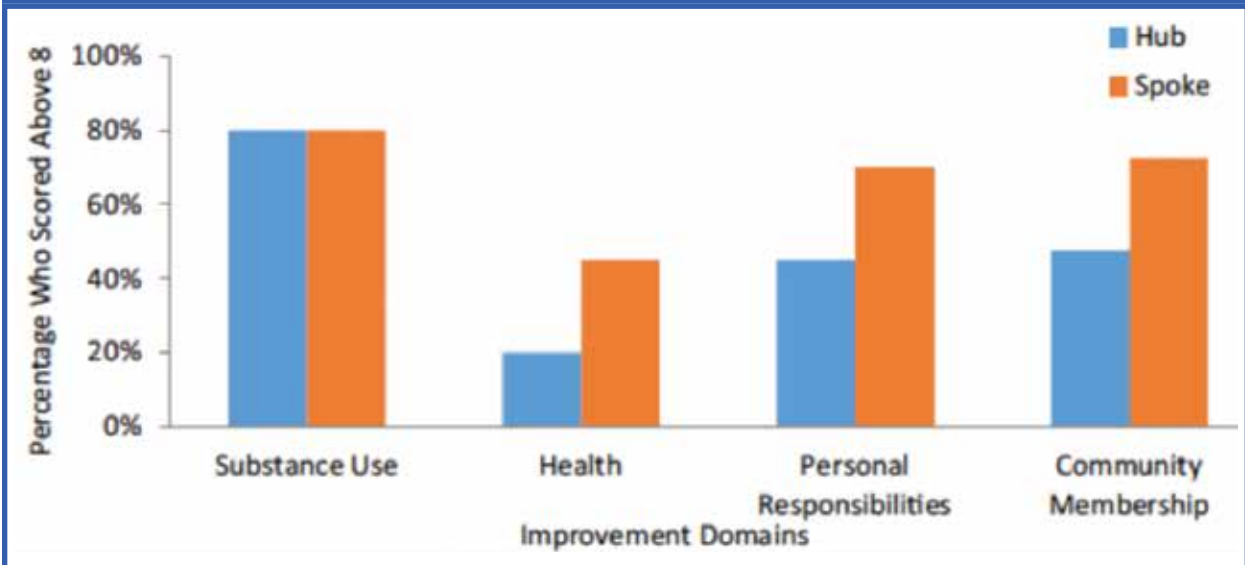
Appendix Figure 2

### Opioid Use Among In-treatment Group Participants (N = 80)



Appendix Figure 3

### Treatment (n = 80) Scores of Hub vs. Spoke Participants



# GLOSSARY OF TERMS

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**Buprenorphine (brand name *Subutex*)** • partial opioid agonist used to treat opioid addiction, acute pain, and chronic pain.

**Long-term detoxification** • methadone initiation, stabilization and withdrawal lasting up to 180 days.

**Medication-assisted treatment** • use of FDA-approved medications, in combination with counseling and behavioral therapies, to provide a holistic approach to the treatment of substance use disorders.

**Methadone (brand name *Dolophine*)** • an opioid used for medication-assisted treatment in opioid use disorder, and for pain.

**Methadone maintenance treatment (MMT)** • methadone initiation, stabilization and ongoing treatment with reviews at specified intervals to establish that ongoing treatment is still medically necessary.

**Naloxone (brand name *Narcan*)** • non-selective and competitive opioid antagonist, recommended for the immediate treatment of the respiratory depression due to opioid overdose.

**Naltrexone (brand names *ReVia* and *Vivitrol*)** • opioid antagonist used for the treatment of opioid use disorder by blocking the effects of opioids.

**Neonatal abstinence syndrome (NAS)** • withdrawal syndrome of infants after birth caused by in utero exposure to addictive opioids, alcohol, nicotine, benzodiazepines or any other prescription or illicit drug (or combination of drugs) producing withdrawal upon abrupt cessation.

**Opioid** • umbrella term including alkaloids extracted from the resin of the opium poppy, simple chemical derivatives of these (semi-synthetic opiates) and synthetic opioids.

**Opioid agonist treatment (OAT)** • treatment of opioid use disorder involving the use of opioid agonists such as methadone or buprenorphine to target opioid receptors.

**Opioid treatment program (OTP)** • a SAMHSA-certified program that provides medication-assisted treatment (MAT) for people diagnosed with an opioid-use disorder.

**Opioid use disorder (OUD)** • diagnosis defined by repeated occurrence of 2 or more of 11 problems as defined by the DSM-5, including withdrawal, giving up important life events in order to use opioids, and excessive time spent using opioids within a 12-month period.

**Short-term detoxification** • methadone administered in decreasing doses for up to 30 days.

**Substance use disorder (SUD)** • diagnosis of significant clinical and functional impairment due to substance use, as defined by the DSM-5, such as health problems, disability, and failure to meet major life responsibilities

**Torsades de pointes (TDP)** • an abnormal heart rhythm, specifically an uncommon type of ventricular tachycardia that is marked by prolongation of the QT interval and increased risk of sudden cardiac death.



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